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<td>230</td>
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</tbody>
</table>
Faculty

Lung Cancer

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## Melanoma (continued)

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<tr>
<th>Name</th>
<th>Position and Affiliation</th>
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<tbody>
<tr>
<td>Jason J Luke, MD</td>
<td>Assistant Professor of Medicine, The University of Chicago, Chicago, Illinois</td>
</tr>
<tr>
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<tr>
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<tr>
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## Genitourinary Cancer

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<tr>
<th>Name</th>
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<tr>
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</tr>
<tr>
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<tr>
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</tr>
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## Faculty

### Genitourinary Cancer (continued)

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<tr>
<td>Elizabeth R Plimack, MD, MS</td>
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</tr>
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### Multiple Myeloma

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Lung Cancer

Current and Future Use of Checkpoint Inhibitors

Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer¹

KEYNOTE-024: Pembrolizumab (pembro) vs platinum-based chemotherapy (chemo) as first-line therapy for advanced NSCLC with a PD-L1 tumor proportion score (TPS) ≥50%²

Reck M et al.
¹ N Engl J Med 2016;[Epub ahead of print].
² Proc ESMO 2016;Abstract LBA8_PR.

Dr Rizvi

The Phase III KEYNOTE-024 trial compared pembrolizumab vs investigator’s choice of a platinum-based doublet chemotherapy in patients with newly diagnosed metastatic non-small cell lung cancer (NSCLC) and PD-L1 expression on at least 50% of cells in their tumor biopsy sample. A threshold of 50% PD-L1 expression has been validated in the second-line setting and encompasses about 25% to 30% of newly diagnosed NSCLC patients. Requiring high-level tumor PD-L1 expression served to enhance the likelihood of a response in this trial by selecting for the subset of lung cancer patients most likely to benefit from immune checkpoint inhibitor therapy. Patients excluded from KEYNOTE-024 included those with EGFR mutations or ALK translocations as well as organ/tissue transplant recipients, patients with an active autoimmune disease requiring treatment within 2 years of enrollment, and patients with untreated brain metastases.

The results of the KEYNOTE-024 trial were strongly positive. The primary endpoint of PFS was significantly improved, with a median PFS of 10.3 months with pembrolizumab vs 6.0 months with chemotherapy (HR: 0.50; p < 0.001). The secondary endpoint of overall survival (OS) was also significantly improved with pembrolizumab (80% vs 72% at 6 months; HR: 0.60; p = 0.005), as was the objective response rate (45% vs 28%).

Particularly remarkable was that nearly 10% of patients, 6 out of 63, achieved a complete response with pembrolizumab vs 1 out of 41 with chemotherapy. In addition to improved efficacy, toxicity with pembrolizumab was significantly lower than with chemotherapy, with fewer treatment-related adverse events of both any grade (73% vs 90%) and Grade 3 or higher (27% vs 53%). With a high bar set by the activity of standard of care chemotherapy in the first-line setting, the data reported for pembrolizumab at ESMO and published in parallel in the The New England Journal of Medicine are truly tremendous, and the FDA rapidly approved first-line therapy with pembrolizumab in PD-L1 positive (≥50%) NSCLC on October 24, 2016.
Dr Spigel

Background
• RPIII industry-sponsored trial to assess the role of pembrolizumab in the first-line treatment of Stage IV PD-L1+ NSCLC

Study/Conduct
• N = 1,934 screened in 16 countries to enroll 305 patients
• Enrolled 9/14-10/15
• Stage IV NSCLC
• ECOG PS 0-1
• Pembrolizumab 200 mg (35 cycles) vs 1 of 5 platinum doublets x 4-6 cycles (carbo/pem, cis/pem, carbo/gem, cis/gem, carbo/pac)
• Primary Aim: PFS (central blinded review)
• Trial stopped early for futility

Results
• PFS: HR 0.5, median 10.3 vs 6.0 mo
• OS: HR 0.60; median OS not reached in either arm
• ORR: 45 vs 28%
• TRAEs lower

Take Home
• Pembrolizumab should be considered a standard first-line treatment for eligible patients
• We still do not know if a patient would do just as well to receive chemotherapy followed by a checkpoint inhibitor (44% on chemotherapy crossed over to pembrolizumab)
• 305/1,934 (16%) patients had samples that could be assessed for PD-L1
• No comparison with a Bev regimen
• ‘Negative’ patients who do not qualify for up-front pembrolizumab are still eligible for nivolumab/atezolizumab as a later line of therapy
Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: A randomised, phase 2 cohort of the open-label KEYNOTE-021 study

Randomized, phase 2 study of carboplatin and pemetrexed with or without pembrolizumab as first-line therapy for advanced NSCLC: KEYNOTE-021 cohort G

Langer C et al.  
2 Proc ESMO 2016;Abstract LBA46_PR.

Dr Rizvi

Patients with chemotherapy-naïve, Stage IIIIB or IV nonsquamous NSCLC without targetable EGFR or ALK genetic aberrations were randomly assigned to 4 cycles of pembrolizumab plus carboplatin and pemetrexed every 3 weeks followed by pembrolizumab for 24 months and indefinite pemetrexed maintenance therapy or to 4 cycles of carboplatin and pemetrexed alone followed by indefinite pemetrexed maintenance therapy. The primary endpoint was response. 123 patients were enrolled; 60 were randomly assigned to the pembrolizumab plus chemotherapy group and 63 to the chemotherapy alone group. The response rate in the pembrolizumab plus chemotherapy group was 55% vs 29% in the chemotherapy alone group.

No complete responses were observed in either arm. The response rate in the 20 patients with TPS of at least 50% was 80%. The incidence of Grade 3 or worse treatment-related adverse events was similar between groups. The PFS was 13 months with pembro + chemotherapy vs 8.9 months with chemotherapy alone (HR 0.53). OS was the same (HR 0.9). 48% of chemotherapy-only patients received subsequent PD-1 or PD-L1 antibody therapy.

Dr Spigel

Background

- RPII industry-sponsored trial to assess the role of pembrolizumab and chemotherapy vs chemotherapy in the first-line treatment of Stage IV nonsquamous NSCLC

Study/Conduct

- N = 123 enrolled in 2 countries
- Enrolled 11/14-1/16
- Stage IIIIB/IV nonsquamous NSCLC
- ECOG PS 0-1
- Pembrolizumab 200 mg (2 yrs) + carbo/pemetrexed (4 cycles + pem maintenance) vs chemotherapy alone
- Primary Aim: ORR (blinded independent central review [BICR])
Results

- ORR: 55 vs 29% (PD-L1 <1%: 57% vs 13%; ≥1%: 54% vs ?; 1%-49%: 26% vs 39%; ≥50%: 80% vs 35%)
- PFS: HR 0.53, median 13 vs 8.9 mo
- OS: HR 0.9
- Severe TRAEs similar

Take Home

- Pembrolizumab + chemotherapy appears to be more active than chemotherapy alone
- But this trial is small and PD-L1 subsets are very small
- Await Phase III data (KEYNOTE-189 and 407 squamous NSCLC with carbo/pac or nab-pac trials ongoing)

CheckMate 026: A Phase 3 trial of nivolumab vs investigator’s choice (IC) of platinum-based doublet chemotherapy (PT-DC) as first-line therapy for stage IV/recurrent programmed death ligand 1 (PD-L1)-positive NSCLC

Socinski M et al. 
Proc ESMO 2016;Abstract LBA7_PR.

Dr Spigel

Background

- PIII industry-sponsored trial to assess the role of nivolumab vs chemotherapy in the first-line treatment of Stage IV NSCLC

Study/Conduct

- N = 541 enrolled (global)
- Enrolled 9/14-10/15
- Stage IV NSCLC
- PD-L1 ≥1%
- Nivolumab 3 mg/kg (48 weeks) vs platinum doublet up to 6 cycles (carbo/pem, cis/pem, carbo/gem, cis/gem, carbo/pac)
- Primary Aim: PFS (PD-L1 >5%) — BICR
- Crossover on the chemotherapy arm
- Trial stopped early for futility

Results

- Nivo arm had fewer female patients, 32% vs 45%; fewer patients with PD-L1 expression: ≥25%, 49% vs 61%; ≥50%, 33% vs 47%; ≥75%, 21% vs 27%
The potential for nivolumab and ipilimumab immunotherapy has been demonstrated in melanoma, leading to FDA approval of this combination with ipilimumab 3 mg/kg every 3 weeks x 4 doses and nivolumab 1 mg/kg every 3 weeks x 4 doses followed by nivolumab 3 mg/kg every 2 weeks. This dose and schedule initially studied in Check-Mate 012 NSCLC patients was not tolerated, with increased immune-related AEs. Check-Mate 012 was modified to study nivolumab 3 mg/kg q2wk plus ipilimumab 1 mg/kg (q6wk or q12wk), with greater tolerability; the frequency of treatment-related AEs leading to discontinuation was similar to that with nivolumab monotherapy (11%-13%) and there were no treatment-related deaths.

Nivolumab plus ipilimumab has promising efficacy with a 39%-47% ORR and median duration of response not reached. Efficacy with nivolumab plus ipilimumab is enhanced with increasing PD-L1 expression, and in ≥1% tumor PD-L1 expression there were a 57% ORR and 83%-90% 1-year OS rates. For ≥50% tumor PD-L1 expression response rate was 92% (12/13). Nivolumab 3 mg/kg q2wk plus ipilimumab 1 mg/kg q6wk schedule is being evaluated in further studies, including the Phase III CheckMate 227 trial (NCT02477826).

**Take Home**
- Nivolumab is not superior to chemotherapy — regardless of PD-L1 expression
- This trial was not designed to assess noninferiority
- Nivolumab remains a drug for patients in the second line and beyond

**CheckMate 012:** Safety and efficacy of first-line (1L) nivolumab (nivo; N) and ipilimumab (ipi; I) in advanced (adv) NSCLC

Hellmann MD et al. Proc ASCO 2016;Abstract 3001.

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**Dr Rizvi**

The potential for nivolumab and ipilimumab immunotherapy has been demonstrated in melanoma, leading to FDA approval of this combination with ipilimumab 3 mg/kg every 3 weeks x 4 doses and nivolumab 1 mg/kg every 3 weeks x 4 doses followed by nivolumab 3 mg/kg every 2 weeks. This dose and schedule initially studied in Check-Mate 012 NSCLC patients was not tolerated, with increased immune-related AEs. Check-Mate 012 was modified to study nivolumab 3 mg/kg q2wk plus ipilimumab 1 mg/kg (q6wk or q12wk), with greater tolerability; the frequency of treatment-related AEs leading to discontinuation was similar to that with nivolumab monotherapy (11%-13%) and there were no treatment-related deaths.

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**Dr Spigel**

**Background**
- PI industry-sponsored trial to assess the role of nivolumab + ipilimumab in the first-line treatment of Stage IV NSCLC: Cohort update

**Study/Conduct**
- N = 77
- Stage IIIIB/IV NSCLC
- ECOG PS 0-1
- Nivo 3/ipi 1 q12wk; nivo 3/ipi 1 q6wk
- Primary Aim: Safety and tolerability

Results
- ORR: 47%, 39% (PD-L1 ≥50%-92%, 50%)
- PFS: Median 8.1 mo, 3.9 mo
- OS: 1 year – NC/69%
- TRAEs: Any grade/severe 82%/37%, 72%/33%
- TRAEs leading to discontinuation: Any grade/severe 11%/5%, 13%/8%

Take Home
- Nivo/ipi appears to be more active than nivo alone (20% — second line and beyond)
- PD-L1 status may not matter with the ipi combination
- Await Phase III trials
- Toxicity is high (but manageable) — may be a serious barrier to development (or use over pembrolizumab alone)

Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): A randomised controlled trial


Dr Goldberg

Until recently, docetaxel was the standard second-line treatment for patients with advanced NSCLC, and this trial compared docetaxel to the PD-1 inhibitor pembrolizumab in patients previously treated with platinum-based chemotherapy. In a prior Phase I trial with pembrolizumab, patients whose tumors expressed PD-L1 had better outcomes than those without PD-L1 expression, and therefore this trial required PD-L1 expression for eligibility. Patients were randomized to 1 of 3 arms: pembro at 2 mg/kg or 10 mg/kg or docetaxel 75 mg/m² every 3 weeks. Of the 2,222 patients tested for PD-L1 expression, 1,475 (66%) were found to have expression in at least 1% of tumor cells and 633 (28%) had expression in >50% of tumor cells.

Overall survival was improved with pembro at either dose compared to docetaxel, as were progression free survival (statistically significant for the 10-mg/kg dose only) and response rate. This held true for those with >50% PD-L1 expression and for the total population (ie, >1% PD-L1 expression). Toxicity was better with pembro compared to docetaxel, a trend seen in several other studies comparing immunotherapy to chemotherapy. This study clearly demonstrates that pembrolizumab is superior to docetaxel.
in patients with NSCLC that expresses PD-L1, and it represents a new standard of care for these patients. It remains unknown whether pembro is superior to other immunotherapies in this patient population.

It is currently being studied in the first-line setting compared to chemotherapy and in combination with many other agents, including chemotherapy, targeted therapy, anti-angiogenics and other immunotherapies.

Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC

Barlesi F et al. Proc ESMO 2016;Abstract LBA44_PR.

Dr Rizvi
Atezolizumab was compared to docetaxel in metastatic NSCLC patients who have received 1-2 prior lines of therapy. Primary endpoint was OS in ITT and OS in at least 1% PD-L1 expression. OS HR was 0.73 for atezolizumab over docetaxel. Crossover to immunotherapy in the docetaxel group was 17%. The benefit was observed across PD-L1 expression and histology. As expected, EGFR mutant NSCLC performed less well, with a HR of 1.24, but interestingly, never smokers had a HR similar to that for prior smokers (0.71 vs 0.74). Pneumonitis was seen in only 1% of patients with atezolizumab. On October 18, 2016 atezolizumab was FDA approved for unselected patients with chemotherapy pretreated NSCLC.

Dr Spigel
Background
- PIII industry-sponsored trial to assess the role of atezolizumab vs chemotherapy in the second-line treatment of Stage IV NSCLC

Study/Conduct
- N = 850 enrolled (global)
- Enrolled 9/14-10/15
- Stage IV NSCLC
- Any PD-L1 status
- Atezolizumab 1,200 mg q3wk vs docetaxel 75
- Primary Aim: OS (ITT), OS (PD-L1 >1% TC or IC) — BICR
- Crossover on the chemotherapy arm
- Trial stopped early for futility

Results
- PFS: HR 1.15, median 4.2 vs 5.9 mo
- OS: HR 0.73, median OS 13.8 vs 9.6 mo
• OS PD-L1 ≥1% TC or IC: HR 0.74; median OS 15.7 vs 10.3 mo
• OS PD-L1 <1% TC or IC: HR 0.75; median OS 12.6 vs 8.9 mo
• OS PD-L1 ≥50% TC or IC: HR 0.41; median OS 20.5 vs 8.9 mo
• PFS PD-L1 any PD-L1 TC or IC: HR 0.95; median OS 2.8 vs 4 mo
• ORR: 52 vs 18%
• TRAEs any/severe: 64/15 vs 86%/43%

Take Home
• Atezolizumab is superior to docetaxel in refractory NSCLC — regardless of PD-L1 status or histology
• Atezolizumab may be preferred over nivolumab in the community due to q3wk dosing
• No (yet) known difference between PD-1 and PD-L1 inhibitors

Atezolizumab versus docetaxel for patients with previously treated non-small-cell lung cancer (POPLAR): A multicentre, open-label, phase 2 randomised controlled trial


Dr Goldberg
Randomized Phase III trials have demonstrated the benefit of the PD-1 inhibitors nivolumab and pembrolizumab compared to docetaxel for second-line treatment of NSCLC, leading to FDA approval for their use in this setting. The POPLAR trial is a randomized Phase II trial that is the first to compare a PD-L1 inhibitor to docetaxel in previously treated NSCLC. In this trial, patients with advanced NSCLC were randomized to atezolizumab at a fixed dose of 1,200 mg versus docetaxel 75 mg/m² every 3 weeks. The PD-L1 biomarker was not used for patient selection but was analyzed retrospectively. The trial found a statistically significant improvement in overall survival with atezolizumab compared to docetaxel (median 12.6 with atezo versus 9.7 months with docetaxel).

The overall survival benefit (as well as progression free survival and response rate benefit) was greater in those with PD-L1 expression on either tumor cells or immune cells; those without PD-L1 expression in either cell population did not appear to have a benefit with atezo compared to chemotherapy. Atezo was better tolerated, with fewer patients discontinuing treatment for toxicity and fewer treatment-related Grade 3-5 adverse events compared to docetaxel. This trial is the first to demonstrate a survival benefit with a PD-L1 inhibitor compared to chemotherapy in patients with NSCLC. Similar to other PD-1 inhibitors, the toxicity profile is better than with chemotherapy.

Although not yet approved by the FDA for use in patients with NSCLC, atezolizumab appears very promising in this patient population and is being tested in many clinical
trials alone and in combination with other agents. Additionally, this study shows us that the PD-L1 biomarker may be important when selecting patients for treatment with atezolizumab.

Safety and antitumour activity of durvalumab plus tremelimumab in non-small cell lung cancer: A multicentre, phase 1b study

Antonia S et al. 

**Dr Goldberg**

Inhibiting both the PD-1 and CTLA-4 pathways is a strategy that has been successful in patients with melanoma and is currently under investigation in patients with NSCLC. The combination of nivolumab and ipilimumab appears to have activity in NSCLC, but toxicity is greater and it is unknown whether the combination is better than single-agent PD-1 axis inhibitors. This study is the first to evaluate the combination of a PD-L1 inhibitor with a CTLA-4 inhibitor in NSCLC. In this Phase I trial, patients with advanced NSCLC were treated with durvalumab and tremelimumab at escalating doses and evaluated for toxicity and efficacy. The study found a higher rate of Grade 3-4 adverse events and treatment discontinuation for toxicity than in trials with single-agent PD-1 or PD-L1 inhibitors.

The response rate was 23% in the durvalumab 10-20 mg/kg and tremelimumab 1 mg/kg cohort, and importantly, patients with PD-L1 positive and negative tumors had responses, including several patients with no PD-L1 staining. This combination is moving forward in Phase III trials compared to single-agent durvalumab and chemotherapy and is a very promising combination strategy for patients, with the caveat that toxicity is likely to be greater than with a PD-1 or PD-L1 inhibitor alone.

**Dr Rizvi**

Similar to the experience with nivolumab and ipilimumab, higher doses of anti-CTLA-4 (tremelimumab) in NSCLC were intolerable. The optimal dose based on this dose escalation trial was determined to be durvalumab 20 mg/kg every 4 weeks and tremelimumab 1 mg/kg every 4 weeks x 4 doses. This trial was conducted in pretreated NSCLC patients. Evidence of clinical activity was noted both in patients with PD-L1-positive tumors and in those with PD-L1-negative tumors.

Investigator-reported confirmed objective responses were achieved by 6 (23%, 95% CI 9-44) of 26 patients in the combined tremelimumab 1 mg/kg cohort, comprising 2 (22%, 95% CI 3-60) of 9 patients with PD-L1-positive tumors and 4 (29%, 95% CI 8-58) of 14 patients with PD-L1-negative tumors, including those with no PD-L1 staining (4 [40%, 95% CI 12-74] of 10 patients). Based on this trial, the MYSTIC trial comparing durvalumab and tremelimumab versus durvalumab versus chemotherapy in the first-line setting has been fully enrolled and data are eagerly anticipated.
Dr Spigel

Background

- PIb industry-sponsored trial to assess the role of durvalumab/tremelimumab in Stage IV NSCLC

Study/Conduct

- N = 102
- Enrolled 10/13-4/15
- Stage IIIb/IV NSCLC
- 0-4+ prior lines of therapy
- Durva 3 mg/kg, 10 mg/kg, 15 mg/kg, 20 mg/kg q4wk or 10 mg/kg q2wk + Trem 1 mg/kg, 3 mg/kg or 10 mg/kg q4wk
- Primary Aim: Safety and tolerability

Results

- RP2D: Durva 20 mg/kg q4wk + Trem 1 mg/kg; ORR: 47%, 39% (PD-L1 ≥50%-92%, 50%)
- ORR: 0%-23%
- TRAEs: Severe, diarrhea 7%-18%, pneumonitis 6%, transaminitis 3%-4%
- TRAEs leading to discontinuation: 28%

Take Home

- Durva/Trem is an active regimen — with ORRs that appear higher with Durva alone
- Benefit not clearly associated with PD-L1 expression
- Diarrhea/colitis and TRAEs leading to discontinuation are of concern
- Phase III trials in first line pending (NEPTUNE and MYSTIC)

Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): A multicentre, open-label, phase 1/2 trial

Antonia SJ et al. 

Dr Goldberg

The current standard therapy for recurrent small cell lung cancer is chemotherapy. However, response rates are low and survival is typically poor. This is the first trial to evaluate immunotherapy in patients with SCLC. Patients were treated with nivolumab every 2 weeks or nivolumab plus ipilimumab at various doses every 3 weeks for 4 cycles followed by nivolumab alone every 2 weeks. Patients treated with monotherapy nivolumab had a 10% response rate, while patients receiving the combination had
a response rate between 19% and 23%, depending on the dose cohort. Toxicity appeared to be greater among patients receiving combination therapy. Patients in monotherapy and combination treatment groups had durable responses, several of which lasted longer than 6 months.

This trial demonstrates that nivolumab and nivolumab plus ipilimumab have activity in patients with small cell lung cancer, in some cases durable activity. If confirmed in further trials, this could represent a huge advance in the treatment of patients with SCLC.

**Avelumab (MSB0010718C; anti-PD-L1) in patients with advanced unresectable mesothelioma from the JAVELIN solid tumor phase Ib trial: Safety, clinical activity, and PD-L1 expression**

Hassan R et al.  
Proc ASCO 2016;Abstract 8503.

**Dr Goldberg**

After progression on platinum/pemetrexed, there are no standard therapy options for patients with unresectable pleural mesothelioma, and immunotherapy has not yet been explored in this patient population. This is a Phase Ib trial of the PD-L1 inhibitor avelumab for patients with multiple tumor types, including a cohort for previously treated unresectable mesothelioma. Patients were treated regardless of PD-L1 expression. Among the 53 patients with mesothelioma treated, 5 had a partial response for an overall response rate of 9.4%. Four of the 5 patients who responded continued to show a response at the time of data cut-off. Responses were seen in tumors with and without PD-L1 expression (RR 14.3% in PD-L1+ vs 8% in PD-L1-).

Treatment was well tolerated, and toxicity appeared similar to that seen with PD-1 axis agents in lung cancer. This is a small cohort of patients but does demonstrate that PD-1 axis inhibitors can have activity in patients with mesothelioma. Further trials with PD-1/PD-L1 agents in mesothelioma are ongoing or planned.

**Adjuvant Chemotherapy; Chemoradiation Therapy for Stage III Disease**

**E1505: Adjuvant chemotherapy +/- bevacizumab for early stage NSCLC — Outcomes based on chemotherapy subsets**

Wakelee HA et al.  
Proc ASCO 2016;Abstract 8507.

**Dr Goldberg**

Although the majority of the prospective randomized clinical trials of adjuvant chemotherapy for NSCLC have been done with cisplatin/vinorelbine, many other regimens are used in practice because of the difficulty with tolerability and schedule with this regimen. Additionally, studies performed in the metastatic setting have proven the superiority of other regimens and these data are often extrapolated for use in the
adjuvant setting. This large Phase III trial randomized patients with early-stage NSCLC to receive adjuvant therapy with or without bevacizumab. While the overall trial was negative for its primary endpoint, this abstract reports on another important finding in the trial, namely the difference between the various chemotherapy regimens used as adjuvant therapy.

This aspect of the trial was not randomized; the chemotherapy regimen chosen was investigators choice. Options were 4 cycles of cisplatin plus vinorelbine, docetaxel, gemcitabine, or pemetrexed (for non-squamous patients only). 1,501 patients were enrolled on this trial, with 25% receiving vinorelbine, 23% docetaxel, 19% gemcitabine, and 33% pemetrexed. There was no overall or disease-free survival difference between the 4 groups when balanced for squam/non-squam and bevacizumab/placebo. Pemetrexed appeared to be the best-tolerated regimen, with less Grade 3-5 toxicity compared to other regimens. Although this was not a randomized trial, these data support the use of the various other regimens in the adjuvant setting.

The choice of chemotherapy should therefore be decided based on toxicity profile, with a particular emphasis on pemetrexed for non-squamous NSCLC given the good toxicity profile and similar survival compared to the other regimens studied.

Dr Rizvi

The addition of bevacizumab to adjuvant chemotherapy did not improve OS for patients with surgically resected early-stage NSCLC in data initially presented at the 2015 World Conference on Lung Cancer. The Phase III trial randomized 1,501 patients with NSCLC in a 1:1 ratio to chemotherapy with bevacizumab (n = 752) or without (n = 749). Data showed that OS did not differ between the 2 arms (HR, 0.99; 95% CI, 0.81-1.21; p = .93). Median OS was more than 72 months in both cohorts. Similar data were reported with disease-free survival, a secondary endpoint, between the 2 arms (HR, 0.98; 95% CI, 0.84-1.14; p = 0.75).

At ASCO 2016 outcomes based on chemotherapy subsets were presented. In this analysis, patients were pooled across arms (with or without bevacizumab) and divided into nonsquamous and squamous cohorts with DFS and OS curves calculated for each chemotherapy group. The chemotherapy arms included cisplatin with either vinorelbine (25%), docetaxel (23%), gemcitabine (19%) or pemetrexed (33%). No differences in OS or DFS were observed. The vinorelbine arm was associated with greater neutropenia and febrile neutropenia; gemcitabine with increased thrombocytopenia and pemetrexed with fewer total Grade 3-5 toxicities.

Dr Spigel

Background

• RPIII cooperative group pivotal trial to assess the role of bevacizumab (Bev) in the adjuvant NSCLC setting

Study/Conduct

• N = 1,501 — Enrolled 7/07 – 9/13
• Stage IB (4 cm/+- IIIA)
• Any NSC histology
• Choice of chemotherapy platform regimen (cisplatin/vinorelbine [V], docetaxel [D], gemcitabine [G], pemetrexed [P])
• Primary Aim: Overall survival (OS)
• Trial stopped early for futility
• Not designed to allow meaningful chemotherapy subset comparisons

Results
• 475 OS events (70% of planned)
• IB 26%, II 44%, IIIA 30%
• V 25%, D 23%, G 19%, P 33%
• OS: HR 0.99; median OS chemo alone NR, Bev 86 mo
• DFS: HR 0.99
• Pooled analyses: No differences
• Safety: Neutropenia and HTN higher with Bev

Take Home
• There is no role for Bev in the adjuvant treatment of NSCLC
• The enthusiasm for any adjuvant therapy has waned since the original pivotal trials. We now focus on Stage II-IIIA. Carboplatin is frequently used at some point in care. RT is used judiciously in node positive settings. The next big questions (and ongoing trials are addressing) are in EGFR and ALK settings — with perhaps the biggest question being around the role of immunotherapy in the early stage setting including recent limited data with nivolumab in the preop setting (Forde, ESMO 2016)

PROCLAIM: Randomized Phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer


Dr Goldberg
The optimal chemotherapy regimen to use with concurrent radiation therapy for patients with locally advanced NSCLC is unknown. Common regimens used in practice include cisplatin/etoposide and weekly low-dose carboplatin/paclitaxel, but there have been no randomized trials comparing the different chemotherapy regimens for Stage III disease. This trial is the first to compare the current standard of cisplatin/etoposide versus cisplatin/pemetrexed plus radiation therapy for Stage III NSCLC. Patients
receiving cis/etop received 2 cycles of chemotherapy during RT and then went on to receive consolidation chemotherapy with cisplatin plus either etoposide or vinorelbine or carboplatin plus paclitaxel x 2 cycles, whereas those receiving cis/pem had 3 cycles with RT and then received consolidation pem x 4 cycles.

Radiation doses were 60-66 Gy. There was no statistically significant difference in overall survival between the 2 arms of the trial (median 26.8 for cis/pem vs 25.0 months for cis/etop). There was a significant difference in toxicity between the arms, with lower incidence of Grade 3-4 adverse events in the cis/pem arm (64.0% vs 76.8%). This trial provides rationale for choosing cisplatin/pemetrexed as an alternative to the standard cisplatin/etoposide for patients with Stage III NSCLC when treating with concurrent chemoradiation therapy. While there was no survival benefit, survival appeared similar between the 2 regimens and there was a better toxicity profile with pemetrexed. It remains unknown how weekly carboplatin/paclitaxel compares to this regimen as it has not been compared in a prospective randomized Phase III trial.

Dr Rizvi

The Phase III PROCLAIM study evaluated overall survival (OS) with concurrent pemetrexed-cisplatin and thoracic radiation therapy (TRT) followed by consolidation pemetrexed, versus etoposide-cisplatin and TRT followed by nonpemetrexed doublet consolidation therapy. Patients with Stage IIIA/B unresectable nonsquamous NSCLC randomly received (1:1) pemetrexed 500 mg/m² and cisplatin 75 mg/m² intravenously every 3 weeks for 3 cycles plus concurrent TRT (60 to 66 Gy) followed by pemetrexed consolidation every 3 weeks for 4 cycles (arm A), or standard therapy with etoposide 50 mg/m² and cisplatin 50 mg/m² intravenously every 4 weeks for 2 cycles plus concurrent TRT (60 to 66 Gy) followed by 2 cycles of consolidation platinum-based doublet chemotherapy (arm B).

The primary objective was OS. The study was designed as a superiority trial with 80% power to detect an OS hazard ratio of 0.74 with a type 1 error of 0.05. Enrollment was stopped early because of futility. Arm A had a significantly lower incidence of any drug-related Grade 3 to 4 adverse events (64.0% vs 76.8%; p = 0.001), including neutropenia (24.4% vs 44.5%; p < 0.001) during the overall treatment period. Pemetrexed-cisplatin combined with TRT followed by consolidation pemetrexed was not superior to standard chemoradiotherapy for Stage III unresectable nonsquamous NSCLC.

Dr Spigel

Background

- RPIII industry-sponsored trial to assess the role of pemetrexed (Pem) in the management of Stage III nonsquamous NSCLC

Study/Conduct

- N = 598
- Enrolled 10/08 – 8/12
• Stage IIIA/B
• Cisplatin/Pem x 3 cycles with Pem consolidation (4 cycles) vs cisplatin/etoposide x 2 cycles + RT with chemotherapy consolidation
• Primary Aim: OS
• Trial stopped early for futility
• Not designed for noninferiority comparison

Results
• OS: HR 0.98; median OS 27 vs 25 mo
• Pem with fewer dose-reducing-SAEs (neutropenia)

Take Home
• Pem is not better than etoposide for Stage III disease
• This trial does not justify the use of Pem in Stage III disease
• Carboplatin/paclitaxel still commonly used in the community
• Immunotherapy (durvalumab — the Pacific trial) is the next big trial that can impact care (no consolidation therapy used)

Management of Patients with EGFR, ALK or ROS1 Alterations

Afatinib versus gefitinib as first-line treatment of patients with EGFR mutation-positive non-small-cell lung cancer (LUX-Lung 7): A phase 2B, open-label, randomised controlled trial

Afatinib (A) vs gefitinib (G) in patients (pts) with EGFR mutation-positive (EGFRm+) non-small-cell lung cancer (NSCLC): Overall survival (OS) data from the phase IIb trial LUX-Lung 7 (LL7)


Dr Riely
The available first- and second-generation EGFR TKIs erlotinib, gefitinib, and afatinib have been compared to chemotherapy in a number of trials enrolling patients with EGFR mutations. In each of these trials, these EGFR TKIs have been found to be superior to chemotherapy. However, there are few data that directly compare EGFR TKIs in patients with EGFR mutations. In that setting, we saw this initial report comparing afatinib and gefitinib in patients with EGFR mutant NSCLC. In this small study of 319 patients, patients were randomized to the approved dose of either agent (afatinib 40 mg/d or gefitinib 250 mg/d). While OS data are immature, there was
an improvement in response rate and progression-free survival (HR 0.73) for those patients who received afatinib rather than gefitinib.

All subsets examined appeared to derive equal benefit from afatinib (HR for PFS benefit was equivalent in EGFR exon 19 deletion and EGFR L858R patients). Since both these drugs target wild-type EGFR, and afatinib was dosed at the maximum tolerated dose but gefitinib was dosed at 50% or less of the MTD, as expected there was a difference in toxicity for these 2 agents. Patients treated with afatinib had a much higher rate of serious treatment drug-related adverse events (11% vs 4%).

One other piece of data that describes both the toxicities observed and pill sizes available: More than 40% of afatinib treated patients required a dose reduction as compared to 2% of those treated with gefitinib (there is only one pill size of gefitinib, essentially making it impossible to dose reduce). Taken together, there is modest improvement in TTF with afatinib compared to erlotinib, but this is associated with a modest increase in select toxicities. How afatinib compares to erlotinib in patients with EGFR mutant NSCLC is not clear from these data.

Dr Sequist

LUX-Lung 7 is one of the first randomized studies to compare one EGFR TKI to another head to head in the front-line setting among EGFR mutants. It was a randomized Phase IIb study in which over 300 patients with newly diagnosed, advanced EGFR mutation-positive disease were given either afatinib 40 mg QD or gefitinib 250 mg QD until progression.

Afatinib showed a slight advantage over gefitinib, with higher response rate (70% vs 56%) and median PFS fairly similar (11.0 months for afatinib, 10.9 for gefitinib), but the curves separated after the median such that the hazard ratio for PFS favored afatinib (HR 0.73, 95% CI 0.57-0.95). Both the del(19p) and L858R subgroups showed PFS trends favoring afatinib as well, but neither had a statistically significant result. OS data are not yet mature. Adverse events were as expected, with more patients having Grade 3 rash, diarrhea and fatigue in the afatinib group comparatively. However, the rates of drug discontinuation due to AEs were low and equal in both arms.

Recently at ESMO 2016 we saw the final OS results from this study and there was no difference in OS between the arms, with median OS 27.9 months for afatinib and 24.5 months for gefitinib, HR 0.86, 95% CI 0.66-1.12. From all of these results, my conclusion is that there is no consistent evidence that any of the first-line TKIs are significantly different from the others.

Dr Oxnard

The first randomized trial comparing 2 TKIs in EGFR-mutant lung cancer randomized 319 patients to gefitinib or afatinib. Median PFS was numerically similar (11 months) but the HR favored afatinib (0.73, p = 0.017) apparently due to a “tail on the curve” that favored afatinib. PFS difference was similar in both del(19) and L858R. ORR was better with afatinib (70% vs 56%, p = 0.008), and with both drugs the responses were deeper in patients with del 19. As expected, the rate of Grade 3+ events was higher with afatinib (31%) than with gefitinib (18%).
This trial tells me that afatinib is a preferred first-line option over gefitinib in patients with EGFR exon 19 deletion or L858R, possibly because gefitinib is administered at a flat dose and cannot be dose adjusted for patients who need a lower dose. But still no head to head data comparing afatinib with erlotinib in this population, which means that erlotinib remains the standard first-line EGFR TKI for many oncologists.

**Dr Wakelee**

LUX-Lung 7 was a randomized Phase IIb study of first-line afatinib (40 mg daily) versus gefitinib (250 mg daily) for patients with advanced stage EGFR-mutant (del19 or L858R) NSCLC (N = 319). Response rate favored afatinib, as did PFS with a HR of 0.73 (95% CI 0.57-0.95), \( p = 0.0165 \). The median PFS was 11.0 months (afatinib) vs 10.9 months (gefitinib). Overall toxicity rates were higher with afatinib and dose reductions were more common with afatinib. Patients who required a dose reduction did as well as those who did not require a dose reduction. Updates at ESMO 2016 showed no OS benefit, with a HR 0.86, \( p \)-value 0.258 and median OS 27.9 versus 24.5 months favoring afatinib.

There were 3 co-primary endpoints, including PFS (PFS by independent review, TTF and OS) (Paz-Ares et al. ESMO 2016;Abstract LBA43). Taken together these data support the use of either first line afatinib or gefitinib for patients with newly diagnosed EGFR-mutant NSCLC. The response rate and PFS do favor afatinib but with some increase in risk for toxicity and without a clear survival advantage. Erlotinib is also an appropriate first line option in this patient population, but that was not addressed in this trial.

**Dr Riely**

Similar to the presentation by Dr Wakelee and colleagues, Dr Oxnard and colleagues looked at plasma testing for EGFR T790M, but rather than rociletinib, explored this testing in patients who were treated with osimertinib, the recently FDA-approved third-generation EGFR TKI that is specific for EGFR T790M. Using tissue testing as the gold standard, they described a sensitivity of 70% for plasma testing for EGFR T790M. As can be expected, in patients with EGFR T790M-negative tumors, just over 30% had EGFR T790M detectable by the assay (BEAMing) in the plasma. Again, as we don’t know what should be the true gold standard, it’s important to evaluate patient outcomes with osimertinib to determine the significance of the identification of EGFR T790M. In doing that, Oxnard and colleagues...
found that if the T790M was detected in plasma or tissue, the response rate and median PFS were nearly identical. In general, my interpretation of this data set and data like it is that if you detect an EGFR T790M mutation, you can likely treat based upon that information. If you don’t find EGFR T790M in a non-invasive assay of plasma, then I think it’s important to proceed to tissue testing to maximize the opportunity for detection of T790M to allow utilization of this class of agents.

**Dr Sequist**

This is an analysis of plasma samples from patients who were on the Phase I AURA study, which led to FDA approval of osimertinib, a third-generation EGFR TKI. Note that both T790M-positive and negative patients were allowed on the early phase of this study. Plasma collection for ctDNA was mandatory. Plasma was studied with the BEAMing assay and tumor tissue with the cobas® assay. This analysis focused on 308 patients who had either L858R or del 19 as their activating mutation and were treated in the first- or later-line setting on AURA. Of these, 237 had successful central tissue genotyping results, 271 had successful central plasma genotyping and 216 had both. Among the 216 with both tumor and plasma analyses, the sensitivity of the plasma ctDNA was 82% for exon 19 deletion, 86% for L858R and 70% for T790M. The T790M mutation was highly unlikely to be identified in the absence of an activating mutation, and the false-positive rate was found to be low. Specifically, among 58 patients with tumors testing negative for T790M, 18 (31%) had a positive T790M plasma test, and the majority of these (n = 14) had T790M confirmed in the plasma by an alternative assay, suggesting that plasma-positive/tissue-negative T790M cases are more likely explained by tumor heterogeneity than by plasma false-positive results. Response to osimertinib was seen in 62% of those with tissue T790M and 63% of those with plasma T790M.

The authors conclude, and I agree, that a new clinical paradigm should be considered in which patients with acquired resistance to a first-line EGFR TKI first undergo a plasma test for T790M. If positive, which may be expected in roughly 50% of patients, they can proceed to osimertinib, but if negative they should be referred for tissue biopsy. Approximately 40% of those who were negative on plasma can still be expected to be T790M positive on tissue biopsy and can be treated with osimertinib. Those who are negative on both plasma and tissue testing are much less likely to benefit from osimertinib and should seek alternative therapy. Importantly, if a patient with EGFR-positive disease does not have a detectable activating mutation in the plasma, this is a clue that the tumor is not shedding DNA and the test is therefore not informative.

**Dr Oxnard**

This study reviewed outcomes among patients treated with osimertinib on the AURA trial, comparing tumor and plasma genotyping for T790M. Plasma analysis was performed with a digital PCR assay (BEAMing). Using tumor genotyping as a comparator, plasma genotyping had modest sensitivity (70%-86%). False positives were rare for EGFR driver mutations (97% specificity) but relatively common for T790M mutations (69% specificity); these “false positives” for T790M often could be confirmed with another plasma assay, suggesting they may be explained by heterogeneity. Despite this discordance, outcomes were excellent (63% ORR, 9.7-mo PFS) in patients positive for T790M either using the tumor or blood assay.
However, plasma T790M-negatives did unexpectedly well on osimertinib, with a 46% ORR and 8.2-mo median PFS — this group represents a mixture of true negatives and false negatives. Tumor genotyping for the plasma T790M-negatives can distinguish a tumor-positive group that does better (16.2-mo median PFS) and a tumor-negative group that does worse (2.8-mo median PFS). These data suggest plasma T790M testing can be used as a screening test — acted upon if positive, but reflex to a biopsy for tumor testing if negative. The cobas® EGFR assay was just approved for plasma T790M testing for this purpose.

**Epidermal growth factor receptor (EGFR) genotyping of matched urine, plasma and tumor tissue from non-small cell lung cancer (NSCLC) patients (pts) treated with rociletinib**

Wakelee HA et al.
*Proc ASCO 2016;Abstract 9001.*

**Dr Riely**

While rociletinib’s clinical development has been discontinued, at ASCO 2016 we saw data presented from one of the large trials exploring its efficacy, but this study evaluated the role of urine, plasma, and tissue for testing for EGFR mutations, including the T790M that is associated with resistance. The authors used 3 different mutation detection techniques on tissue, plasma, and urine in patients who were treated with rociletinib. In these data, using tissue as the reference, the sensitivity of plasma testing was over 80%. Since it is quite possible that tissue can have false negatives, comparing the proportion of patients who are identified as having EGFR T790M mutation is appropriate as well, and in that context, approximately the same number of patients were found to have EGFR T790M when looking at plasma or tissue.

**Dr Wakelee**

Osimertinib is the only FDA approved third generation EGFR TKI and has significant activity against the T790M resistance mutation with response rates >60% in patients with tumors harboring T790M. This paper looked at plasma T790M testing in patients on the initial osimertinib study (AURA Phase I). Samples from 271 patients were available for cell-free plasma DNA analysis with BEAMing technology. Using tissue analysis as a reference (N = 216 had matched tumor and plasma available), the sensitivity of the plasma analysis to detect T790M was 70%, in keeping with other similar analyses such as that from the Tiger-X trial. Of note, 18/58 (31%) patients with T790M negative tumors by tissue analysis had T790M positive plasma analyses.

The key finding of this study was that regardless of whether T790M was detected by tissue or plasma, the response to osimertinib was similar (ORR 63% and PFS 9.7 months with plasma detection compared to ORR 62% and PFS 9.7 months with tissue detection). Plasma T790M detection is now FDA approved. A positive plasma test is sufficient to consider osimertinib therapy, but a negative test should be followed by tissue analysis as there is at least a 30% false negative rate per this publication.
Urine testing appeared just as sensitive. Importantly, since it’s not clear what the “gold standard” assay is, the response rate to rociletinib can serve as an indicator as to whether one assay was “too sensitive,” detecting patients whose tumor was not driven by EGFR T790M. To that end, the tumor response rate for patients was essentially equivalent whether the mutation was identified in plasma, tissue, or urine, suggesting that all are equally useful clinically.

Importantly, there are a broad array of assays that are commercially available, and the assays reported are unlikely to be the ones you have available in clinic. In general, my interpretation of this data set and data like it is that if you detect an EGFR T790M mutation, you can likely treat based upon that information. If you don’t find EGFR T790M mutation in a non-invasive assay of urine or plasma, then I think it’s important to proceed to tissue testing to maximize the opportunity for detection of T790M to allow utilization of this class of agents.

Dr Sequist

This ASCO abstract examined the concordance of EGFR T790M mutation testing across various types of samples (urine, plasma and tissue) from patients who were screened for inclusion in the TIGER-X Phase I/II study of rociletinib, a third-generation EGFR TKI. In this trial, tissue and plasma submission was mandatory, urine collection was optional. The analysis focused on 540 tissue samples tested with the therascreen PCR-based assay, 482 plasma samples tested with the BEAMing PCR/flow cytometry assay, and 213 urine samples tested with the targeted NGS assay.

Both plasma and urine had a sensitivity of 81% for T790M using tissue as a reference. Similarly, each methodology picked up some T790M-positive cases that were “negative” on tissue testing. As an illustration, in a subset of 181 patients who had all 3 types of samples available, 104 (57%) were concordant T790M positive by all 3 methods, 174 (96%) were positive by at least 1 method, and between 4 and 8 samples were only positive by 1 modality but negative by the other two. Importantly, the confirmed response rates and PFS were similar for patients who were positive by any of the 3 modalities, suggesting that any type of positive test is likely equally good for predicting response to treatment. Both the plasma and urine results were more likely to be concordant with tumor testing if the patient had M1b disease (as opposed to M1a disease).

In future studies with EGFR inhibitors and in clinical practice, plasma testing and urine testing can be considered as robust alternatives for identifying patients with T790M mutations as tissue testing, especially if tissue is not available. Patients who are negative by 1 modality perhaps should be tested with a second modality, particularly if they have only M1a disease, which may not shed as much DNA into the circulation. We now have FDA-approved plasma tests for both activating EGFR mutations as well as the T790M mutation.

Dr Oxnard

This study compares tumor, urine and plasma genotyping in patients from the TIGER-X trial of rociletinib. Using central tumor T790M testing as a reference, both plasma and urine genotyping had a sensitivity of 80%. Of 181 cases that underwent all 3 tests,
57% were positive by all 3 testing methods and 96% were positive by 1 of the 3 testing methods. Looking at cases T790M-positive by each method, clinical outcomes were similar (ORR 33%-36%). These data support that noninvasive genotyping is a potentially valuable complement to tumor genotyping, though is not always concordant — the source of this discordance (assay error versus heterogeneity) remains not well understood.

But these data (a post-hoc analysis of specimens from a trial with unclear clinical significance) are not enough to make urine genotyping a routine part of my practice. Prospective validation versus tissue genotyping is needed.

**Dr Wakelee**

The TIGER-X trial included the Phase I dose escalation then dose expansion analysis of rociletinib (CO-1686). The final results were presented in a poster (Goldman et al. ASCO 2016) with a confirmed ORR of 33.9% in 443 efficacy evaluable patients. The drug is no longer in clinical development, given that the ORR was lower than with osimertinib and toxicities, including hyperglycemia and QTc prolongation, were challenging to manage. This ASCO presentation focused on detection of the T790M resistance mutation in tissue versus plasma versus urine in patients with matched samples. Using tissue (therascreen) as a reference, plasma T790M detection by BEAMing had a sensitivity of 80.9% (313/387 samples). Similarly, the urine assay had a sensitivity of 81.1% (142/175 samples).

Of the 181 patients with matched tissue, plasma and urine samples, only 104 patients were positive by all 3 assays (57%), but 96% were positive by at least 1 sample type, with 8 positive only by tissue, 5 by urine and 4 by plasma. Response rates to rociletinib were similar regardless of which assay detected T790M. Plasma EGFR testing is rapidly becoming a standard option for patients, and this report supports that approach and also provides the largest data set to date looking at the urine assay.

**Osimertinib activity in patients with leptomeningeal (LM) disease from non-small cell lung cancer (NSCLC): Updated results from BLOOM, a phase I study**

**Phase I study of AZD3759, a CNS penetrable EGFR inhibitor, for the treatment of non-small-cell lung cancer (NSCLC) with brain metastasis (BM) and leptomeningeal metastasis (LM)**

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**Dr Riely**

A persistent problem in patients with a variety of oncogene-driven malignancies is the development of CNS metastases as a site of poor disease control. While drugs like erlotinib, gefitinib, and afatinib have fair CNS penetration and treatment can lead to
clinically important responses in patients with CNS metastases, oftentimes CNS metastases progress or patients develop leptomeningeal disease. In that context these 2 abstracts attempt to explore the value of 2 newer agents, osimertinib and AZD3759, in patients with brain metastases and leptomeningeal disease. In the abstract looking at osimertinib, Dr Yang and colleagues demonstrate that osimertinib has clear CNS activity. In patients with proven leptomeningeal disease, treatment with osimertinib 160 mg daily (double the approved dose in the US) led to radiological improvements, neurologic function improvement, and clearance of CSF. These data suggest that there is some modest activity of osimertinib in this very challenging clinical situation.

Similarly, Ahn and colleagues explored the value of AZD3759, a new EGFR inhibitor that is directed at wild-type and mutant EGFR, in patients with brain metastases and leptomeningeal disease. While identifying the MTD of this drug, they were able to treat patients with advanced CNS disease and observed radiographic improvement as well as clearance of cytology from cerebrospinal fluid.

While these data are very early, it is clear that testing drugs in this patient population, which we deal with routinely in clinical practice, can lead to drug responses. We welcome more information about the CNS activity of all drugs being developed for patients with lung cancer.

**Dr Sequist**

BLOOM was a Phase I study with 2 separate components, each looking at patients with EGFR mutation-positive NSCLC with brain and leptomeningeal metastases (LMD). Because of the relatively longer survival for patients with EGFR-positive disease, CNS disease is a major issue for this population.

One part of the study (presented by Dr Yang) looked at osimertinib in EGFR mutation-positive NSCLC with LMD proven by positive cytology on CSF. In pre-clinical animal models osimertinib seems to have very good blood-brain barrier penetration, and there have been several case reports and case studies highlighting LMD responses in patients. The cohort reported at ASCO had to also have stable extra-cranial disease and was treated with osimertinib at 160 mg QD (twice the approved dose). 21 patients were treated, and all but 1 of these had had prior systemic response or stable disease to an EGFR TKI. Two patients had T790M detected in the CSF, 6 in the plasma. Drug tolerance at 160 mg QD was not much different from what we have seen at 80 mg. There was 1 Grade 3 diarrhea and 1 Grade 3 fatigue event. Two patients dose reduced osimertinib. 7 patients had confirmed radiologic improvement, 2 had CSF clearance and 5 had documented improved neurologic function. A formal PFS was not presented, but 15 patients remained on treatment at the data cutoff, including 7 who had been on treatment for 9 or more months.

The second part of the BLOOM study looked at another compound called AZD3759. This is a third-generation EGFR TKI with strong preclinical evidence of good CNS penetration. Dr Ahn presented data from the dose escalation for this drug, in which patients were treated with doses ranging from 50 mg BID to 500 mg BID. All patients had EGFR mutations, at least 1 prior line of EGFR TKI and chemotherapy, and measurable CNS lesions and/or documented positive CSF cytology. 29 patients were treated. The side
effects were similar to those expected for first-generation TKIs, with rash and diarrhea in >40% of patients and stomatitis and paronychia in >20%. AEs were dose dependent, but a recommended Phase II dose has not yet been declared. CSF PK analyses were included and confirmed that the drug did cross the blood-brain barrier. 52% of those with measurable CNS lesions had a response and 36% of those with measurable extracranial disease had a response.

There are dose expansion cohorts of the study ongoing for AZD3759, and it remains to be seen if there is an advantage for this third-generation EGFR TKI over others already widely used in the clinic. Osimertinib does seem to have excellent brain penetration, and further data about this are expected to emerge soon.

Dr Oxnard
The BLOOM trial looked at 2 therapies for EGFR-mutant lung cancer with CNS metastases — osimertinib at 160 mg daily and a new CNS-penetrable EGFR TKI, AZD3759. In 21 patients with leptomeningeal disease, osimertinib 160 mg was well tolerated, with a 33% response rate in the brain. Unclear if this activity is dependent upon T790M presence. AZD3759 was dose escalated, with EGFR toxicity seen at higher doses; dose expansion is ongoing at both 200 mg and 300 mg BID. RR in CNS was 28%. Overall this study tells me that osimertinib is active in the CNS and may be more active (and still tolerable) at 160 mg daily.

Dr Wakelee
The BLOOM trial focuses on patients with EGFR-mutant NSCLC with CNS involvement. Preliminary data from 2 of the arms were presented at ASCO 2016, both showing significant activity in patients with leptomeningeal metastases. Osimertinib was given at 160 mg daily (twice the usual recommended dose of 80 mg orally daily) to 21 patients with leptomeningeal metastases, with a confirmed ORR of 33% and disease stabilization in the majority. Of the 10 patients with neurologic symptoms, 5 had confirmed improvement and 3 others had unconfirmed improvement and only 1 of those without neurological symptoms initially developed any during the course of the trial. Many of the patients had durable responses.

These results are striking given the challenge in treating leptomeningeal metastases, and no unexpected toxicities were reported. AZD3759 is a highly CNS penetrant reversible EGFR TKI, and the presentation focused on 29 patients treated at doses ranging from 50 to 500 mg twice daily orally. As opposed to osimertinib, this compound is for patients with sensitizing EGFR mutations and not T790M. CSF evaluation in a subset of patients showed tumor clearance. Over half of the patients with measureable brain metastases showed tumor shrinkage. Toxicity is primarily skin rash and diarrhea with this compound.
Since the identification of rociletinib and osimertinib, multiple new compounds that target EGFR T790M mutation have entered clinical trials. Such agents include EGF816, ASP8273 and HM61713. As we evaluate these compounds, we put them into the context of toxicity and efficacy seen with osimertinib (that received accelerated approval by the FDA) and rociletinib (which was not approved by the FDA for an accelerated approval and whose subsequent development was ended). In this poster, Dr Yu presented the data from an early-phase trial of ASP8273 in patients, focusing on patients who received 300 mg, their recommended Phase II dose. In these 63 patients, there was a 30% response rate. Looking only at the 58 patients with EGFR T790M mutation by local lab testing, the response rate was similar at 31%.

The median PFS was 6 months for all patients. Seventeen percent of patients discontinued the drug due to treatment emergent adverse events. The toxicities observed were the types that we are used to seeing in EGFR inhibitor trials, including diarrhea, but others that we see less frequently, like nausea (27%), hyponatremia (13% Grade 3) and paresthesia (14%). In the small group of patients, there were no problems with QTc prolongation or ILD. There did not appear to be a significant rate of hyperglycemia, either. Based on the numbers reported, this compound does not appear to be superior to osimertinib in terms of efficacy or toxicity. How this and other newer third-generation EGFR TKIs are incorporated into our treatment paradigms will depend significantly on understanding whether there is cross-sensitivity/cross-resistance among these agents. For instance, do patients who progress on osimertinib respond to ASP8273?

Dr Sequist

This ASCO abstract described interim results from the Phase I study of the third-generation EGFR TKI ASP8273, focusing on safety and efficacy in the 63 patients treated at the recommended Phase II dose of 300 mg QD. The patients were EGFR mutation-positive and resistant to a first-line EGFR TKI. They were required to be T790M-positive, but local testing was allowed (ie, central confirmation was not required). The confirmed response rate was 30%, and median PFS was 6.0 months. Side effects were moderate. Low-grade diarrhea and nausea were the most common events, but about 25% of patients had Grade 3 or 4 AEs, including hyponatremia, peripheral neuropathy and elevated transaminases. This drug is likely not going to be able to compete with the approved standard of care, osimertinib. Like the former drug rociletinib, this compound seems to have less efficacy and a less favorable toxicity profile compared to osimertinib.
Dr Oxnard

ASP8273 is the latest mutant-specific EGFR inhibitor targeting T790M, in addition to osimertinib (approved), rociletinib (development halted) and olmutinib (developed in Korea only). Yu et al report on the global Phase I trial of this compound (there is also a Japan-only Phase I trial) that enrolled patients with EGFR-mutant lung cancer and resistance to prior TKI. This report focuses on the 63 subjects treated at the Phase II dose, 300 mg daily. While there was minimal rash or hypoglycemia at this dose, there was 1 case of Grade 3 diarrhea and 8 cases of Grade 3 hyponatremia (of unknown etiology). ORR was 30% in patients with T790M, with a median PFS of 6.8 months, somewhat disappointing compared to the known activity of osimertinib in this population.

The drug is now being compared to erlotinib as a first-line therapy. However, development is going to be challenging given the favorable toxicity and activity with osimertinib.

Dr Wakelee

ASP8273 is an oral, once daily EGFR TKI with activity against known sensitive EGFR mutations and also T790M. The drug was studied initially at 25 mg orally daily with dose escalation to 300 mg orally daily as the recommended dose in expansion for those with a known T790M resistance mutation. This ASCO 2016 poster focused on patients treated at the 300-mg oral daily dose (N = 63). The ORR was 30% at this dose (31% if confirmed T790M+) with a PFS of 6.0 months. Toxicities were similar to other EGFR TKIs and consisted of diarrhea, nausea, dizziness, fatigue and hyponatremia, but most toxicity was Grade <3. The drug is currently in a Phase III trial comparing it to first line erlotinib or gefitinib. However, neither the response rate nor the toxicity profile compare favorably to osimertinib.

Adjuvant erlotinib versus placebo in patients with Stage IB-IIIA non-small-cell lung cancer (RADIANT): A randomized, double-blind, Phase III trial


Dr Riely

Given the superior efficacy of EGFR TKIs over cisplatin-based chemotherapy as first-line therapy for patients with advanced EGFR mutant NSCLC, an important open question is whether they have a role in early-stage resected disease. While there have been retrospective studies that have suggested efficacy of these drugs in the adjuvant setting, we still await a prospective trial that evaluates the efficacy of an EGFR TKI in patients with resected EGFR mutant NSCLC, either in addition to platinum-based chemotherapy or instead of chemotherapy. Multiple ongoing trials are exploring this issue, including the NCI’s ALCHEMIST trial. Until such data are available, we have these data that explored the value for a broad population of patients with resected early-stage NSCLC.
To enroll in this study reported by Kelly et al, patients had to have EGFR protein present (by immunohistochemistry), increased EGFR gene copy number (by FISH), or EGFR mutation. In the analysis of this trial, there was no value to erlotinib as compared with placebo in the overall population. In the subset of patients with EGFR mutations (just ~16% of enrolled patients), disease-free survival was markedly better for patients who received erlotinib (HR 0.61, \( p < 0.001 \)).

While OS data are immature, this marked improvement in DFS suggests there may very well be a benefit with an adjuvant EGFR TKI. We await the results of prospective studies testing this.

**Dr Sequist**

The much anticipated RADIANT trial was a randomized placebo-controlled trial examining the role of the EGFR TKI erlotinib after chemotherapy in surgically resected early stage lung adenocarcinoma. The trial was designed back in the 2006 era, when there were some who believed that EGFR gene expression was a powerful predictor of response to EGFR TKIs among metastatic patients (this has subsequently been proven erroneous and EGFR mutations confirmed as the best biomarker of response). Hence, the trial design included patients with completely resected Stage IB to IIIA disease with positive EGFR gene expression by FISH. After adjuvant chemo (if indicated) patients were randomized 2:1 to 2 years of erlotinib at 150 mg QD or placebo. The primary endpoint was disease-free survival, and the statistical design mandated an initial analysis of the intent-to-treat population; only if results in this population were positive, then sub-group analyses were statistically “allowed.”

973 patients were included (623 randomized to erlotinib and 350 to placebo) and there were 161 with EGFR mutations (102 on erlotinib, 59 on placebo). At the time of analysis the median follow-up was 47 months and there was no difference in the ITT DFS between arms, with a median of 51 months for erlotinib and 48 months for placebo (HR 0.90; 95% CI 0.74-1.1). Because of this, according to the statistical plan, the subgroup analysis for EGFR mutants could not be considered statistically significant regardless of results. When looking numerically at the EGFR subgroup, median disease-free survival was 28.5 months in the placebo group and 46.4 months in the erlotinib group, a striking difference. Overall survival among the EGFR mutants was immature but showed no difference between treatment arms.

While the results of RADIANT were disappointing in the overall group, it remains unknown if there could be an advantage to this approach among patients with EGFR mutation-positive disease. The population within RADIANT that was EGFR mutation-positive was small and likely underpowered to show a survival advantage. In addition, it is possible 2 years is not the optimal duration of therapy. Recall in patients with resected GIST, initially imatinib x 1 year looked as if it could improve DFS but not OS compared to placebo — yet in a larger study examining 1 vs 3 years of adjuvant imatinib, 3 years showed improved DFS and OS. The definitive answer about whether there is a benefit to 2 years of adjuvant erlotinib compared to placebo among patients with EGFR-mutant lung cancer will come from the ongoing ALCHEMIST study, and many still wonder if we should be looking at a longer duration of treatment.
Dr Oxnard
The RADIANT trial studied 24 months of erlotinib vs placebo in 973 patients with resected NSCLC who were “EGFR positive” using an IHC assay. Outcomes in the 161 patients with EGFR mutations were studied as a secondary endpoint. Median treatment duration with both erlotinib and placebo was 21 months in the EGFR-mutant cohort; 46% of patients on erlotinib required dose reductions. While there was no DFS benefit in the overall population, DFS was better in the EGFR-mutant population receiving erlotinib (46.4 mo) rather than placebo (28.5 mo), though patients on the erlotinib arm had a more favorable stage; this difference was not statistically significant.

Overall this highlights that adjuvant targeted therapy remains a compelling approach in biomarker-selected patients, and while it likely improves DFS it is not clear this will impact the “cure rate” or overall survival. This is now being studied further in the ALCHEMIST trial, looking at erlotinib vs placebo in EGFR patients and crizotinib vs placebo in ALK patients. Outside of trials like this, adjuvant erlotinib is not currently used routinely since it is highly effective when given at time of recurrence.

Dr Wakelee
The RADIANT trial randomized 973 early stage (IB-IIIA) NSCLC patients after surgery (and systemic chemotherapy if given) to receive placebo or erlotinib (150 mg orally daily) as adjuvant therapy for up to 2 years. Patients were selected if they had tumors with expression of EGFR protein by immunohistochemistry or EGFR amplification by FISH. For all patients the disease free survival (DFS) hazard ratio (HR) was 0.90, NS. For the 161 patients who had an EGFR-mutant NSCLC the DFS favored erlotinib with a median of 46.4 versus 28.5 months, HR 0.61, but this was not considered statistically significant as the study was designed with a hierarchical testing procedure such that nothing was statistically significant if the primary endpoint (DFS in all patients) was negative.

Though OS was not mature at the time of publication, the data as presented to date have failed to show a clear separation of the curves, even in the patients with resected EGFR-mutant tumors. The data are provocative and certainly support the ongoing trials looking at this question in Asia and the North American ALCHEMIST study. However, they do not support routine use of adjuvant EGFR TKIs outside of clinical trials.

Alectinib versus crizotinib in ALK-inhibitor naive ALK-positive non-small cell lung cancer: Primary results from the J-ALEX study
Nokihara H et al.
Proc ASCO 2016;Abstract 9008.

Dr Riely
Given the efficacy of next-generation ALK inhibitors that have been tested, and approved, in patients who previously received crizotinib, a natural course is to study these drugs as initial therapy for the treatment of ALK-positive NSCLC. In this report of
the Japanese study of first-line alectinib vs crizotinib, the authors were able to demonstrate a markedly superior median PFS for patients who received first-line alectinib rather than crizotinib. The magnitude of the improvement in PFS was significant (mPFS of 10 months from crizotinib vs not reached for alectinib). This was more than the likely PFS from multiple other trials that treated patients after first-line crizotinib, suggesting that first-line alectinib might indeed be superior to the sequence of first-line crizotinib followed by alectinib or ceritinib.

There are some caveats to the data that seem to have slowed rapid clinical adoption of this approach. The trial was conducted only in Japan, using the approved dose in Japan (300 mg twice daily), which is half the dose approved in the US. Perhaps most importantly, there was a marked imbalance in the number of patients with baseline brain metastases in the crizotinib arm (almost double the number in the alectinib arm). Since alectinib is likely superior to crizotinib in the CNS, this profound difference in baseline characteristics likely significantly affected the results. We await the global ALEX trial results for confirmation of these data and extension to a broader population.

**Dr Sequist**

This was a randomized Phase III study performed in Japan that is analogous to the global ALEX Phase III trial (which is completed but has not yet been reported) comparing first-line alectinib to crizotinib. Alectinib is a second-generation ALK inhibitor that has good activity in patients with resistance to crizotinib and also has very good CNS penetration, a feature that crizotinib lacks. The results were presented at ASCO in 2016, earlier than expected as an interim data committee recommended stopping the data collection early because the alectinib arm was outperforming the crizotinib arm.

207 patients with ALK rearrangements and no prior ALK TKI (up to 1 prior chemo was allowed) were 1:1 randomized to receive crizotinib at 250 mg BID or alectinib at 300 mg BID.

The primary endpoint was PFS. The only major imbalance in the randomization was presence of CNS mets, with 14% of alectinib patients having CNS mets and 28% of crizotinib patients. Both drugs displayed their expected side-effect profiles. Grade 3 or 4 AEs were seen in 26% for alectinib and 52% for crizotinib. Responses were excellent and were 85% in the alectinib arm and 70% in the crizotinib arm. Median PFS was not reached yet in the alectinib arm and 10.2 months for crizotinib, HR 0.34 (95% CI 0.17-0.71). All of the various subgroups analyzed were in close correlation with the ITT population except for those with CNS mets, which more dramatically favored alectinib (HR 0.08, 95% CI 0.01-0.61).

Most experts in the US are awaiting the ALEX results, but if confirmed, alectinib would be the new standard first-line choice for patients with ALK-positive disease. Even now, I recommend alectinib to any patient with ALK-positive disease who presents with CNS mets. Some are probably offering it to all patients based on J-ALEX.
Dr Oxnard
The J-ALEX trial enrolled 207 Japanese patients with TKI-naïve ALK+ NSCLC and randomized them to crizotinib versus alectinib (given at the Japanese dose of 300 mg BID). The 2 arms were mostly balanced, though more patients with CNS metastases were randomized to crizotinib. All endpoints favored alectinib, including median PFS (NR vs 10 mo), RR (85% vs 70%), and discontinuation due to AE (9% vs 20%). These data support the idea that a potent ALK inhibitor may be better first line than crizotinib, an approach being studied in multiple trials with alectinib and its competitors.

There are a few reservations about the generalizability of the J-ALEX data, including the brain metastasis imbalance, the alectinib dosing, and the strict criteria for ALK positivity. These data give me a very low threshold to switch patients from first-line crizotinib to subsequent alectinib.

Dr Wakelee
The J-ALEX trial was the most exciting presentation in NSCLC at ASCO 2016. The study randomized 207 ALK TKI naïve (prior chemotherapy acceptable) ALK+ NSCLC patients in Japan to be treated with alectinib at 300 mg twice daily or crizotinib 250 mg twice daily. ALK positivity was centrally confirmed. Toxicities were as expected, but the rate of Grade 3 or 4 adverse events was significantly higher in the crizotinib group at 51.9% versus the alectinib group at 26.2%. Response rates favored alectinib at 91.6% versus 78.9% by independent review. PFS by independent review was the primary endpoint of the trial and significantly favored alectinib with a hazard ratio of 0.34 (95% CI 0.17-0.71), \( p < 0.0001 \) and a median in excess of 24 months compared to a median PFS of 10.2 months with crizotinib.

If the results of the global ALEX trial confirm these findings, first-line alectinib will likely be a global standard, especially if the PFS is truly in excess of 24 months. One of the theoretical concerns of bringing next generation ALK inhibitors into the first line is the potential that the PFS of the next generation agent in the first line might not exceed the PFS of first-line crizotinib followed by the PFS of the next generation agent as a second-line therapy. If the 24+ month PFS of first-line alectinib holds true, however, that would be in excess of the expected PFS of crizotinib followed by alectinib.

Brigatinib in patients with crizotinib-refractory ALK+ non-small cell lung cancer: First report of efficacy and safety from a pivotal randomized phase 2 trial (ALTA)

Kim D et al.
Proc ASCO 2016;Abstract 9007.

Dr Riely
While there are 2 available next-generation ALK inhibitors, ceritinib and alectinib, development of other ALK inhibitors offers opportunity for patients who are not able to tolerate one of these agents and raises the potential that there may be slight differences in efficacy for patients with some mutations seen after development of resis-
In that context, we saw additional data for patients treated with brigatinib, a next-generation ALK inhibitor with a clinical and pre-clinical profile that suggests it should lead to responses in patients with crizotinib-refractory ALK-positive lung cancer. The drug was associated with pulmonary toxicity in early phase trials, leading the authors to explore an initial, low, 90-mg lead-in dose for 7 days prior to the full dose of 180 mg daily.

This trial explored the initial 90 mg with dose escalation to 180 mg at 1 week or simply treatment with 90 mg daily as the full dose. In this trial, there were no severe pulmonary toxicity events at the higher dose of 180 mg. There were high overall (54%) and intracranial (67%) radiographic response rates. We await results of further studies in patients with previously crizotinib-treated disease as well as a randomized trial of patients with newly diagnosed ALK-positive NSCLC randomizing to brigatinib vs crizotinib.

Dr Sequist

Brigatinib is another second-generation ALK inhibitor that has activity in crizotinib resistance and good CNS penetration. This abstract presented the results of ALTA, a randomized Phase II study that looked at 2 doses of brigatinib, 90 mg or 180 mg, in 222 patients. Patients had all progressed on crizotinib and they not been treated with any other additional ALK TKI. Most patients had also had prior chemotherapy. Asymptomatic CNS mets were allowed.

The response rate was 45% at 90 mg and 54% at 180 mg. Median PFS was 9.2 mo for 90 mg and 12.9 mo at 180 mg. Among those with measurable CNS mets (n = 43), the brain response rate was 36% at 90 mg and 67% at 180 mg. Adverse events were primarily Grade 1 or 2 nausea, fatigue and headache. Grade 3 events were rare — the most common was hypertension. However, there were 14 (6%) so-called “pulmonary toxicities” — this has been seen before with brigatinib when there is acute sudden-onset ILD-like toxicity within the first few days of dosing, which can be serious.

The FDA has granted brigatinib breakthrough status, and a randomized Phase III study against crizotinib in the front line has begun (ALTA-1L). I am personally a bit wary of the low but real incidence of pulmonary toxicity, given the alternative availability of alectinib, but we have to wait to see more data. Brigatinib has good activity in both systemic and CNS disease for patients progressing on crizotinib.

Dr Oxnard

The ALTA trial randomized 222 ALK+ NSCLC patients with crizotinib resistance to 2 different dosing schemes for brigatinib. One arm received 90 mg daily, and the other received a 90-mg lead-in for 1 week followed by 180 mg daily. The goal was to study efficacy and tolerability of each arm. The 1-week lead-in at 90 mg is believed to reduce the incidence of early pulmonary toxicity, which can be seen acutely with brigatinib in a subset of patients. RR was high in both arms (45%-54%). PFS was impressive in the higher-dose arm at 12.9 mo median. CNS control was excellent. Early pulmonary toxicity was seen in 6% of patients (3% Grade >3) and could be managed with dose interruption and re-treatment. Overall this is an ALK inhibitor with broad activity against resistance, with a very favorable PFS compared to alectinib and ceritinib.
**Dr Riely**

ALK-positive lung cancer was initially identified in a patient with a fusion of EML4 and ALK genes. Subsequent investigation found that many patients had ALK genes fused to other genes that also led to activation. We lump these together as ALK-positive lung cancer, but there remains the possibility that there is some difference with regard to response to treatment or natural history for the different variants of ALK. Yoshida and colleagues looked at the value of ALK fusion variants to predict outcomes in a sample of 35 patients treated with standard ALK inhibitors. They noticed modest but real differences between various ALK fusion variants.

Given that we cannot modify the ALK fusion variant that a given patient has and that there is no evidence of differential efficacy for available ALK inhibitors (that would lead you to start with, say, alectinib in a patient with ALK variant 2), I find that these data, while provocative, are not clinically useful.

**Dr Sequist**

This is a retrospective single center analysis of 55 patients with ALK rearrangements treated with crizotinib, correlating clinical outcome with variant of ALK fusion. Just as there is not one single EGFR mutation but rather various different types of mutation, an ALK fusion or rearrangement may be partnered with one of multiple genes and the fusion points may occur at various breakpoints in the gene. These authors showed that perhaps variant 1 of EML4-ALK (the most common) may have higher levels of sensitivity to crizotinib compared to other variants. However, this work should be interpreted with caution as it included very small numbers of patients with each variant (other than 1) and other studies have found contradictory results. At this time there is no clinical reason...

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**Differential crizotinib response duration among ALK fusion variants in ALK-positive non-small-cell lung cancer**


**Dr Wakelee**

The ALTA trial is a randomized Phase II trial of brigatinib in crizotinib-refractory ALK+ NSCLC. Patients (N = 222) who had experienced disease progression on crizotinib but had never had any other ALK TKIs were randomized 1:1 to brigatinib at 90 mg daily or 180 mg daily (with a 7-day lead-in at 90 mg to reduce the unusual respiratory symptoms that develop initially in some patients at the higher dose). The confirmed response rate was 45% at 90 mg and 54% at 180 mg, and intracranial responses were similar to systemic response rates. A median PFS of 12.9 months was reported at the 180-mg dose and overall survival data were pending. Toxicity data were encouraging, but the CPK elevations of at least Grade 3 were at 9% at the 180-mg dose.

Brigatinib has activity against many of the known resistance mutations to crizotinib. The data are encouraging, but it is not clear where brigatinib will fit into the crowded ALK TKI landscape. A first line trial is ongoing versus crizotinib.
to treat patients with ALK-positive disease differently based on mutation subtype. However, further work should be done in this area.

**Dr Oxnard**

These investigators studied 35 patients with ALK+ NSCLC treated with crizotinib. The most common variant on RT-PCR was “v1” in 54% of patients. Median PFS was 11 mo in this group, whereas it was 4.2 mo in the remaining “non-v1” patients. This finding remained significant on multivariate analysis. The editorial urges caution before adopting these findings into practice due to the lack of any biologic basis for this finding and the fact that, even with these overall differences, some patients with v1 do quite poorly (several with PFS <6 mo) and some with non-v1 do quite well (2 with PFS >2 years). In my practice, I will continue to treat all ALK+ NSCLC patients with ALK TKI and do not plan to test for the variant using RT-PCR given the lack of any clear treatment implication.

**Dr Wakelee**

The use of ALK TKIs for patients with ALK rearranged NSCLC has dramatically improved outcomes for patients with this subset of NSCLC. Knowledge is rapidly expanding about sub-categories of ALK rearrangements and of specific ALK mutations that lead to resistance. This current publication looked at subsets of the most common ALK fusion partner, echinoderm microtubule-associated protein-like 4 (EML4). The most frequent variant (variant 1) involves exon 13 of EML4 fused to exon 20 of ALK. Other variants involve either exon 20 or exon 6a or 6b of EML4 fused to exon 20 of ALK. There are also variants involving other exons of ALK, and of course other fusion partners have been identified besides EML4. This analysis involved 35 patients with known EML4-ALK variants and found variant 1 in 54% of the patients and an association between that variant and a slightly higher response rate to crizotinib (74% versus 63% for the others) and a longer median PFS with crizotinib of 11.0 months versus 4.2 months, \( p < 0.05 \). With numbers this small and with other variables it is hard to draw any definitive conclusions, but this paper provides further insight into the complexity of ALK fusions.

**Targeted Therapies for Other Mutations in NSCLC**

**Efficacy and safety of crizotinib in patients (pts) with advanced MET exon 14-altered non-small cell lung cancer (NSCLC)**

Drilon AE et al.  
Proc ASCO 2016;Abstract 108.

**Dr Vokes**

Drilon et al present an interesting early exploration of treating patients with MET exon 14-altered NSCLC with crizotinib. MET exon 14-related lung cancer has been shown to occur in about 3% of patients. These patients have been described as older than patients with EGFR mutant disease and a lower proportion of never-smokers. Drilon et al presented a Phase II trial administering crizotinib to 21 patients and reporting a
partial response rate of 44% and stable disease of 50% and general good tolerance of
treatment. Based on this observation, MET exon 14 mutation appears to be a distinct
clinical pathologic entity that is amenable to targeted therapies. Clinical evaluations of
this and similar compounds are currently continuing.

Dr Johnson

- Crizotinib is FDA approved now for pts with ALK and ROS rearrangements but was
  originally developed as a MET inhibitor. Ross Camidge reported a study at ASCO in
  2014 demonstrating CRZ activity in pts with high levels of MET amplification by FISH,
  but this study was confined to pts with mutations in the TKI portion of MET only.

- MET exon 14 skipping mutations result in increased MET R attached to the tumor
  cell surface and increased MET signaling. MET point mutations occur in 3%-4% of
  non-squamous NSCLC (just as many as ALK!) and 20%-30% of sarcomatous lung
  cancer. MET+ pts tend to be older, former smokers.

- The PROFILE 1001 study was an open-label multi-center Phase I trial evalu-
  ating CRZ for pts with MET mutations found by local testing. 18 pts were treated;
  median age 68. All but 3 had received prior therapies for their lung cancers.
  Patients were treated with CRZ 250 mg BID. Primary endpoint was ORR.

- 44% of pts had a PR. Another 50% of pts had SD. Patients stayed on therapy for a
  median of 5.3 mo.

- Exploratory analysis looked at whether these pts also had MET expression within
  their tumors, but only 1 did. AEs were what we have come to expect with CRZ:
  edema, GI, visual disturbances. This trial continues to accrue — for a goal of 50 pts.

- Great option for this subset of pts — especially since CRZ already has 2 other
  FDA indications and is commercially available. I’ve used it in pts who were not
  clinical trial candidates for whatever reason — whether MET mutated or MET
  over-expressed. Key point here is that — with MET and all the mutations we’ll talk
  about beyond EGFR and ALK — if you don’t test for it (ie, comprehensive NGS)
  you won’t know it’s there.

Dr Stinchcombe

MET exon 14 encodes a juxtamembrane domain involved in receptor degradation,
and the introns adjacent to exon 14 are removed during normal splicing mechanisms.
MET mutations disrupt the splice sites adjacent to exon 14, leading to increased MET
receptor recycling to the tumor cell surface and impaired degradation. MET exon 14
alterations are found on 3% to 4% of non-squamous NSCLC and approximately 20%
to 30% of sarcomatoid lung cancers. Of the patients with MET exon 14 mutations,
approximately 20% had a high level of MET copy gain. MET exon 14 mutation and MET
copy number amplification should be thought of as distinct molecular alterations that
have been observed in patients with disease progression after an EGFR tyrosine kinase
inhibitor (TKI).

Crizotinib is an ATP competitive TKI, and the activity of crizotinib was investigated in
a cohort of patients with MET exon 14 mutations as part of an ongoing Phase I trial.
In the 18 response-evaluable patients, the objective response rate is 44% (95% CI,
22%-69%) and the median progression-free survival could not be calculated. These results are very promising, and crizotinib should be considered a treatment option for patients who have exhausted standard therapies and have a known MET exon 14 mutation. Patients who do not have a known molecular alteration, especially patients with sarcomatoid lung cancer, should undergo testing for MET exon 14 deletions.

Dabrafenib plus trametinib in patients with previously treated BRAFV600E-mutant metastatic non-small-cell lung cancer: An open-label, multicentre phase 2 trial


Dr Vokes

BRAF mutations, in particular the BRAF V600E variant, have been shown to occur in approximately 2% of patients with lung adenocarcinomas. In a previous trial, the BRAF inhibitor dabrafenib was shown to have clinical activity. Based on similar observations in patients with melanoma indicating that dual inhibition of BRAF and MEK further improve anti-tumor activity, these investigators initiated a Phase II trial in 59 patients reporting a 63.2% response rate and 9.7 months progression-free survival. These data clearly suggest that further investigation of this combination is indicated. It should be emphasized that these data are applicable only to those patients who have the specific BRAF V600E mutation.

Dr Johnson

- BRAF, MEK are members of the MAPK pathway. Combining these inhibitors together is a strategy well known from melanoma and colon cancer, and so here it was studied in NSCLC.
- BRAF V600E mutations account for 1% of NSCLC pts — often these pts have more aggressive NSCLC and poorer prognoses. We know these pts actually don’t do very well with second line chemotherapy — ORR only 9%.
- This trial was actually part of a multi-center, multi-cohort Phase II trial that also studied the BRAF inhibitor dabrafenib alone and in combination with the MEK inhibitor trametinib for pts in 3 cohorts: D alone, D + T or D + T for treatment-naïve pts. In about a year, 59 pts from 30 centers in 9 countries were enrolled.
- The single agent cohort was completed first in 78 pts, and the results were reported a few years ago at ASCO 2013, published earlier in 2016 reporting ORR 33%, PFS 5.5 mo, OS 12.7 mo.
- Now the combination D + T is reported for 58 pts enrolled, median age 64. 1/3 had been treated with 2 prior lines of chemotherapy. Near doubling of ORR to 63% compared with single agent D, with PFS 9.7 mo and DOR of 9 mo.
- Adding MEKi to BRAFi definitely improved outcomes and represents a step forward in the treatment of pts with BRAF mutations. However, this obvious benefit does come at a cost in terms of the Grade 3-4 AEs, which were noted in
approximately 50% of pts — pyrexia, GI, rash were most common (the side effect table in the journal article was 2 columns long!). 12% of pts discontinued the drug early for toxicity. AEs are manageable with dose reduction so not a deal-breaker for me right now, although there were cases of hemoptysis and hemorrhage that will need to be investigated further in future trials.

- Wonder if the toxicity might be less in pts untreated for their cancers with chemotherapy.
- Haven’t used this combination yet but would for pts whose PS would allow — and will be interested in the results for the treatment-naïve pts.

**Dr Stinchcombe**

BRAF V600E mutations are present in approximately 2% of non-small cell lung cancer (NSCLC) cases. This mutation occurs at a higher rate among patients with a history of tobacco use compared to EGFR mutations and ALK rearrangements. Two Phase II trials were performed in patients with metastatic NSCLC with a confirmed BRAF V600E mutation: dabrafenib, a BRAF inhibitor, alone and with trametinib, a MEK inhibitor. Approximately a third of patients enrolled in the 2 trials were never smokers. With single agent dabrafenib the investigator-assessed overall response rate was 33% (95% CI, 23% to 45%), and the median progression-free survival was 5.5 months (95% CI, 3.4 to 7.3).

With the combination the investigator-assessed response rate was 63.2% (95% CI, 49.3% to 75.6%) and the median progression-free survival was 9.7 months (95% CI, 6.9 to 19.6). Given the numerically superior response rate and progression-free survival, the combination therapy will be the preferred therapy. The most common Grade 3-4 adverse events observed with the combination were neutropenia (9%), hyponatremia (7%), and anemia (5%). The combination of dabrafenib and trametinib has significant clinical activity, and testing for BRAF mutations should be performed on patients with adenocarcinoma. Single agent and combination therapy should not be used in patients with non-V600E BRAF mutations.

**Dr Vokes**

Similarly to BRAF, RET-rearrangements can be found in a small percentage of NSCLC patients. Investigations to assess the potential targetability of this mutation have been initiated. In this trial, 20 patients were treated with the anti-RET agent cabozantinib, which also targets VEGFR2 and MET. The authors report a confirmed partial response rate of 36% and objective response rate of 38%. Median progression-free survival was 7 months. These data indicate limited activity of this approach and do identify RET as a potential targetable mutation. It will be of interest whether other, more specific anti-RET agents might have higher levels of activity.
Dr Johnson

- RET rearrangements — in particular KIF5B-RET, which is the most common — account for another 1%-2% of lung cancers. These pts tend to be younger and, actually, never or light smokers. RET rearrangements can be diagnosed by FISH or NGS.
- Cabozantinib is a multi-tyrosine kinase inhibitor that hits RET rearrangements but also MET and VEGFR2. It is FDA approved for medullary thyroid cancer.
- Drilon and colleagues evaluated cabo in an open-label, Phase II, single-arm, single-center trial performed at MSKCC that enrolled 16 pts: median age 59, all but 4 previously treated. 50% had received bevacizumab. Pts were treated with cabo 60 mg qd.
- Primary endpoint ORR was 38%, and another 56% of pts had SD. ORR at 12 wk/3 mo was 36%, suggesting durability of response. Median DOR 8 mo. Median PFS 7 mo and median OS 10 mo.
- SEs with cabo were reported as mostly Grade 1-2 but frequently cited — in particular fatigue, diarrhea, mucositis and palmar-plantar erythrodysesthesia. 50% of pts had 1 dose reduction and 20% had 2 — so here again, clinical benefit that comes at some cost. 2 of the 16 discontinued the drug prematurely, and there was another with retroperitoneal bleeding.
- Early days for this drug in this indication — I’ll be interested to see more safety data here as this trial enrolls its second stage to see if the benefit continues to outweigh the risk for this drug.

Dr Stinchcombe

RET rearrangements occur when the tyrosine kinase domain is fused to a partner. The most common fusion partner is KIF5B, but other fusion partners include CCDC6, NCOA4, TRIM33 and KIAA1468. The frequency of this rearrangement is approximately 1% to 2%, but the rate may be higher in never or light smokers with adenocarcinoma or in patients who have been tested for and lack commonly identified oncogenic alterations. A single arm Phase II trial investigated cabozantinib 60 mg daily, which is approved for treatment of metastatic medullary thyroid cancers. This study used a 2-stage design, and in the first stage 16 patients were enrolled.

The median age was 59 years (range 38 to 80), 12 patients were never-smokers and 3 patients had a light smoking history (<15 pack years), and all patients had adenocarcinoma. The objective response rate was 38% (95% CI, 15%-65%), median duration of response was 8 months (range 5 to 26) and the median progression-free survival was 7 months (95% CI, 5 to not available). The Grade 3 adverse events observed were fatigue, mucositis, palmar-plantar erythrodysesthesia, hypertension, retroperitoneal hemorrhage, increased liver tests, lipase increase, hypophosphatemia, and thrombocytopenia. Eight patients needed a dose reduction to 40 mg daily, and 2 patients needed a second dose reduction to 20 mg daily. Patients who underwent a dose reduction appeared to derive benefit.
This trial demonstrated the activity of cabozantinib in patients with RET rearranged NSCLC but raised concerns about the optimal dose and tolerability. Other agents are being investigated in RET rearranged NSCLC, including vandetanib and sunitinib. Because of the small number of patients and limited efficacy data available, it is unclear if the fusion partner influences the activity of the agent. My practice is to test for RET rearrangements in patients with adenocarcinoma if our standard next-generation sequencing mutation panel, ALK FISH, and ROS1 FISH testing do not reveal an oncogenic alteration.

Association between younger age and targetable genomic alterations and prognosis in non-small-cell lung cancer


Dr Vokes

Sacher et al have conducted an interesting evaluation of NSCLC in younger patients. They evaluated a cohort of over 2,000 patients who were genotyped at the Dana-Farber Cancer Institute and evaluated the frequency of targetable genomic alterations by age category of the total cohort. Of 2,237 participants, 87% had histologically confirmed adenocarcinoma. Gene mutations for EGFR and ALK were associated with cancer diagnosis at younger age, with a similar trend for ERBB2 but not BRAF V600E. Younger age was associated with an increased frequency of a targetable genotype. Furthermore, the youngest and oldest groups were shown to have a poorer survival outcome when compared to patients in their 50s and 60s.

This paper as well as an editorial by Jack West identifies younger patients with lung cancer as a subset with high likelihood of a targetable mutation and a comparatively poorer outcome. Testing of such patients preferably with a next-generation platform seems highly indicated in order to provide best chances of active therapy.

Dr Johnson

- This is a retrospective chart review of >2,200 lung cancer pts treated at DFCI over a 12-y period. Sacher and colleagues collected pt characteristics, genotype and outcome data and looked for an association between age and genotype.
- 1,325 pts were genotyped for a core group of 5 genes: EGFR, ALK, ROS1, ERBB2 and BRAF. Younger pts (<50) were found to be 59% more likely to harbor 1 of these 5 genetic alterations than pts diagnosed at >50. Also it was the oldest and the youngest pts who seemed to have the shortest survival or poorest outcomes — suggesting that the very youngest pts diagnosed with lung cancer have a distinct natural history and so if you’re going to do comprehensive testing on anybody it should be these younger pts.
- Great analysis in that it confirmed what we intuitively think to be the case — younger pts are more likely to harbor a mutation. Reinforces the importance of comprehensive NGS if the local result is negative. The fact that they do less well even with
TKI therapy was interesting, especially given the study was performed at a tertiary referral center, where pts seem to do better regardless compared to the community.

- Interesting that the incidence of KRAS/BRAF mutations appears to increase with pt age.

**Dr Stinchcombe**

A cohort of 2,237 patients with non-small cell lung cancer underwent genotyping, and multivariate logistic regression was used to assess the relationship between age and mutation status of 5 common oncogenic drivers (EGFR, ALK, ROS1, ERBB2, and BRAF). The median age was 62 years (range 20 to 95), 87% of patients had adenocarcinoma, and 27% of patients had never smoked. A statistically significant relationship was found between age and EGFR mutations ($p = 0.02$) and anaplastic lymphoma kinase (ALK) rearrangement ($p < 0.001$), but no significant association was noted for ROS1 ($p = 0.10$), ERBB2 (HER2) ($p = 0.15$), or BRAF V600E ($p = 0.43$). Among patients younger than 50 years 78% had a molecular alteration, and among patients ≥50 years 49% had a genomic alteration. A Cox regression analysis was performed controlling for the presence of a targetable genomic alteration, use of targeted therapy, metastatic disease at diagnosis, sex, histologically confirmed adenocarcinoma histology, presence of brain metastases, and the year of metastatic disease. The presence of a targetable genomic alteration that received a targeted therapy was associated with improved survival. In contrast, the presence of a targetable alteration that did not receive a targeted therapy was not associated with an improvement in survival.

This study demonstrates that patients younger than 50 years have a higher rate of genomic alterations and patients should undergo a diligent work-up, including repeat biopsy if safe and feasible or cell-free DNA testing, to identify genomic alterations since receipt of a targeted therapy is associated with better survival. Since this study was performed at a tertiary referral center, the prevalence of genomic alterations and younger patients may be higher than at other clinical centers.

**ALCHEMIST trials: A golden opportunity to transform outcomes in early-stage non-small cell lung cancer**


**Dr Vokes**

In recent years the treatment for patients with EGFR mutant or ALK+ advanced stage NSCLC has clearly been identified. It remains unknown however, whether offering similar treatment to early stage patients in the adjuvant setting is of benefit. ALCHEMIST is a large national trial sponsored by the National Clinical Trials Network (NCTN) that originally consisted of 3 components and recently was amended to include a fourth. In the main protocol, several thousand patients with operable lung adenocarcinoma will be genotyped for EGFR mutations and ALK rearrangements and are subsequently eligible for randomization to erlotinib or crizotinib respectively vs placebo.
The backbone ALCHEMIST trial will provide an opportunity to incorporate complex genomic studies and to further characterize all lung cancers and understand their complex mechanisms of resistance to therapy. Recently, an additional treatment arm was added in which patients without targetable mutation, including those with squamous cell histology, are randomized to either nivolumab or observation. Thus, ALCHEMIST is poised to add important new insights to our understanding and optimal management of early stage NSCLC.

Dr Johnson

- The fact that pts with metastatic lung cancer have improved survival when treated with targeted therapies has been well established. Yet trials evaluating the efficacy of TKIs — in particular EGFR and ALK — for pts with resectable lung cancer have been under-powered to evaluate the true impact of these therapies on OS.
- ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial) is a large NCI-sponsored nationwide initiative to characterize the survival outcomes of EGFR- and ALK-directed therapy for pts with Stage IB-IIIA NSCLC.
- Actually, this study is 2 separate prospective, randomized double-blinded Phase III trials in one: EGFR pts on one, ALK pts on the other. Patients can enroll before/after surgery or after adjuvant chemo. They'll provide tissue for EGFR/ALK genotyping and tissue/blood for genomic research. Patients with EGFR mutations will be randomized to E x 2 y vs placebo (n = 410). Patients with ALK rearrangements will be randomized to CRZ x 2 y vs placebo (n = 360). There are also plans to enroll EGFR/ALK WT pts into a separate arm to receive Nivo or placebo for 1 year (n = 710).
- Primary endpoint is OS, and the trial assumes 6K-8K pts will need to be screened in order to enroll both efforts fully.
- Patients will come from both academic and community sites for this trial. Really important trial and effort, especially because it may represent one of the only projects in the US where all sites are working together to participate in the trial.
- SCRI not participating in this trial. Competing trials evaluating afatinib (92 pts) and AZD9291 (700 pts).

Dr Stinchcombe

Treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors and anaplastic lymphoma (ALK) tyrosine kinase inhibitors have revolutionized the care of patients with metastatic non-small cell lung cancer (NSCLC) with the appropriate molecular alterations. There are hopes that adjuvant treatment with targeted therapy in patients with completely resected NSCLC harboring the appropriate mutation will lead to better long-term survival rates. A retrospective subset analysis of a Phase III trial of erlotinib for resected NSCLC in patients with EGFR mutant NSCLC revealed an improvement in disease-free survival but not overall survival. The difference in disease-free survival was not statistically significant due to the hierarchical testing procedure used in the study design.
The National Cancer Institute (NCI) National Clinical Trials Network is investigating targeted therapy in the adjuvant setting. The first part of the trial is genomic screening of patients, and patients will undergo testing for EGFR mutations and ALK rearrangements as part of the trial. Samples will undergo whole exome or genome analysis by the NCI. Patients are assigned to the study based on EGFR mutation and ALK rearrangement status. Patients with EGFR mutation are assigned to 2 years of erlotinib or placebo, and patients with an ALK rearrangement are assigned to 2 years of crizotinib or placebo. The primary endpoint is overall survival. Recently a third arm for patients who do not harbor an EGFR or ALK alteration was added, and patients will be assigned to 1 year of nivolumab or observation.

The addition of the last arm has the potential to facilitate enrollment since the majority of patients with NSCLC do not have an EGFR mutation or ALK rearrangement. Patients are required to have resected Stage IB (≥4 cm) to IIIA NSCLC and can still receive adjuvant chemotherapy. Adjuvant trials are inherently difficult to enroll and complete, and they require long follow-up. This trial is a high priority since it will prospectively investigate the role of targeted therapies and immunotherapy as adjuvant therapy.

**Cabozantinib (C), erlotinib (E) or the combination (E+C) as second- or third-line therapy in patients with EGFR wild-type (wt) non-small cell lung cancer (NSCLC): A randomized phase 2 trial of the ECOG-ACRIN Cancer Research Group (E1512)**

Neal JW et al.  
*Proc ASCO 2015;Abstract 8003.*

**Dr Vokes**

Neal et al reported on an ECOG trial investigating cabozantinib, erlotinib or the combination in the second- or third-line treatment of patients with wild-type NSCLC. 125 patients were enrolled, of which 113 were eligible and treated. The others reported a significantly improved progression-free survival for cabozantinib or the combination of cabozantinib and erlotinib at the price of higher grade hypertension, mucositis and diarrhea. These data indicate need to further follow up on this observation in EGFR wild-type patients with NSCLC, for which erlotinib is a current standard therapy option.

**Dr Johnson**

- After all this talk of targeted inhibitors for biomarker-positive pts, here’s something a little different.
- This was a randomized Phase II trial sponsored by ECOG-ACRIN that enrolled pts to receive cabo alone, cabo plus erlotinib or erlotinib alone for second- or third-line EGFR wild-type NSCLC.
- There were safety data to use these drugs in combination from Heather Wakelee reporting at ASCO 2010 that combining erlotinib + cabo for pts with acquired resistance to erlotinib alone had activity and showed an ORR of 30% in pts with EGFR mutations and MET amplifications. 12 of 54 pts (25%) had dose-limiting
toxicities, so Joel Neal wasn’t kidding when he said in his presentation that the combination was “fairly well tolerated.”

- Over 18 months, 113 were enrolled, around 40 pts in each arm.
- The combination was harder to tolerate than especially cabo alone because of the overlapping toxicities seen with those 2 drugs — nearly 1/3 had Grade 3 diarrhea (>7 stools over baseline), 15% had Grade 3 fatigue. Cabo-alone pts had Grade 3-4 hypertension and mucositis.
- The trial did meet its primary endpoint of PFS — 4.7 mo for pts treated with the combination and 4.2 mo for pts treated with cabo alone vs 1.9 mo with erlotinib alone. And pts lived longer when treated with the combination and with cabo alone vs erlotinib.
- I’d be curious to know the rate of discontinuation on this trial.
- Remember that EGFR WT means there were probably a handful of pts with MET, RET, ROS1 mutations that are likely the reason that those arms performed so much better than the pts who received erlotinib alone.
- But more importantly, in this age of immunotherapy I think we’ve moved on from treating EGFR WT lung cancer with erlotinib and/or other targeted agents meant for oncogene-driven subsets. The minimal benefit is not worth the risk when there are other, more effective therapies.
- You might ask, what about after immunotherapy? But that’s a brave new world as far as I can see, where immunotherapy combinations will play a role.

**Other Issues in the Treatment of Lung Cancer**

**Nab-Paclitaxel + carboplatin (nab-P/C) in advanced non-small cell lung cancer (NSCLC): Outcomes in elderly patients (pts) with squamous (SCC) histology**

Gridelli C et al.  
Proc ELCC 2016;Abstract 216PD.

**Dr Vokes**

The combination of nab paclitaxel and carboplatin has been shown to be superior to paclitaxel and carboplatin in patients with advanced non-small cell lung cancer (NSCLC). Progression-free survival and overall survival were not statistically significant. Gridelli et al now present a subset analysis of patients in that trial who had squamous cell carcinoma (450 of 1,052 patients). Most of these patients were male with an ECOG PS of 1. For patients over the age of 70, the authors report a significantly higher objective response rate for nab paclitaxel (46% vs 20%) and an increase in median overall survival from 8.6 to 16.9 months favoring nab paclitaxel. Progression-free survival did not differ. When looking at outcomes for various age groups, nab paclitaxel was superior in all 3 age groups tested.
These results indicate the possible superiority of nab paclitaxel in squamous cell carcinoma lung cancer patients. It needs to be noted that this is a retrospective subset analysis and that further prospective validation would be required for higher statistical certainty. However, it is unlikely that substantial additional work will be done in this regard given the current focus on immuno-oncology and its emerging role in the first-line setting.

**Dr Johnson**

- We all remember the Socinski nab paclitaxel data published a few years ago. It was a randomized Phase III trial of carb/nab-P vs carb/pac for pts with advanced NSCLC. The primary endpoint was ORR 33% vs 25%, and in the SCC sub-group 41% vs 24%, although PFS and OS were statistically similar. Patients treated with nab-P were more likely to have thrombocytopenia/anemia while pts treated with standard pac, neuropathy, neutropenia and myalgias/arthritis. Sub-group analysis showed pts over 70 y of age trended towards more favorable survival.
- This abstract was a post hoc analysis of pts with SCC by age.
- 450 pts were included (of 1,052 enrolled in the Phase III trial); 65 were 70 or older. The improved ORR persisted in the oldest subset of pts: ORR 46% vs 20% in pts ≥70 or <70. Exploratory look at survival in this sub-group (remember this was a retrospective, post hoc analysis) showed this elderly subset also had improved OS when treated with carb/nab-P vs carb/pac.
- Interesting analysis. Hard to make much of it given it was done post hoc. It’s easy to wonder if maybe the elderly pts included in the Socinski trial were particularly fit. However, I will say my partners and I use a lot of carb/nab-P — it’s easier to give weekly as opposed to once every 3 weeks. Seeing pts weekly allows a closer level of follow-up that means TRAEs are managed more quickly; they aren’t allowed to worsen. Cytopenias are managed with transfusions in a more timely manner.

**Dr Stinchcombe**

A Phase III trial compared carboplatin every 3 weeks and weekly nab-paclitaxel to carboplatin and standard formulation paclitaxel every 3 weeks and revealed a statistically significant higher response rate in the intent-to-treat patient population and in the squamous histology subset. This post-hoc analysis investigated the clinical outcomes of patients with squamous histology stratified by age. Of the 1,052 patients enrolled, 450 had squamous histology, and 65 patients with squamous histology were age ≥70 years. In the cohort of patients age ≥70 years with squamous histology, the objective response rate was higher with carboplatin and nab-paclitaxel compared to carboplatin and paclitaxel (46% vs 20%; \( p = 0.029 \)) and the overall survival was longer (hazard ratio [HR] of 0.50, \( p = 0.018 \); median 16.9 vs 8.6 months, respectively).

The difference in objective response rate remains statistically significant with age cut-offs of ≥65 years (n = 137) and ≥60 years (n = 226). The difference in overall survival remains statistically significant with the age cut-offs of ≥65 years (HR of 0.62, \( p = 0.019 \); median 13.9 and 9.4 months, respectively) and 60 years (HR of 0.70, \( p = 0.027 \); median 11.8 and
9.5 months, respectively). The small size and the post-hoc nature of the analysis limit the interpretation of the results since imbalances in prognostic factors and subsequent therapies may have impacted the survival results. Carboplatin and weekly nab-paclitaxel is a treatment option for elderly patients with squamous histology.

**Safety and efficacy of single-agent rovalpituzumab tesirine (SC16LD6.5), a delta-like protein 3 (DLL3)-targeted antibody-drug conjugate (ADC) in recurrent or refractory small cell lung cancer (SCLC)**

Rudin CM et al.  
*Proc ASCO* 2016;Abstract LBA8505.

**Dr Vokes**

Little progress has been made for patients with SCLC in the last 3 decades. Rovalpituzumab tesirine is an antibody-drug conjugate comprised of a humanized monoclonal antibody against DLL3, a linker and a chemotherapy dimer toxin (PBD). DLL3 is highly expressed in endocrine tumors, including SCLC. Rudin et al updated data on a Phase II trial of patients having failed at least 1 prior systemic therapy. 74 patients were enrolled at various doses. Among high expressers of DLL3 (over 50% of cells) the response rate in the third-line setting was 50% and median overall survival, 5.8 months. Most common side effects, Grade 3 toxicities included serosal effusions, thrombocytopenia and skin reactions.

**Dr Johnson**

• Finally! Something for SCLC after nearly 30 years of unsuccessful attempts to identify a biomarker in this disease.

• DLL3 is an atypical inhibitory Notch ligand — atypical in that it downregulates Notch when induced by neuroendocrine transcription factor ASCL1. Notch is expressed in 80% of SCLC and lung cancer/neuroendocrine tumors but not in normal lung tissue.

• Rova-T is an ADC directed against DLL3. (Ab-cathepsin B; linker-PBD warhead)

• Charlie Rudin reported the results of the FIH dose-escalation Phase I trial at ASCO this year, which included 74 pts treated with a variety of doses. 88% of pts expressed at least 1% DLL3 on tumor cells, and 67% expressed at least 50% on tumor cells.

• Patients were treated with escalating doses of the drug every 3 weeks until the side effect profile started to emerge: With cumulative doses pts developed Grade 3 thrombocytopenia, pleural and pericardial effusions and edema as well as a rash — largely in sun-exposed areas. Actually we found we only needed to give 2 doses of the Rova-T with potent results.

• ORR was 18% overall but 40% in pts whose tumors were DLL3 high; remembering SCLC is not an indolent disease, the CBR or DCR was 68% in all pts and 89% in
pts with DLL3-high tumors. These responses were observed in second- and third-line pts.

- Very exciting results! But very early days — but TRINITY is a second/third-line single-arm trial that enrolls DLL3-high pts and is ongoing. The TAHOE trial randomized against Topo and MERU evaluating Rova-T as maintenance are planned.

Dr Stinchcombe

Improvements in the treatment of small cell lung cancer (SCLC) have lagged behind improvements in the treatment of NSCLC due to the lack of identified biomarkers and novel agents. Rovalpituzumab tesirine (Rova-T) is an antibody-drug conjugate that targets the delta-like protein 3 (DLL-3), a protein that is expressed on SCLC and large cell neuroendocrine cancer but not on normal tissue. This agent was investigated in a Phase I trial, and the recommended dose for Phase II trials was 0.3 mg/kg every 6 weeks for 2 treatments. Of the 74 patients enrolled, 39 (53%) had received 1 prior line of therapy and 35 (47%) had received 2 prior lines of therapy, 39 (53%) were considered platinum-sensitive and 23 (31%) were considered platinum-resistant; 7 (9%) had progressive disease on first-line therapy.

Of the patients tested, 88% had DLL-3 expression in ≥1% of tumor cells, and 67% had DLL-3 expression in ≥50% of tumor cells. The central review objective response rate for all patients was 16%, and for patients with DLL-3 expression ≥50% it was 31%. The response rates for patients with DLL-3 ≥50% by central review in the second- (n = 14) and third-line (n = 12) settings were 29% and 50%, respectively. In the cohort of patients with DLL-3 expression ≥50% the median overall survival and 1-year overall survival rate were 5.8 months and 32%, respectively. The common Grade 3 or higher adverse events were thrombocytopenia (12%), serosal effusions (11%), and skin reaction (8%). Serosal effusions included pleural or pericardial effusions, ascites, or “capillary leak syndrome.”

This trial demonstrated significant activity of Rova-T in patients with DLL-3 expression ≥50%. An ongoing single arm Phase II trial is investigating this agent in the third-line setting, and most likely this agent will be developed further in earlier treatment settings and as part of combination therapy.
Colorectal and Anal Cancers

**Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): A proof-of-concept, multicentre, open-label, phase 2 trial**

Sartore-Bianchi A et al.  

**Dr Lenz**

It has been shown that dual HER2 blockade with trastuzumab and lapatinib led to inhibition of tumor growth in patient-derived xenografts of HER2-amplified metastatic colorectal cancer. It also has been reported that HER2 amplification is seen in about 5% of patients with mCRC and can be found as a molecular escape from EGFR blockade, particularly in left sided colon cancers. HERACLES was a proof-of-concept, multicenter, open-label, Phase II trial that enrolled patients with KRAS exon 2 (codons 12 and 13) wild-type and HER2-positive metastatic colorectal cancer refractory to standard of care (including cetuximab or panitumumab). We defined HER2 positivity in tumor samples by use of immunohistochemistry and fluorescence in-situ hybridization. 914 patients with KRAS exon 2 (codons 12 and 13) wild-type metastatic colorectal cancer were screened to identify 48 (5%) patients with HER2-positive tumors. Of these patients, 27 were eligible for the trial. Eight (30%, 95% CI 14-50) of 27 patients had achieved an objective response, with 1 patient (4%, 95% CI -3 to 11) achieving a complete response, and 7 (26%, 95% CI 9-43) achieving partial responses. Treatment was well tolerated with no Grade 4 or 5 adverse events reported. These data suggest that dual blockage of HER2 has significant clinical activity in patients with HER2-positive colon cancer. These data are now the basis of a randomized Phase II SWOG trial. Molecular screening for HER2 positivity in mCRC should be considered.

**Dr Grothey**

Until recently, the analysis of molecular predictive biomarkers in metastatic CRC was mainly performed to exclude patients from certain treatment interventions. A sequence of studies had shown that (K)RAS mutations led to resistance of CRC against EGFR mAbs, which led to changes in guidelines and drug labels. Positive predictive biomarkers, markers that identify a patient population as target for a specific intervention, had long been elusive. The data presented in the HERACLES single-arm Phase II study now identified HER2 overexpression in treatment refractory, KRAS exon 2 wild-type CRC as a biomarker for the activity of a dual-targeted agent approach: the combination of trastuzumab and lapatinib.

In this proof-of-principle study, an unprecedented high response rate of 30% was achieved when these 2 biologic agents were administered, with some of the responses lasting for several months. These findings have already led to the design (and hopefully
sooner activation) of randomized trials that will definitively establish the efficacy of HER2 targeted agents in CRC. It is of note that only about 2.5% of all CRC are thought to have HER2 overexpression but that HER2 is likely also a marker of resistance to EGFR mAbs. It is conceivable that HER2 testing will soon become one of the standard biomarker tests applied in CRC, joining the ranks of RAS/BRAF and MSI.

**Dr Philip**

Targeting HER2 in colon cancer was investigated in pre-clinical models and shown to be effective using a combined anti-HER2 strategy. Sartore-Bianchi and colleagues studied patients with metastatic colorectal cancers who had KRAS wild type tumors. Patients were refractory to standard therapies, including anti-EGFR agents. Of the 914 patients screened, 5% were HER2 positive. Twenty-seven eligible patients received standard dosing of trastuzumab and lapatinib at 1,000 mg per day until disease progression. The primary endpoint was centrally determined objective response rate. Eight of 27 (30%) patients had an objective response, with 1 patient (4%) achieving a complete response, and 12 (44%) had stable disease.

Median PFS was 21 weeks. Six had Grade 3 side effects consisting of fatigue (4), skin rash (1), and hyperbilirubinemia (1). Based on this small pilot trial, the combination of trastuzumab and lapatinib is active and well tolerated in treatment-refractory patients with KRAS wild type and HER2-positive metastatic colorectal cancer. In my practice I screen RAS wild type patients for HER2, and I would consider trastuzumab plus lapatinib in patients who are HER2 positive. There is also need to consider anti-HER2 therapy in earlier lines of therapy, HER2 positivity predicting resistance to anti-EGFR agents. A randomized trial is currently in development to test anti-HER treatment strategy in patients with HER2-positive tumors in the second-line setting. The NCI-NSABP FC7 trial is also investigating the combination of neratinib (a tyrosine kinase inhibitor targeting EGFR, HER2, and HER4) and cetuximab in HER2-positive patients.

**Dr Lenz**

Patients with BRAF mutations are known to have a poor prognosis. New treatment strategies are being developed to target BRAF-mutant tumors. Using single agent BRAF inhibitors demonstrated only disappointing activity. In vitro and in vivo colon cancer models suggested that the combination of BRAF inhibitors with MEK inhibitors, PI3K inhibitors, EGFR inhibitors and chemotherapy significantly increased activity. Corcoran et al report on the efficacy of dabrafenib, a selective BRAF inhibitor, combined with trametinib, a selective MEK inhibitor, in patients with BRAF V600-mutant metastatic colorectal cancer (mCRC). Of 43 patients enrolled, 5 (12%) achieved a partial response or better, including 1 (2%) complete response, with durable responses. These data suggest promising activity of this dual combination.
The authors also showed in an extensive biomarker approach that during-treatment biopsies reduced levels of phosphorylated ERK relative to pretreatment biopsies and that the patient achieving a complete response and 2 of 3 evaluable patients achieving a partial response had PIK3CA mutations. Clinical activity was comparable with the PDX models generated from the clinical trial patients. These clinical data suggest that the combination of dabrafenib plus trametinib has activity in a subset of patients with BRAF V600-mutant mCRC. Other trials are being conducted in combination with cetuximab, irinotecan, PI3K inhibitors and MEK inhibitors. A registration trial of a BRAF inhibitor with cetuximab and a MEK inhibitor is ongoing.

Dr Grothey

BRAF V600E mutated CRC is characterized by distinct clinical features. This activating mutation is associated with poor prognosis and likely resistance to EGFR mAbs either alone or in combination with systemic chemotherapy. Specific BRAF inhibitors have high activity in melanoma, even if the duration of responses is commonly short. In melanoma, combining BRAF and MEK inhibitors enhances the anti-tumor activity. In CRC, the use of single agent vemurafenib, a BRAF inhibitor in BRAF V600 mutated cancers, has only shown disappointing activity (RR 5%), likely due to the activation of redundant pathways.

The combination of BRAF and MEK inhibitors now increased the RR to 12% in a 43 patient single arm study, but this activity still falls way short of what has been reported in melanoma for the same treatment approach. Preclinical and early clinical data suggest that the antitumor activity of BRAF blockade with or without concomitant MEK inhibition can be enhanced when EGFR mAbs are added to the combination. In this approach, EGFR inhibition is meant to counteract EGFR activation by feedback loops when pERK levels decrease after BRAF/MEK blockade. Intergroup/SWOG study 1406, which investigated the combination of vemurafenib, cetuximab, and irinotecan in a randomized Phase II trial, has recently completed accrual. Other trials targeting BRAF V600E mutated CRC are under way.

Dr Philip

Corcoran and colleagues investigated targeted combination therapy in a subset of tumors that harbor BRAF V600 mutation. Of note, those patients have inferior overall response times and unlike patients with melanoma do not respond to single agent BRAF targeting. A total of 43 patients were treated with anti-BRAF dabrafenib (150 mg twice daily) plus anti-MEK1/2 trametinib (2 mg daily). 17 patients underwent pharmacodynamic correlative studies that included genomic profiling and establishment of patient derived xenografts. Five (12%) achieved a partial response or better, including one (2%) complete response. Ten patients (23%) remained on study treatment for >6 months. Median PFS was a modest 3.5 months.

On-treatment biopsies confirmed partial (47%) reduction of phosphorylated ERK and possible association between response and PIK3CA mutations. The benefit seen in this study with a combined anti-BRAF/anti-MEK approach needs further confirmation, and such patients must be enrolled on ongoing clinical trials. A recently completed trial
Dr Lenz

TAS-102 is comprised of a thymidine-based nucleoside analog, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride. It was reported in the *NEJM* that TAS-102 increased PFS and OS in refractory mCRC patients vs placebo, and based on the OS data TAS-102 was approved by the FDA. The final efficacy data from RECOURSE were reported at ASCO GI 2016. The updated results confirmed that OS benefit with TAS-102 was maintained and increased to a full 2 months; improvement in 1-year survival surpassed 10% in these heavily pretreated patients. The most frequently observed clinically significant adverse events associated with TAS-102 were neutropenia, which occurred in 38% of those treated, and leukopenia, which occurred in 21%. It has been hypothesized that neutropenia was associated with a relatively high FTD concentration in patients.

At ASCO Ohtsu reported that the onset of neutropenia at any cycle was associated with longer median OS and PFS compared with no neutropenia. A consistent survival benefit was observed regardless of the cycle of initial onset of neutropenia, suggesting that further analyses are required to fully determine whether FTD pharmacokinetics correlate with TAS-102 efficacy and onset of neutropenia, and whether cycle initiation delays affect response. These data also suggest potential polymorphisms in the metabolic pathway of FTD. Analyses are ongoing.

Dr Grothey

In the era of drug development focusing on biologics, TAS-102, the combination of trifluridine and tipiracil, represents conventional cytotoxic chemotherapy. The RECOURSE Phase III trial established the efficacy of TAS-102 as salvage therapy in treatment refractory CRC with moderate but significant and clinically relevant improvement in overall survival. The activity of TAS-102 is very similar to what has been described for regorafenib, but both agents have very different toxicity profiles. In spite

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**TAS-102 versus placebo plus best supportive care in patients with metastatic colorectal cancer refractory to standard therapies: Final survival results of the phase III RECOURSE trial**

**Onset of neutropenia as an indicator of treatment response in the phase III RECOURSE trial of TAS-102 vs placebo in patients with metastatic colorectal cancer**

1 Mayer RJ et al. Gastrointestinal Cancers Symposium 2016;Abstract 634.
of the fact that TAS-102 is a fluoropyrimidine, it does not cause hand-foot syndrome or diarrhea in most patients. Its main side effect is myelotoxicity, mainly neutropenia, with fortunately very few patients experiencing neutropenic fever. In a retrospective analysis, Grade 3/4 neutropenia was found to be associated with improved outcomes on TAS-102. In fact, patients who never experienced neutropenia in any treatment cycle did not have better survival outcomes than with placebo. Pharmacokinetic analyses could not provide a convincing explanation for these findings, which were corroborated by 2 other studies presented at ASCO 2016. The consequence for clinical practice could be that in patients who develop neutropenia on TAS-102 and who cannot continue treatment every 4 weeks due to low neutrophil counts, the dose should not be lowered, but rather the cycle length should be increased.

**Dr Philip**

Mayer and colleagues recently updated the survival results of the Phase III trial of TAS-102 versus a placebo in 800 patients with metastatic colorectal cancer. Patients were included irrespective of RAS status. Previously reported improvement in OS was maintained: 7.2 vs 5.2 months, HR 0.69, \( p < 0.0001 \), 1-year OS rate 27.1% vs 16.6%. The drug is generally well tolerated, with predictable neutropenia. Ohtsu and colleagues further analyzed the data specifically looking at patients who experienced Grade 3 or 4 neutropenia and reported that the onset of neutropenia at any cycle was associated with longer median OS and PFS compared with no neutropenia. A consistent survival benefit was observed regardless of the cycle of initial onset of neutropenia. In my practice I use TAS-102 in patients who have failed all standard regimens, and in my opinion there is no established sequence when choosing between TAS-102 and the other oral agent, regorafenib. Ongoing studies are addressing the role of TAS-102 in earlier lines of therapy and in combination with other agents, such as nivolumab.

**Nivolumab ± ipilimumab in treatment (tx) of patients (pts) with metastatic colorectal cancer (mCRC) with and without high microsatellite instability (MSI-H): CheckMate-142 interim results**


**Dr Lenz**

Recent publication in *NEJM* showed a high response rate in MSI-high colorectal cancers. These responses were fast and durable and treatment was well tolerated. There was no benefit in MSS colorectal cancer patients. New strategies include combination of immune checkpoint inhibitors with CTLA4 inhibitors or IDO1 inhibitors. Overman et al reported at ASCO efficacy and safety data with nivolumab (N) in combination with ipilimumab (I), a humanized anti-CTLA4 mAb, in MSI-H mCRC. This combination has been shown to have favorable safety and efficacy in other tumors. CheckMate 142, a Phase II study, evaluates N ± I in patients with mCRC, MSI-H and non-MSI-H. The primary endpoint was investigator-reported ORR by RECIST 1.1. MSS mCRC did not show clinical benefit. However, N and N + I demonstrated encouraging
clinical activity and survival in MSI-H mCRC with a confirmed response rate of 25.5% (N3) and 33% (N3 and I1). In MSI-H patients, most common TRAEs were diarrhea and fatigue (approximately 15% each; N3) and diarrhea (43%; N3 + I1). Grade 3-4 TRAEs occurred in 10 (N3) and 8 patients (N3 + I1).

These early clinical data suggest that N and N + I were well tolerated in most patients and demonstrated promising clinical activity in MSI-H mCRC consistent with previously reported data.

Combinational therapies should be further explored. Immune checkpoint inhibitors are now also explored in first line chemotherapy and in adjuvant therapy.

Dr Grothey
The activity of PD-1/PD-L1 immune checkpoint inhibitors in hypermutated (MSI-H) disease was convincingly demonstrated in 2015 with the results of pembrolizumab, which generated an unprecedented response rate in this patient population. Nivolumab is another PD-1 antibody with documented activity (and FDA approval) in various malignancies. In melanoma, the combination of nivolumab and ipilimumab has shown increased activity over nivolumab alone. At ASCO 2016, a multi-arm cohort study was presented that investigated the activity of nivolumab as a single agent in MSI-H CRC and in combination with ipilimumab in MSI-H and MSS cancers.

The addition of ipilimumab to nivolumab in MSI-H CRC appeared to increase response rates numerically (33% vs 25%), but in a cohort-by-cohort comparison side effects were found to be more common with the dual immunotherapy. In cross-trial comparison, the nivolumab single agent data seemed less convincing than what was reported for pembrolizumab (updated at ASCO 2016, 57% RR), but these differences could be related to the fact that different patient populations were accrued in the studies. In patients with MSS CRC, 1 of 10 patients treated with the nivolumab/ipilimumab combination had an objective response, but the data were too preliminary to draw conclusions of the immunotherapy combination in this patient group. Overall, the activity of PD-1 checkpoint inhibitors in MSI-H CRC has been confirmed. It is unclear yet if the addition of a CTLA-4 inhibitor will provide clinically meaningful improvements in outcome.

Dr Philip
CheckMate 142 is a Phase II international study that is still ongoing. It evaluates nivolumab (anti-PD-1) with or without ipilimumab (anti-CTLA4) in patients with metastatic CRC who have MSI-stable and MSI-high tumors. The dose of the combination was optimized in patients with MSI-stable tumors. Patients must have ECOG PS 0-1 and intolerance/progression on ≥1 line of prior therapy and can be of any RAS mutational status. Primary endpoint of the study is objective tumor response. Nivolumab exhibited single agent activity in MSI-high tumors: response rate 25.5%, median PFS 5.3 months, and median overall survival 17.1 months. Nivolumab plus ipilimumab showed a higher level of activity: response rate 33.3%, median PFS and overall survival not reached. In the 10 patients with MSI-stable disease there was only 1 objective response with the combination.
Collectively the data thus far support the use of immune checkpoint inhibitors in MSI-high metastatic CRC, in line with prior information with pembrolizumab. The combination of nivolumab and ipilimumab appeared to have more activity but with added toxicity: the rate of Grade 3 or 4 toxicities was doubled with the combination (14.3% to 26.7%) and more patients had to discontinue treatment because of toxicity with the combination (13.3% vs 2.9%). At this time, offering patients with metastatic CRC with MSI-high tumors (4%-5% of all metastatic patients) therapy with a PD-1 inhibitor is reasonable. The combination of a PD-1 inhibitor with ipilimumab still awaits maturity of data, but there will be concerns about toxicity and cost.

Newer studies are looking at the use of PD-1 and PD-L1 inhibitors in earlier lines (including front line) of therapy and also in the adjuvant setting in patients who have MSI-high tumors.

Clinical activity and safety of cobimetinib (cobi) and atezolizumab in colorectal cancer (CRC)


Dr Lenz

Immunotherapies have not shown promising efficacy in MSS mCRC. Ongoing preclinical models have suggested that MEK inhibitors can increase immunogenicity. Inhibition of MEK leads to upregulation of MHC I on tumor cells and induces intratumoral T-cell infiltration, enhancing anti-PD-L1 activity. Bendell reported at ASCO the efficacy and safety data of a Phase Ib study combining atezolizumab (atezo), an engineered antibody binding of PD-L1 to its receptors, PD-1 and B7.1, and cobimetinib (cobi) in MSS mCRC. Cobi was escalated from 20 to 60 mg daily (21 days on/7 days off) and combined with atezo 800 mg IV q2w. Tumor-specific expansion cohorts, including KRAS-mutant CRC, and serial biopsy cohorts in solid tumors were opened upon determination of the MTD.

Safety, tolerability and confirmed ORR by RECIST v1.1 were evaluated. 23 CRC (22 KRAS mutant, 1 WT) patients were enrolled during escalation and expansion. No dose-limiting toxicities were observed, and expansion occurred at atezo 800 mg q2w and cobi 60 mg.

Median follow-up for safety in CRC patients was 3.8 mo (range, 1.1-15.1). The most common treatment-related AEs included diarrhea (70%), fatigue (52%), dermatitis acneiform (44%), rash (35%), maculopapular rash (26%), pruritus (26%) and nausea (26%). Incidence of treatment-related G3-4 AEs was 35%. The response rate was 17% (4 PR, 5 SD). Three responders were mismatch repair-proficient, and 1 was unknown. Response was not associated with baseline PD-L1 expression.

Results from the serial biopsy cohort showed enhanced PD-L1 upregulation, CD8 T-cell infiltration and MHC I expression on treatment, providing mechanistic rationale for the combination.
This early Phase Ib trial suggests that inhibition of MEK can increase efficacy of immune checkpoint inhibitors in MSS mCRC. Whether there is a differential effect in WT RAS or mt RAS needs to examined. These data are an important proof of principle trial showing for the first time that RAS/MEK signaling are involved in immune response. A Phase III registration trial has been initiated.

Dr Grothey
The efficacy of PD-1/PD-L1 checkpoint inhibition in MSI-H metastatic CRC has been well established over the last 2 years. However, MSI-H CRC constitutes only about 4%-5% of all patients with metastatic disease. Thus, patients who carry MSS cancers, which are a priori nonimmunogenic since they conceivably lack the hypermutated phenotype, are not yet considered candidates for immunotherapy. Preclinical data suggest that combining an immune checkpoint inhibitor like atezolizumab (PD-L1 antibody) with a MEK inhibitor can lead to infiltration of T-lymphocytes in MSS CRC and increase the expression levels of MHC class 1, a prerequisite for immune activation.

In a Phase I/Ib study atezolizumab and cobimetinib were combined in patients with refractory metastatic CRC. In 20 patients with KRAS exon 2 mutated cancers, a response was seen in 4 patients (20%). At least 3 of these patients had MSS cancers; 1 patient had an unknown MSI status. Four additional patients experienced stable disease. These findings are intriguing since atezolizumab and cobimetinib alone have not been shown to induce any responses in this patient population. While the sample size investigated precludes farther-reaching conclusions, the results served as a basis for the initiation of a Phase III trial comparing the atezolizumab/cobimetinib combination with atezolizumab alone and regorafenib as control arm in a 2:1:1 randomization.

Dr Philip
Bendell and colleagues tested the combination of atezolizumab (atezo), an anti-PD-L1 antibody that blocks signaling through PD-1 and B7.1, and the MEK inhibitor cobimetinib (cobi). They reported on the expansion cohort in metastatic CRC. Pre-clinically, MEK inhibition led to upregulation of MHC I on tumor cells, induced intratumoral T-cell infiltration and enhanced anti-PD-L1 activity. No dose-limiting toxicities were observed in the Phase Ib portion of the study, and expansion occurred at full doses of atezo 800 mg q2w and cobi 60 mg daily. The expansion cohort (n = 23) included predominantly KRAS-mutant CRC patients who had received a median of 3 prior regimens. Incidence of treatment-related Grade 3 or 4 adverse events was 35%.

The only treatment-related Grade 3 or 4 adverse event in ≥2 patients was diarrhea (9%). Four patients discontinued therapy because of toxicity. The objective response was 17% (4 PR, 5 SD) and median duration of response was not reached. At 6 months a third of patients were without progression and three quarters were alive. Three responders were mismatch repair (MMR) proficient and 1 was of unknown MMR status. On-treatment tumor biopsy showed enhanced PD-L1 upregulation, CD8 T-cell infiltration and MHC I expression on treatment. These findings are certainly of interest and potential value for patients with MSI-stable tumors and also those with KRAS mutant tumors.
There is an ongoing prospective 3-arm randomized Phase III trial to test the combination versus atezo alone with regorafenib as the control arm. This is in patients who received at least 2 lines of prior therapy and is agnostic for MSI status or RAS mutations. I would await results of the randomized trial before adopting this combination regimen in my practice, noting the lack of mature randomized data at this time.

NCI9673: A multi-institutional ETCTN phase II study of nivolumab in refractory metastatic squamous cell carcinoma of the anal canal (SCCA)

Morris VK et al. Proc ASCO 2016;Abstract 3503.

Dr Lenz
Squamous cell carcinoma of the anal canal is largely driven by immune evasion of HPV-specific CD8 and CD4 T cells, which promote oncogenesis for SCCA. There are no established treatment options for patients with metastatic disease. Recent preclinical and clinical data suggested that virus induced cancer may benefit from immune checkpoint inhibitor therapies. This ETCTN study is the first Phase II trial of nivolumab for patients with refractory metastatic SCCA. Nivo, a monoclonal antibody targeting PD-1 on T cells, promotes immune-mediated anti-tumor activity of T cells against HPV-positive cells in vitro. 39 patients were screened across the ETCTN network; 37 were eligible with a median number of prior therapies of 2 (range 1-7). Seven of 34 (21%) had a partial response and 17 (50%) had stable disease. Median progression-free survival was 3.9 mo. Common adverse events (AE): fatigue, nausea, and rash. PD-L1 expression was not required. HIV+ (CD4 count >300/uL) and hepatitis B/C patients were eligible. These data suggest that immune checkpoint inhibitors demonstrate promising clinical activity and warrant further development. Combinational treatment strategies should be explored for this patient population lacking a consensus approach.

Dr Grothey
Squamous cell anal cancer is a relatively rare malignancy characterized by unique clinical and molecular features. About 80%-95% of cases are linked to HPV infections, which makes the cancer a potential target for immunotherapy due to the presence of unique virus-induced antigens presented on the surface of cancer cells. The development of distant metastases is uncommon in anal cancer, but apart from a cisplatin/fluoropyrimidine combination, no other treatment options are currently listed in NCCN guidelines. In a single arm study presented at ASCO 2016, nivolumab was investigated as a single agent in patients with metastatic anal cancer who had received at least 1 prior line of therapy.

This study deserves recognition for the fact that the investigators provided a very precise and easy-to-apply definition of pseudoprogression — even though none of the 37 patients enrolled in the study actually met these criteria. In the end, responses were observed in about 24% of patients, with 2 patients experiencing complete responses.
Unfortunately, median PFS was only 3.9 months and, in contrast to other tumor entities treated with checkpoint inhibitors, no plateau was observed in the PFS curve. Thus, the clinical utility of nivolumab compared with other potential systemic interventions (eg, taxane-based chemotherapy) is unclear at this point.

**Dr Philip**

Morris and colleagues studied for the first time nivolumab (PD-1 inhibitor) in patients with metastatic and advanced anal squamous cell cancer. Anal cancer is largely driven by immune evasion of HPV-specific CD8 and CD4 T cells leading to cancer formation. 37 patients with chemotherapy refractory metastatic anal SCC (median 2 prior treatments) received nivolumab. Treatment was well tolerated even in the HIV-positive subgroup. Primary endpoint was objective response, which was achieved in 24.3% of patients. Median PFS was 3.9 months. No data were included regarding duration of remission or survival at this point. The investigators were able to show some interesting correlations between specific immune cell profiles (CD8+PD-1+, CD45+PD-L1+) and benefit of therapy. In this first prospective Phase II trial of nivolumab in refractory metastatic SCCA, the overall benefit appears to be modest but worthwhile in the refractory disease setting and in the absence of other therapies. As such, nivolumab would be a therapy worthy of consideration. Whether similar outcomes would be anticipated with other PD-1/PD-L1 inhibitors remains to be seen. It is also likely that selecting patients with a better chance of response based on their immune profile will be a future strategy in treating anal SCC with nivolumab and other immune checkpoint inhibitors.

**Impact of primary tumor location on overall survival and progression-free survival in patients with metastatic colorectal cancer: Analysis of CALGB/SWOG 80405 (Alliance)**


**Dr Lenz**

Tumor location was known to be prognostic in patients with mCRC treated with chemotherapy, but it was not known to be predictive when chemo was combined with
targeted agents. Molecular characterization of right vs left colon cancer suggests that there are significant differences, such as frequency of KRAS, BRAF mutations, microsatellite instability, chromosomal alterations and activation of the HER pathway. FIRE-3 analyses suggested that right sided colon cancers are associated with poor prognosis and left sided colon cancers benefit significantly from cetuximab-based chemotherapy. In CALGB/SWOG 80405 the analysis of tumor location and outcome showed an OS difference statistically significant after adjustment for age, gender, race, biologic, chemotherapy and prior therapies, confirming the data shown in FIRE-3.

Right sided tumors had significantly worse PFS and OS and left sided colon cancer had significant benefit from cetuximab-based chemotherapy. Lee et al showed in his presentation that molecular differences such as MSI and BRAF might not explain the differences in the outcome of right vs left sided colon cancer. Methylation pattern needs to be explored.

In a SEER analysis tumor location showed a clear prognostic effect in all stages of colon cancer. It will be critical to understand the molecular mechanisms behind the poor prognosis to be able to develop more effective therapeutic regimens.

Dr Grothey

One of the most important results presented at ASCO 2016 in colorectal cancer (CRC) was the consistent data on the prognostic and potentially predictive influence of sidedness on treatment outcomes. The prognostic implication of sidedness had long been known but has routinely been ignored. With the emergence of routine molecular profiling and gene expression studies, differences in pathway alteration and genetic markers between right- and left-sided cancers have been identified. Consistently, all results presented so far, whether derived from the SEER population database or clinical trials, demonstrate that right-sided cancers (cecum to splenic flexure) are associated with worse prognosis.

The most intriguing findings with potential immediate treatment implications came from an analysis of the large Phase III trial 80405, which compared chemotherapy plus cetuximab or bevacizumab in KRAS wild-type CRC. The prognostic implication of sidedness was confirmed with a difference of about 14 months in favor of left-sided cancers when all treatment arms were combined. Importantly, though, the difference in overall survival for sidedness in patients treated with bevacizumab was much smaller compared to the difference observed for cetuximab (7 vs 19 months; BEV R vs L: 24.2 vs 31.4 months, CET R vs L: 16.7 vs 36.0 months).

These results, which are very consistent with data presented from the FIRE-3 trial about 2 years ago, raise important questions for clinical practice: Should EGFR mAbs ever be considered for right-sided cancers at all? If the answer is “no,” would this only be applicable to first-line therapy or include later lines, too? On the other hand, should EGFR mAbs be considered the biologics of choice for first-line therapy of left-sided cancers? In addition, what are the biologic reasons for the apparent poorer outcome and the lack of (or at least lower) activity of EGFR mAbs in right-sided colon cancers? It has long been known that right-sided cancers are characterized by a higher rate of BRAF V600E mutations, more frequent MSI-H status, older age, and female sex.
A single institution study explored additional molecular features like CIMP (methylation status), RAS mutations, as well as EGFR ligand expression levels, and found that when all these factors were put into a multivariate analysis, sidedness was no longer statistically significant for overall survival. The retrospective, non-randomized data could provide us a way forward to find a molecular explanation for the observed outcomes results, perhaps with added information from microbiome studies. Having said that, the simplicity of sidedness as a prognostic and conceivably predictive marker in addition to RAS, BRAF mutation and MSI testing makes it an attractive and readily available parameter to help guide clinical decision-making.

**Dr Philip**

The Alliance/SWOG 80405 study was further analyzed based on location of primary tumor. As a reminder, this Phase III trial in patients with metastatic colorectal cancer compared the overall survival of patients randomized to receive chemotherapy (mostly FOLFOX but also FOLFIRI) combined with either bevacizumab or cetuximab. Results were presented at ASCO 2014 and showed no difference in overall survival for patients treated with either biologic. Analysis of data showed right-sided tumors had a significantly worse survival (median survival 19.4 versus 33.3 months). Furthermore, the median survival of patients with left-sided tumors who received cetuximab was superior to that of those who received bevacizumab.

Schrag and colleagues used the Surveillance Epidemiology and End Results Program (SEER) to study sidedness of colon cancers in patients diagnosed between 2007 and 2011 and followed through 2013. Their findings confirmed the worse prognosis of right-sided colon tumors compared to left-sided and rectal cancers, and this difference persisted even after adjusting for differences in other clinical and demographic characteristics. The association between sidedness and prognosis was less consistent for Stage I and II cancers. Lee and colleagues retrospectively studied 198 KRAS wild-type metastatic CRC tumors for CIMP status and mutations in BRAF and RAS. They found that outcome on anti-EGFR therapy (PFS and OS) was influenced by primary tumor site. Furthermore, molecular analyses suggested that BRAF mutant, NRAS mutant, molecular subtypes and tumor methylation status accounted for this differential effect. This may provide some of the biologic explanation for the association of benefit from anti-EGFR therapy and sidedness. However, it is very likely that there are other molecular differences to account for this. In my practice I would always start off with bevacizumab when treating right-sided tumors. In the left side with data favoring use of anti-EGFR agents, I would present the patient who has RAS wild type tumor the option of chemotherapy plus either bevacizumab or anti-EGFR antibody. I will also include in my discussion issues of skin rash with anti-EGFR antibodies.

In those with left-sided tumors and borderline resectable metastatic disease who require a deeper response, I will consider an anti-EGFR agent up front. Ongoing analyses of the 80405 study are focusing on understanding the role of molecular subtypes of colorectal cancer in the discrepancies of outcome between right- and left-sided colon cancers. Future trials in metastatic colorectal cancer will be stratifying patients based on side of colon primary.
Dr Lenz

It remains unclear how to treat patients with resectable gastric cancer after neoadjuvant chemotherapy and successful resection. Postoperative chemotherapy or postoperative chemoradiation have shown survival benefit in patients with resected gastric cancer compared to surgery alone. High recurrence rates and poor survival with recurrence are significant clinical challenges. Verheij et al report their first results from a randomized Phase III trial testing whether chemotherapy or chemoradiation after neoadjuvant chemotherapy and adequate resection (D2) will lead to improved survival. Furthermore, toxicity of both treatment regimens was explored. Patients with Stage IB-IVA resectable gastric cancer were randomized after diagnosis.

Neoadjuvant CT was prescribed in both arms and consisted of 3 courses of epirubicin, cisplatin/oxaliplatin and capecitabine (ECC/EOC). After gastric cancer resection, patients received another 3 courses of ECC/EOC or CRT (45 Gy in 25 fractions combined with weekly cisplatin and daily capecitabine). The primary endpoint is OS. 788 patients from the Netherlands, Sweden and Denmark were randomized (393 CT; 395 CRT).

After a median follow-up of 50 months, 405 patients have died. The 5-year survival is 40.8% for CT and 40.9% for CRT ($p = 0.99$). Toxicity was mainly hematological (Grade 3 or higher: 44% vs 34%; $p = 0.01$) and gastrointestinal (Grade 3 or higher: 37% vs 42%; $p = 0.14$) for CT and CRT.

These first data show that no significant difference in overall survival was found between postoperative chemotherapy and chemoradiotherapy for patients who received neoadjuvant chemotherapy. However, there was more hematological toxicity in the chemotherapy arm. For whether there are differences in local recurrence, we need to wait for updates from this trial.

Dr Grothey

The standard perioperative management of gastric cancer varies by geographic region worldwide. Most commonly, peri- or postoperative chemotherapy is utilized, in particular, in Europe and Asia, whereas in the United States some centers still adhere to postoperative radiochemotherapy based on a randomized Intergroup study published 15 years ago. In this study, however, the radicality of lymph node dissection did not represent current standards, which recommend a routine D2 resection. In addition, the main benefit of postoperative radio-chemotherapy was in reducing locoregional but
not distant metastatic recurrences. A few studies have since then investigated the role of radiotherapy as a component of peri- or postoperative management of patients with resected gastric cancer.

The ARTIST trial published in 2011 randomized patients with D2 resected gastric cancer to adjuvant chemotherapy or radio-chemotherapy. No difference in DFS was noted, with the exception of patients with confirmed lymph node metastases, but since these results were obtained in a subgroup analysis, they were not considered definitive. At ASCO 2016, the CRITICS trial now revisited the question of adjuvant radiochemotherapy in a trial that used a perioperative treatment approach. About 50% of patients underwent a D1 lymph node dissection only. No difference in overall and progression-free survival was noted between the chemotherapy alone and the radiochemotherapy arm.

Outcomes data on the subgroup of patients with LN-positive disease are pending. In conclusion, the role of radiation therapy in the context of gastric cancer resection is not well established. The emphasis of peri- or postoperative therapy should lie on chemotherapy, conceivably with a fluoropyrimidine/platinum combination.

**Dr Philip**

The randomized Phase III CRITICS study investigated the debated role of chemo-radiotherapy after neoadjuvant chemotherapy and adequate gastric (D2) surgery. It included patients with Stage IB-IVA resectable gastric cancer (n = 788). Neoadjuvant chemotherapy consisted of 3 cycles of epirubicin, cisplatin/oxaliplatin and capecitabine (ECC/EOC). After resection, patients received 3 courses of ECC/EOC or CRT (45 Gy in 25 fractions combined with weekly cisplatin and daily capecitabine). Primary endpoint was overall survival. 83% completed 3 preoperative cycles. In the chemotherapy arm 47% and in the chemo-radiotherapy arm 52% completed treatment according to protocol.

The 5-year survival was 40.8% for chemotherapy and 40.9% for chemo-radiotherapy ($p = 0.99$). This study demonstrated that administration of combination perioperative chemotherapy for 6 cycles with a D2 dissection would make adjuvant chemo-radiotherapy unnecessary in patients with resectable gastric cancer. The requirement of a D2 resection in this study distinguishes it from the intergroup trial of McDonald et al, on which more than 50% of patients had D1 or less dissection. Chemo-radiotherapy may still be beneficial in certain subsets of patients, such as those who undergo suboptimal lymph node dissection (D1 or less).

At this time, research is focused on developing better systemic therapies using some of the newer agents, such as immune checkpoint inhibitors, in patients who have resectable gastric cancer.
Dr Lenz

Targeting cancer stem cells (CSC) is critical to improving outcomes in patients with metastatic disease since they represent the ultimate resistance to chemotherapy. BBI608, a CSC inhibitor that works through inhibiting Stat3, has shown potent synergistic anti-tumor and anti-metastatic activity with paclitaxel in vivo. By targeting Stat3, BBI608 blocks CSC self-renewal and survival through suppressing stemness pathways, including Stat3, β-catenin as well as immune checkpoint gene expression. Potent anti-tumor and anti-metastatic activity was observed in preclinical models, with marked synergy between BBI608 and paclitaxel.

In a Phase Ib dose escalation study in patients with advanced solid tumors, BBI608 + weekly paclitaxel was well tolerated. 46 patients with advanced, pre-treated gastric and gastro-esophageal junction (GEJ) adenocarcinoma were enrolled in a Phase Ib/II extension study to assess safety, tolerability, and preliminary anti-cancer activity.

The most common adverse events were diarrhea, abdominal cramps, nausea, and vomiting. In 16 patients who had not received a taxane in the metastatic setting, the per-protocol ORR was 31% (5/16) and DCR was 75% (12/16); median PFS was 20.6 wks and mOS was 39.3 wks. In 19 patients who failed a prior taxane (3 prior lines), per-protocol ORR was 11% (2/19), and DCR was 68% (13/19); mPFS was 12.6 wks and mOS was 33.1 wks.

In a subset of evaluated patients who received only 1 prior line of therapy without a taxane, the ORR was 50% (3/6) and the DCR was 83% (4/6). These data from this early clinical trial suggest that the CSC inhibitor BBI608 in combination with weekly paclitaxel was safe with promising efficacy data. On the basis of these data, a Phase III trial is being conducted in North America, South America, Europe, Australia, and Asia that will assess the efficacy of BBI608 + paclitaxel vs placebo + paclitaxel in patients with pre-treated, advanced gastric and GEJ adenocarcinoma (target n = 700). Primary endpoint is overall survival (OS) in the general study population. Interestingly, one of the secondary endpoints includes OS and PFS in a predefined biomarker (nuclear β-catenin)-positive sub-population.
Dr Grothey

BBI-608 (napabucasin) is a novel agent, a STAT3 inhibitor, that inhibits cancer stem cells and presumably also has immune modulatory properties. In preclinical studies it has shown synergistic activity when added to various chemotherapy backbones, including irinotecan and taxanes. In a Phase Ib/II second-/third-line study BBI-608 was combined with paclitaxel in 46 patients with metastatic gastric cancer, 26 of whom had shown prior progression on taxane therapy. In the 16 taxane-naïve patients, RR was 31% with a disease control rate (DCR) of 75%. RR and DCR in patients with progression on prior taxanes were 11% and 68%, respectively. Main toxicities were diarrhea and vomiting. These encouraging results led to the initiation of a worldwide Phase III registration trial (BRIGHTER), which compares paclitaxel as control arm to paclitaxel plus BBI-608 in second-line gastric cancer. The trial is more than halfway accrued and will hopefully confirm the efficacy of this innovative treatment approach.

Dr Philip

Becerra and colleagues studied BBI-608, a first-in-class cancer stemness inhibitor, in previously treated advanced gastric and GEJ cancers. This was the extension phase of a Phase Ib/II study. Patients must have received ≥1 line of prior treatment including a platinum + fluoropyrimidine/TS inhibitor. BBI-608 was administered orally at 480 mg or 500 mg twice daily with paclitaxel 80 mg/m² IV weekly 3 of every 4 weeks. 46 patients were enrolled, and most had received 2 or more lines of therapy. In 16 patients who were taxane naïve, objective response was 31% and DCR 75%. Median PFS and overall survival were 20.6 weeks and 39.3 weeks, respectively. In 19 patients who failed a prior taxane (median 3 prior lines), response was 11% and DCR was 68%.

In those patients, median PFS and overall survival were 12.6 weeks and 33.1 weeks, respectively. Common adverse events were Grade 1 to 2 diarrhea, abdominal pain, nausea, and vomiting. Grade 3 AEs included vomiting (9%), diarrhea of 5 days or longer (7%), fatigue (7%), and abdominal pain, nausea, dehydration (2% each). On the basis of these data, a Phase III trial is being conducted in in multiple countries to assess the efficacy of BBI-608 plus either paclitaxel or placebo in patients with advanced gastric and GEJ adenocarcinoma (projected n = 700). Patients must have failed 1 prior line of therapy containing a fluoropyrimidine/platinum doublet. Primary endpoint is overall survival.
Dr O’Reilly

To date, single agent gemcitabine is a standard adjuvant option for resected pancreas adenocarcinoma. The ESPAC-4 trial evaluated the addition of capecitabine to gemcitabine in an adjuvant setting. Eligibility included resected pancreas adenocarcinoma, either R0 or R1 within 12 weeks of surgery and WHO performance status of 0-2. Gemcitabine was given days 1, 8, 15 q4wk for 6 cycles, and capecitabine was dosed at 1,660 mg/m²/d for days 1-21 q4wk for 6 cycles. The statistical design called for a 10% improvement in 2-year survival. The trial results were recommended to be disclosed by the Data and Safety Monitoring Committee. Patients were randomized based on R0 and nodal status. Seven hundred and thirty patients were enrolled, primarily in the UK. Patient and disease characteristics were well balanced. The investigators reported a median OS of 25.5 months for the gemcitabine arm and 28 months for the combination arm, HR 0.82, p = 0.032. The estimated 5-year survival for gemcitabine was 16.3% and 28.8% for the combination arm. Analyses based on known prognostic factors favored the combination. The investigators concluded that gemcitabine combined with capecitabine represents the standard of care for resected pancreas adenocarcinoma.

The results reflect a real world experience for this combination and reflect an incremental gain for the addition of capecitabine to gemcitabine at an acceptable level of additional toxicity.

Nonetheless, several questions remain, including an understanding of what the relapse-free survival was (not reported), an understanding of the impact of subsequent therapies at recurrence (not reported) and an understanding of other factors contributing to outcome. For now, this new regimen represents a standard of care, and the results are in line with the activity of combination cytotoxic regimens in other pancreas cancer disease settings and displace the anomaly of single agent gemcitabine as a reference standard. Ongoing/recently completed trials are evaluating the addition of nab paclitaxel to gemcitabine compared to gemcitabine and mFOLFIRINOX compared to gemcitabine, results of which may further impact the standard of care.

Dr Hecht

Of the minority of patients with PDAC who are operable, most unfortunately succumb to recurrent disease. The ESPAC group has led several large trials in adjuvant pancre-
atic cancer, including the somewhat confusing ESPAC-1 trial demonstrating a small advantage to 5-FU and ESPAC-3 that showed that gemcitabine and 5-FU were equivalent but not that effective, though this is the standard of care. ESPAC-4 compared the combination of gemcitabine and capecitabine (GEMCAP) to gemcitabine alone in a large (n = 722) European, mostly British, adjuvant study reported at ASCO.

While the combination arm had more Grade 3/4 diarrhea, neutropenia and hand-foot syndrome, it was relatively well tolerated. Median overall survival was improved (28.0 vs 25.5 mo; HR 0.82, \( p = 0.032 \)). As the curves are still decreasing at the median, the 5-year survival is more important and was 28.8\% vs 16.3\% (\( p = 0.032 \)). This trial included both R0 (40\%) and R1 (60\%) patients, though there are differences in US and European definitions. In a subgroup analysis, there appeared to be more benefit in R0 patients.

This study establishes GEMCAP as the standard of care for resected pancreatic cancer patients, particularly those with R0 resections. It remains to be seen, however, how long this will last as these results are still poor and Phase III studies with regimens that appear more active in metastatic disease, such as gemcitabine/nab-paclitaxel, have already started or accrued. Furthermore, as in locally advanced pancreatic cancer, there is a trend towards neoadjuvant therapy, which offers the advantage of only operating on patients who remain non-metastatic and administering more chemotherapy because many adjuvant patients have adjuvant delay or no treatment at all due to postoperative complications and decreased performance status.

**Dr Bekaii-Saab**

The role of adjuvant chemotherapy in pancreas cancer is well established. The standard before the results of this study had been adjuvant gemcitabine, which doubled the 5-year survival of patients to more than 20\% (<10\% with surgery alone). The role of radiation therapy has been more controversial and in some cases detrimental, and most practices, including mine, do not include it in the treatment paradigm in this setting. ESPAC-4 is a large randomized Phase III study of gemcitabine + capecitabine compared to gemcitabine alone in patients with resected pancreatic ductal adenocarcinoma (PDAC). The survival on the experimental arm was 28 months vs 25.5 on the control arm (\( p = 0.032 \)). This translated into close to a 30\% 5-year OS with the addition of capecitabine to gemcitabine (GEMCAP). The regimen was fairly well tolerated, with predictable and reversible toxicities.

**Impact on Clinical Practice**

GEMCAP is the new standard of care for resected PDAC. The biggest challenge relates to the dosing strategy with capecitabine given at 1,660 mg/m\(^2\)/day x 21 days every 28 days. From our colorectal experience, US patients will require a lower dose than European counterparts. Since this is a potentially curative setting, my first few patients were placed on the dose as presented, with significant toxicities (HFS, GI toxicities and fatigue). More recent patients were placed on 1,300 mg/m\(^2\)/day x 21 days every 28 days, with significant improvement of the toxicity profile.

In 1 year from now, we will hear about the final results from APACT comparing gemcitabine and nab-paclitaxel to gemcitabine alone in the same patient population.
Depending on the results of this study, there may be different considerations about how to treat this group of patients.

**Dose modification and efficacy of nab-paclitaxel plus gemcitabine vs gemcitabine for patients with metastatic pancreatic cancer: Phase III MPACT trial**

Scheithauer W et al.
*J Gastrointest Oncol* 2016;7(3):469-78.

**Dr O’Reilly**

Scheithauer and colleagues report on a thoughtful post hoc exploratory analysis of dose intensity and cumulative dosing and the association of treatment exposure on efficacy in the MPACT Phase III trial evaluating the addition of nab paclitaxel to gemcitabine in untreated metastatic pancreas adenocarcinoma. The combination arm of nab paclitaxel and gemcitabine was statistically superior to gemcitabine alone with regard to OS, PFS and ORR in the MPACT study. Of the N = 421 patients who received gemcitabine and nab paclitaxel, 41% (N = 172) underwent a dose reduction and 71% (N = 300) experienced a dosing delay for nab paclitaxel.

Patients who underwent a dose modification of nab paclitaxel (typically due to neutropenia, thrombocytopenia, fatigue or neuropathy), compared to those who did not, had a greater treatment exposure, higher number of cycles delivered and greater cumulative dosing of nab paclitaxel. Notably, overall survival was greater (11.4 vs 6.9 months, HR 1.93, *p* < 0.0001) for patients who had a dose modification. Similarly, PFS and ORR were also improved. Comparable observations were seen in the gemcitabine-treated group.

These data are informative for clinical practice and provide a reassurance that dose reductions/delays for the major expected toxicities of myelosuppression, fatigue and neuropathy are appropriate and for a proportion of patients lead to better dose intensity and cumulative dosing and speculatively may provide the explanation for improved outcome over time.

**Dr Hecht**

The MPACT trial of gemcitabine/nab-paclitaxel established the regimen as a standard for the first-line treatment of pancreatic cancer and, in fact, it is the most commonly used multiagent regimen. This company-sponsored retrospective post hoc analysis examined efficacy in patients who had dose delays or reductions compared to those that did not. While studies in other malignancies treated with gemcitabine/nab-paclitaxel have not shown any difference, this study examined both the gemcitabine/nab-paclitaxel and gemcitabine arms. Improved survival in patients with dose delays/reductions was seen in both arms. It is unclear to me what this brings to the literature other than reassuring oncologists that there is no problem with standard recommended dose delays/reductions. A correlation between toxicity and efficacy has been seen in other cytotoxic as well as targeted therapies and may indicate differences in metabolism and higher drug levels or be a marker for immunological or other biological differences.
Dr Bekaii-Saab

Although effective, the combination of weekly gemcitabine and nab-paclitaxel is associated with significant cumulative toxicities and cost. The reported rates of Grade ≥3 neuropathy and/or neutropenia are 17% and 38%, respectively. In the MPACT trial, a large proportion of patients who received the combination of gemcitabine with nab-paclitaxel required a dose reduction (47% for gemcitabine dose and 41% for nab-paclitaxel dose) and 71% had a nab-paclitaxel dose delay. Interestingly (with the caveat of limitations in interpretation), patients with dose modifications did better in terms of their outcome than those with no dose reductions.

The cumulative dose in the dose-modified regimen was higher, which may be attributed to better overall tolerability or the fact that many patients in the non-modified group dropped earlier because of progressive disease.

Impact on Clinical Practice
This study suggests that most patients will require dose modifications that will lead to at least equally good if not improved outcome. Prior studies suggest patients receiving biweekly gemcitabine as a single agent or in combination may not lose efficacy while lessening treatment adverse effects, especially with decreased rates of hematologic toxicities (Heinemann et al 2006, Poplin et al 2009).

We recently published the results of our experience with biweekly gemcitabine and nab-paclitaxel in patients with PDAC (Ahn et al, Therapeutic Advances in Medical Oncology, in press). The median OS and PFS were 10 months and 5.4 months for patients who received the modified regimen as first-line therapy. Grade 3 neurotoxicity occurred in only 1.6% of patients. In my practice, all patients will receive the biweekly regimen of gemcitabine and nab-paclitaxel. The results from Scheithauer reinforce the value of the modification, although a prospective randomized trial is still required to confirm our findings.

FOLFIRINOX and gemcitabine/nab-paclitaxel efficacy in the treatment of locally advanced unresectable pancreatic adenocarcinoma


Dr O’Reilly

Bednar and colleagues evaluated outcomes for patients with locally advanced pancreas adenocarcinoma (LAPC) at the University of Pittsburgh treated with older vs newer regimens. One hundred and seven patients with LAPC treated between 2010 and 2014 were identified. For the overall cohort, the median age was 69 years and 51% were male. Fifteen patients received no therapy; N = 24 received older regimens (gemcitabine or 5-FU); N = 49 received FOLFIRINOX or gemcitabine/nab paclitaxel; N = 19 were downstaged following therapy and underwent surgery. The key observations were that for each of these groups survivals were 1.4, 11, 17.3 and 32 months respectively.
Notably, patients who received FOLFIRINOX or gemcitabine and nab paclitaxel had better outcomes compared to older regimens, and the investigators noted that patients who experienced a CA19-9 decline >50% had improved outcomes.

The results are interesting but limited by a single institution experience, non-randomized design and with all the inherent biases, including patient selection. Nonetheless, the observations are in line with the current interpretation that modern day combination cytotoxic regimens of FOLFIRINOX and gemcitabine and nab paclitaxel optimize outcomes in LAPC, and patients who are downstaged appear to have the best outcomes.

Additional studies are needed to define which is the best regimen and what is the added value of either radiation, chemoradiation or surgery added to optimal systemic therapy in LAPC.

**Dr Hecht**

This was a single institution retrospective series of 107 patients with locally advanced pancreatic cancer who were treated with no chemotherapy, “old chemotherapy” meaning 5-FU or gemcitabine, “new chemotherapy” meaning FOLFIRINOX or gemcitabine/nab-paclitaxel, or surgery. While survival increased from no therapy to old chemotherapy to new chemotherapy to surgery, this nonrandomized trial doesn’t tell us whether the intervention made the difference. Only the upcoming randomized trials in neoadjuvant, adjuvant, borderline resectable and locally advanced disease that are being done worldwide will answer these questions.

**Dr Bekaii-Saab**

Overall, this study reinforces the findings from the Suker study. The impact on clinical practice is similar as well.

**FOLFIRINOX for locally advanced pancreatic cancer: A systematic review and patient-level meta-analysis**


**Dr O’Reilly**

About 30%-35% of patients present with locally advanced pancreas adenocarcinoma (LAPC). There are limited prospective randomized data sets from current modern day cytotoxic regimens that define outcomes. Suker and colleagues conducted a meta-analysis of 13 trials with 689 patients, of which 355 (52%) received FOLFIRINOX in the setting of LAPC (non-uniform definitions between studies). Most of these studies were non-randomized and retrospective in design. The overall survivals per study ranged from 10 to 32.7 months, with the median being 24.2 months. Progression-free survival ranged from 3 to 20 months, with the median being 15 months. Across 10 trials with 490 patients, radiation therapy was utilized in 64%. The pooled proportion of patients who underwent resection was 26%, of which 74% had an R0 resection.
These data support a high level of activity for FOLFIRINOX in this good performance patient population with LAPC. The impact of radiation therapy, chemoradiation therapy and surgery following FOLFIRINOX in the setting of locally advanced disease remains to be defined, along with the comparative value with respect to single agent gemcitabine. An ongoing randomized Phase III trial in Europe (NCT02539537; PRODIGE 29) is evaluating the activity of FOLFIRINOX compared to gemcitabine in N = 170 patients, with a primary endpoint of progression-free survival.

Dr Hecht

While few patients with pancreatic cancer have operable disease, 30%-40% present with locally advanced unresectable disease. Locally advanced pancreatic cancer (LAPC) is defined by vascular involvement seen on imaging that would preclude an R0 resection in the absence of metastatic disease. LAPC may be different genetically from pancreatic cancer that presents with metastatic disease. In the PRODIGE 4/ACCORD 11 trial, Conroy et al showed that FOLFIRINOX improved median survival in a cohort of mostly metastatic pancreatic cancer compared to the then-standard gemcitabine alone (11.1 vs 6.8 mo). To examine the activity of FOLFIRINOX in a larger group of patients with LAPC, this meta-analysis reviews 13 mostly retrospective FOLFIRINOX studies with 355 LAPC patients, 315 of whom have patient level records available to examine outcome.

With the caveats of meta-analysis of retrospective studies the median OS in LAPC was a robust 24.2 months. That being said, it is unclear how these patients were chosen to receive FOLFIRINOX. 57% of these patients had later radiotherapy, indicating that the tumors may have remained locally dominant, though the role of radiotherapy in this disease is controversial. Interestingly, 91/325 patients ended up going for resection and 60 of 81 that recorded resection outcomes had an R0 resection.

In our practice, fit patients with borderline or locally advanced disease usually receive FOLFIRINOX if surgery is ever contemplated. There are multiple ongoing trials looking at FOLFIRINOX in this setting, which should give more concrete data, but many questions remain. These include choice of chemotherapy for these patients (vs gemcitabine/nab-paclitaxel), best dosing of FOLFIRINOX, how do we image patients to determine resectability on treatment and after treatment and do LAPC patients who are downstaged benefit long term from surgery?

Dr Bekaii-Saab

Pancreas cancer remains extremely challenging with almost all patients, including those with early stage disease, dying from progressive or new disease. Most patients will present with metastatic disease, and close to 20%-25% will present with locally advanced pancreas cancer (LAPC). There have been a number of retrospective studies suggesting that various modified regimens of FOLFIRINOX may be relatively safe and effective in the treatment of Stage III pancreas cancer. This is a meta-analysis of 11 studies with a total of 315 patients included. In the pooled analysis mOS was found to be 24.2 months while mPFS was 15 months. Most interestingly, for the pooled group of patients 25.9% of patients had resection with 78.4% having R0 resection.
These results are very interesting and suggest that in a disease that is overwhelmingly lethal, a multidisciplinary aggressive approach may improve outcome. We had previously published our experience in a similar setting with very consistent results (Blazer et al, Ann Surg Oncol 2015;22(4):1153-9). These results, although very interesting, continue to be limited by their retrospective nature and the potential for strong selection bias in this group of patients. Many questions remain unanswered, including the following: 1) Do we need FOLFIRINOX or would a doublet such as gemcitabine + nab-paclitaxel offer a less toxic and equally effective approach? This gains further relevance as we look at integrating biologic questions to build on chemotherapy platforms. 2) Who is a candidate for radiotherapy? Do we need radiotherapy to improve outcome in a disease where this modality is likely non-beneficial for most patients? Finally, in a non-curative setting, does resection improve outcome in those patients who convert to resectable? Some of these questions (except for the resection question) will be answered by several prospective analyses under way through the cooperative groups or clinical research consortia.

Impact on Clinical Practice
All patients with LAPC should be considered for multidisciplinary evaluation assessing the role of radiation, surgical resection and choice of chemotherapy. At this point, all patients under 70 yo with PS of <2 will be considered for mFOLFIRINOX for 2-3 months. For all other patients (>70 and/or borderline PS), I would consider gemcitabine + nab-paclitaxel (biweekly regimen). Radiation is considered on a case-by-case basis in discussion with the multidisciplinary team and will only be delivered if there is concern that an R0 resection is unlikely to be achieved. All patients eligible for resection are encouraged to go to surgery. The results of prospective analyses will likely be available over the next few years.

Dr O’Reilly
The NAPOLI-1 trial evaluated, in a 3-arm design, the comparative value of liposomal irinotecan combined with infusional 5-FU and leucovorin compared to infusional 5-FU/LV and to single agent liposomal irinotecan in gemcitabine-pre-treated pancreas adenocarcinoma. Gemcitabine could have been administered in an adjuvant, neoadjuvant or metastatic disease setting. The primary endpoint was overall survival. A total of N = 417 patients were enrolled in Asia, Europe and the US. The triple drug combination (liposomal irinotecan, infusional 5-FU and leucovorin) compared to infusional 5-FU/LV showed a statistically significant improvement in overall survival (6.1 vs 4.2 months, HR 0.67, p = 0.012), progression-free survival and tumor response.

Single agent liposomal irinotecan did not show a benefit over infusional 5-FU/LV. Major toxicities related to liposomal irinotecan included neutropenia, diarrhea, fatigue and vomiting. The results of the NAPOLI-1 trial led to the FDA approval of the combina-
tion of liposomal irinotecan, infusional 5-FU and leucovorin in gemcitabine-pre-treated pancreas adenocarcinoma.

The results of this trial are not unexpected in that irinotecan has previously demonstrated single-agent and combination activity in pancreas cancer. Nano-liposomal irinotecan is being integrated in later lines of therapy, and an ongoing Phase I/II trial is evaluating the safety combined with oxaliplatin/5-FU and comparative effectiveness of the triplet combination compared to gemcitabine and nab paclitaxel in a front-line setting.

**Dr Hecht**

Unfortunately, for many patients with pancreatic ductal adenocarcinoma (PDAC) who progress on first-line therapy, second-line treatment is not possible due to declining performance status. With the advent of newer multiagent regimens such as FOLFIRINOX and gemcitabine/nab-paclitaxel, however, the number eligible is increasing. The second-line treatment has generally contained a fluoropyrimidine, though there have not been many trials. In CONKO-003 Oettle and colleagues showed that OFF (a German 5-FU and oxaliplatin with weekly 5-FU 4 of 6 weeks) was better than 5-FU (5.9 vs 3.3 mo, hazard ratio [HR] = 0.66, \( p = 0.010 \)). Nanoliposomal irinotecan (nal-IRI) was developed in an attempt to improve the efficacy and toxicity of irinotecan. NAPOLI-1 was an international trial originally designed to compare nal-IRI with 5-FU/LV in patients who had failed gemcitabine-based therapy; however, a third arm was added shortly after starting, combining nal-IRI with 5-FU/LV.

Adding nal-IRI to 5-FU/LV significantly increased toxicity, particularly diarrhea, nausea, fatigue and neutropenia, though there was no decrease in QoL. Despite this increase in toxicity, there was a statistically and clinically significant improvement in OS (6.1 vs 4.2 mo; HR 0.67, \( p = 0.012 \)). Single agent nal-IRI had no improvement compared to 5-FU/LV (4.9 vs 4.2 mo; HR 0.99, \( p = 0.94 \)). These results led to the recent FDA approval of nal-IRI only in combination with 5-FU/LV for patients who progressed on gemcitabine-containing regimens.

These modest results lead to a number of questions. While nal-IRI + 5-FU/LV is better than 5-FU/LV, is it better than the less expensive FOLFOX regimen? The small Canadian PANCREOX trial was just published with the unexpected results of 5-FU/LV doing better than FOLFOX as well as every other arm in any second-line trial (OS 9.9 vs 6.1 mo). What about patients who previously used irinotecan? They were included but there were relatively few. The use of nal-IRI in first-line regimens and adjuvant therapy is already being explored. Finally, is there any way to choose the best chemotherapy? UGT1A1*28, a marker of irinotecan toxicity, was tested but was rare.

**Dr Bekaii-Saab**

PDAC is a universally lethal disease with very few therapeutic options available. Prior to this study, there were 2 options for treatment in the first line with established standards following first line failure. Patients who receive FOLFIRINOX first line would receive gemcitabine +/- agent X (determined by PS, residual neurotoxicity, etc). For those who receive gemcitabine and nab-paclitaxel first line, options include 5FU +/- oxaliplatin or irinotecan (determined by PS, residual neurotoxicity etc). Two recent studies (CONKO...
and PANCREOX) suggested conflicting reports regarding the benefit from oxaliplatin and 5FU following gemcitabine failure in PDAC, eventually limiting the option of using FOLFOX in refractory disease.

On the other hand, the NAPOLI-1 trial suggested a survival benefit to nano-liposomal irinotecan (Nal-Iri) when added to 5FU (FOLFONI) when compared to 5FU alone. Interestingly, in a setting where ORR is typically less than 5%, the combination had a reported 16% response rate (vs 1% in the 5FU arm). The toxicities were predictable and overall the regimen was tolerable. As such, Nal-Iri + 5FU is a welcome addition to a setting where no validated options exist. The caveat, however, is that this option will only apply to patients who failed gemcitabine + nab-paclitaxel in first line. There is no data to suggest that a nano-liposomal formulation of irinotecan will have activity in patients with prior exposure to irinotecan-based regimens (such as FOLFIRINOX). A follow-up study is currently looking at the benefits of Nal-Iri combined with 5FU +/- oxaliplatin vs gemcitabine and nab-paclitaxel in first line PDAC.

Impact on Clinical Practice
For patients with newly diagnosed PDAC, there are 2 options available. The first option is to start with mFOLFIRINOX. Fifteen percent or fewer patients may be eligible for this more toxic approach. I call this the “kitchen sink approach,” leaving very few options for salvage, with none having validated data. The other option, which I strongly favor, allows for a sequencing approach consistent with therapeutic strategies across the cancer care spectrum.

This option includes gemcitabine and nab-paclitaxel (biweekly) in the first line followed by FOLFONI upon progression. In my view, the latter strategy allows for an equally effective approach with significantly improved tolerability (and non-overlapping toxicities, mainly neurotoxicity). It also allows for a more rational platform for drug development.

Safety and activity of nivolumab monotherapy in advanced and metastatic (A/M) gastric or gastroesophageal junction cancer (GC/GEC): Results from the CheckMate-032 study

Le DT et al.

Dr O’Reilly
The CheckMate 032 trial evaluated (1) nivolumab single agent (3 mg/kg), (2) nivolumab 1/ipilimumab 1, (3) nivolumab 1/ipilimumab 3 and (4) nivolumab 3/ipilimumab 1 in patients with previously treated esophagealgastric cancers. Data on cohort of N = 59 patients treated with nivolumab 3 mg/kg q2wk were presented. Median age 60 years and 76% were male. Seventy-one percent had received 2-3 lines of prior therapy. Fifty-three percent had a primary in GE junction. The median number of doses of nivolumab = 5. The primary endpoint was objective response. Eight of 59 (14%) had an objective response (12% PR, 2% CR) and median duration of response was 7 months. One-year survival was 36%. PD-L1 positivity (≥1% and ≥5%) was associated with higher response rate.
Grade 3-4 AEs were identified in 10 (17%). Single agent nivolumab demonstrated activity in previously treated esophagogastric cancers with some durable responses at an acceptable rate of Grade 3-4 toxicity. A combined analysis of the KEYNOTE-012 and CheckMate 032 trials reports relatively similar activity for each of the 2 main PD-1 inhibitors in esophagogastric malignancies.

Additional analyses from the CheckMate 032 trial will report on the combination of PD-1 and anti-CTLA-4 agents in varying doses. The next several years will more fully define the role of checkpoint inhibitors in esophagogastric malignancies alone, with insight on doses and schedules, other combinations and disease settings.

**Dr Hecht**

CheckMate-032 is a Phase I/II trial with nivolumab and ipilimumab and reports only the nivolumab monotherapy arm. Fifty-nine gastric and gastroesophageal cancer patients were enrolled unselected by PD-L1 status and received nivolumab 3 mg/kg every 2 weeks. As in the KEYNOTE-012 trial, the treatment was well tolerated and toxicities were as expected with most being Grade 1/2. Overall 8 out of 59 patients or 14% (6%-25%) responded, with 1 CR noted. As was seen in the KEYNOTE-012 trial, responses were durable with a median duration of response of 7.1 months, and 4 patients remain on treatment. While the response rate is numerically lower than that seen in the pembrolizumab trial, the patient population was different, enrolling both PD-L1 positive and negative patients.

Of note, responses were seen in both groups regardless of whether a 1% or 5% staining cutoff was used, though the response rates were higher in PD-L1 positive patients (up to 33% in PD-L1 ≥5% positive patients). Unfortunately, despite Dr Le being the first author, she did not report how many of these patients had microsatellite instability.

These results corroborate the activity of anti-PD-1 antibodies in upper GI adenocarcinomas and reinforce the need for additional work on biomarkers to help determine who will benefit, as it is unclear to me from these results that we should exclude PD-L1 negative patients from trials and treatment. As with pembrolizumab, combinations with chemotherapy and immunotherapy are being explored.

**Dr Bekaii-Saab**

CheckMate 032 is a 4 arm study that included nivolumab either as monotherapy or in combination with ipilimumab. Le et al present here the nivolumab monotherapy arm results in patients with advanced gastric cancer. The results of this study were historically less impressive than KEYNOTE-012, perhaps partially explained by the fact that 100% of patients were pretreated and the authors included both PD-L1-positive and negative patients on CheckMate 032. Nonetheless, this study confirms the continued interest in developing further PD-1 inhibitors in gastric cancer. Additionally, the question of how to best select patients who would optimally respond to this group of agents remains unclear given that PD-L1-negative tumors responded to nivolumab on this study.
Impact on clinical practice is similar to the KEYNOTE-012 study, and I personally have no clear preference between the 2 PD-1 inhibitors, although given the recent results in lung cancer, I may lean more towards pembrolizumab.

### Pembrolizumab for patients with PD-L1-positive advanced gastric cancer (KEYNOTE-012): A multicentre, open-label, phase 1b trial

Muro K et al.

**Dr O’Reilly**

The KEYNOTE-012 trial evaluated pembrolizumab (10 mg/kg q2wk) in previously treated gastric/GE junction cancers. Eligibility required PD-L1+ (>1% in tumor cells, immune cells or both). N = 39 evaluable (24% of screened); 40% PD-L1-positive. 63% >2 lines of therapy. Primary endpoints: Safety and overall response rates. 8 (22%) had objective response and 5 (13%) had Grade 3-4 AEs. Median duration of response was >40 weeks, with 4 (11%) patients not having progression at time of analysis. Activity was similar in Asian and non-Asian patients. Only 50% of responses were accounted for by MSI-H (approx 22% of all gastric cancers). This trial demonstrates an early signal of activity of PD-1 inhibitors in gastric and GE junction cancers.

The value of the choice of PD-L1 as a biomarker for therapy selection remains a subject of ongoing investigation. Multiple ongoing trials are evaluating checkpoint inhibitors in esophagogastric malignancies: (1) activity in 1st, 2nd and 3rd line settings, (2) role in combination with chemotherapy, (3) role in the adjuvant setting and (4) role of combination of PD-1 and anti-CTLA-4 agents.

**Dr Hecht**

Gastric cancer has a number of biological characteristics, such as a relatively high number of mutations, a large percentage of patients with microsatellite unstable tumors and a subset of patients who have EBV infection and high expression of PD-L1, which may indicate sensitivity to immunotherapy with checkpoint inhibitors. The Phase Ib KEYNOTE-012 trial was the first report of an anti-PD-1 in upper GI tumors. The study enrolled 39 gastric and gastroesophageal adenocarcinoma patients split relatively evenly between Asian and Western subjects using a prototype assay to detect PD-L1 staining (≥1% of cells positive or inflammatory cells at the interface between neoplastic cells and stroma). Approximately 40% of tumors screened were positive by this assay.

The patients were treated with 10 mg/kg of pembrolizumab every 2 weeks. The primary endpoint of the study was response rate, but other clinical endpoints were recorded as well as correlative studies. The treatment was generally well tolerated with expected immune-related toxicities, mostly Grade 1 or 2. About half of the 36 patients with tumors evaluable for response had some tumor regression. Response rate by central review was 22% (10%-39%), all PRs. While median PFS was only 1.9 months (1.8-3.5), what was more interesting was that, as seen in melanoma and lung anti-PD-1 trials, some of the responses were durable, with a median DOR of 40 weeks with 4
ongoing. The authors looked at correlative markers to try to identify those patients most likely to respond. Responses were similar in Asian and non-Asian patients. Four patients had microsatellite instability-high gastric cancer and of those 2 responded. There was no clear correlation with response and the second-generation clinical trial assay, but there was a trend to correlation with an interferon y gene signature from melanoma trials. Tumors were not tested for EBV.

The trial is groundbreaking as it is the first immunotherapy study to show clinical benefit in gastric/gastroesophageal adenocarcinoma. That being said, it leaves a large number of questions to be answered before we can successfully integrate anti-PD-L1 therapy into clinical practice. The first question is how to identify patients who may benefit from such therapy. All patients in this trial were PD-L1 positive by the prototype assay. We also don’t know whether patients who are PD-L1 negative by any of these assays may potentially benefit. This problem was recently brought into focus in the recently reported negative nivolumab trial in unselected lung cancer patients. It is also reassuring that Asian and non-Asian patients appear to have similar outcomes. The fact that MSI patients have a high response rate is consistent with the recent reports, but more importantly, responses were seen in MSS patients. This study has led to a large number of studies of anti-PD-1 and PD-L1 antibodies alone and in combination with standard therapies and immunotherapy in all lines of therapy, including maintenance. It is hoped that these large studies will help determine in whom and how to use the drugs in gastric cancer.

Dr Bekaii-Saab

The prognosis for patients with advanced gastric cancer remains very poor. In KEYNOTE-012, patients selected based on PD-L1 expression were treated with pembrolizumab, an anti-PD-1 antibody. Pembrolizumab on this study was administered at a dose of 10 mg/kg every 2 weeks until progression or toxicity. Patients had scans repeated every 8 weeks for assessment of response. Only 40% of patients initially screened for PD-L1 were found to be positive. From those enrolled on the study, 22% had a partial response with a total of 53% showing evidence of tumor regression. More importantly, these responses were durable, with a median DOR of 40 weeks. Toxicities were predictable and tolerable.

This study provides very intriguing results in a patient population with gastric adenocarcinoma that typically has a very poor outcome, and more so in patients who had progressed on chemotherapy (85% with ≥1 line of chemo on KEYNOTE-012). Nonetheless, many questions remain, starting with the validity of the selection of patients who only expressed PD-L1 on the study. Muro et al report that reassessment of PD-L1 expression found that it only matters if expressed on immune cells and not as much when expressed on tumor cells (the criteria for allowance on study was expression on immune cells and/or tumor cells).

Additionally, repeat testing in 35 patients suggested patients were PD-L1 negative although they seemed to respond to pembrolizumab. To complicate matters further, a recent genomic analysis suggests that 2 groups of gastric cancer patients who are in the setting of either MSI or EBV include >30% of all patients afflicted with this disease.
This may explain some but not all of the observed activity, adding to the uncertainty of how to optimally select patients for pembrolizumab in gastric cancer.

**Impact on Clinical Practice**
At this time it is unclear what role pembrolizumab will have in the treatment of gastric cancer. This study is small, and although intriguing in terms of outcome it does not seem to be superior to other standard therapies in refractory disease. Studies exploring its role in addition to or against SOC in this group of patients are underway. It is also unclear how to optimally select patients who are eligible for this therapy, pending more research. In clinic, I only use PD-1 inhibitors once all standard therapies have been exhausted and no clinical trials are available. My preference is not to select according to PD-L1 expression until more validation is available.

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**Updated results for the advanced esophageal carcinoma cohort of the phase Ib KEYNOTE-028 study of pembrolizumab (MK-3475)**

Doi T et al.
Gastrointestinal Cancers Symposium 2016;Abstract 7.

**Dr O’Reilly**
The KEYNOTE-028 Phase Ib trial evaluated the activity of pembrolizumab 10 mg/kg IV q2wk in previously treated esophageal cancer patients with PD-L1 positivity. Ninety patients were screened, of which 37 (45%) had PD-L1 positivity (≥1% in tumor cells, immune cells or both). Twenty-three patients were treated, with a median age of 65 years, ECOG PS 1, 65% and prior therapy of 2 lines in 39% and ≥3 lines in 48%. Seventeen (74%) had squamous cell cancers and 5 (22%) had adenocarcinoma. The objective response rate (primary endpoint) was 30% (N = 7), of which 5 (29%) occurred in squamous cancers and 2 (40%) in adenocarcinomas. The median time to response was 3.7 months and the median duration of response was not reached at time of analysis.

Grade 3 AEs occurred in 4 (17%). The investigators also evaluated an interferon 6-gene expression signature (IDO, CXCL10 and 9, HLA-DRA, STAT1, IFN-gamma) and, similar to gastric and head and neck malignancies, observed a correlation with higher response activity in patients with a higher immune gene signature score. In esophageal cancers the KEYNOTE 180 trial is evaluating the role of single agent pembrolizumab in N = 100 patients and the KEYNOTE 181 trial is evaluating single agent pembrolizumab vs chemotherapy (taxane or irinotecan) in N = 600 patients in a 2nd-line setting.

**Dr Hecht**
The KEYNOTE-028 trial was similar to the KEYNOTE-012 trial, though it only enrolled esophageal and gastroesophageal patients, most heavily pretreated. Almost ¾ of the patients had squamous cell carcinoma, which was excluded from the previous 2 trials and is biologically and epidemiologically quite different from gastric adenocarcinoma. Patients were screened with the same PD-L1 assay used in KEYNOTE-012, and 45% were positive with 23 patients being enrolled. Patients were treated with pembrolizumab 10 mg/kg every other week. Typical PD-1 toxicities were seen, generally Grade
1 or 2. Seven of 23 patients, or 30% (13%-53%), had responses, which as in the other trials were durable, with median DOR not reached (5.5-11.8+ months), and 4 patients remain on study. Responses were seen in both squamous and adenocarcinomas.

This study is important as it adds squamous cell carcinoma of the esophagus to the list of tumors that may respond to anti-PD-1 therapy. The same questions regarding biomarkers to choose patients for therapy remain, however, and only PD-L1+ patients were entered. The same 6-gene interferon γ signature of tumor inflammation derived from Ribas’ melanoma trial appeared to correlate with response, but the numbers are quite small. This disease has a poor outcome, and while squamous cell esophageal cancer has been declining in the West, it remains a significant problem in non-Western countries, particularly in Asia. As above, larger trials are ongoing.

Dr Bekaii-Saab
KEYNOTE-028 is a study of pembrolizumab with a similar design to that of KEYNOTE-012, with a focus on esophageal cancer. The study included PD-L1+ patients (criteria similar to K012) with squamous cell carcinoma (74%) or adenocarcinoma of the esophagus (22%). There was 1 patient with mucoepidermoid cancer. Ninety-six percent of all patients had prior exposure to chemotherapy. Therapy was well tolerated and activity was again intriguing with a 30% ORR, 52% tumor shrinkage rate and a median DOR not yet reached.

Impact on Clinical Practice
Similar to K012, it is unclear what role pembrolizumab will have in the treatment of esophageal cancer. This study is small. Studies exploring its role in addition to or against SOC in this group of patients are under way. It is also unclear how to optimally select patients who are eligible for this therapy, pending more research. In clinic, I only use PD-1 inhibitors once all standard therapies have been exhausted and no clinical trials are available. My preference is not to select according to PD-L1 expression until more validation is available. Given the recent lung cancer results, I am leaning more on pembrolizumab.

Hepatocellular Cancer

**Efficacy and safety of regorafenib versus placebo in patients with hepatocellular carcinoma progressing on sorafenib: Results of the international, randomized phase 3 RESORCE trial**

Bruix J et al. 
*Proc ESMO World Congress on Gastrointestinal Cancer 2016;Abstract LBA03.*

Dr O’Reilly
The Phase III RESORCE trial evaluated the role of regorafenib following progression of disease on sorafenib in advanced hepatocellular cancer, a setting for which there is no currently accepted treatment standard. Eligibility included good functional status and progression of disease on sorafenib as defined by dosing ≥400 mg for ≥20 days.
Randomization was in a 2:1 ratio of regorafenib 160 mg days 1-21 q4wk or placebo. Patients were stratified based on geography, performance status, AFP level, extra-hepatic disease and vascular invasion. Five hundred and seventy-three patients were enrolled: regorafenib N = 379 and placebo N = 194. For the whole cohort, the median age was 63 years and 88% were male.

The primary endpoint of median OS for the regorafenib patients was 10.6 vs 7.8 months for the placebo patients, HR 0.62, p < 0.001. Additionally, median PFS (3.1 vs 1.5 months) and ORR (10.6% vs 4.1%) favored regorafenib. Key expected side effects in the regorafenib patients included hypertension, fatigue, hand-foot symptoms and diarrhea.

The authors concluded that regorafenib resulted in a statistically significant and clinically meaningful survival compared to placebo in patients previously treated with sorafenib. The results are interesting and somewhat unexpected, and further elucidation of the sorafenib cohort is needed to put these results in context.

Nonetheless, demonstration of an objective response rate and survival improvement in a second-line setting is noteworthy, and further studies will be required to understand where regorafenib best fits in this disease and in particular where to position it with regard to the emerging role of checkpoint inhibitors in HCC.

**Dr Hecht**

There has been only one drug approved for the treatment of advanced HCC, sorafenib. Multiple trials in the first- and second-line setting with different classes of agents have been negative. Based on Phase II data, the Phase III RESORCE trial was performed in second-line HCC patients comparing regorafenib to the standard of care and placebo. The regorafenib group had a 38% reduction in the risk of death (HR 0.62; 95% CI 0.50-0.78; p < 0.001); median OS (regorafenib vs placebo) was 10.6 vs 7.8 months. RR was 11% vs 4%, surprising considering the chemical similarity between sorafenib and regorafenib. Treatment did increase Grade 3/4 toxicity, particularly expected side effects such as hypertension (15.2% vs 4.7%), hand-foot skin reaction (12.6% vs 0.5%), fatigue (9.1% vs 4.7%), and diarrhea (3.2% vs 0%).

This trial changes the standard of care for second-line treatment for HCC, and we hope that there are swift agency approvals. Unanswered questions include patient selection, dosing as most patients do not tolerate the full 160-mg/day dosing and whether regorafenib should be looked at in first-line HCC. Finally, in the setting of strong results with anti-PD-1 antibodies noted above, sequencing and combination studies need to be done.

**Dr Bekaii-Saab**

Patients with advanced HCC have only 1 option available to them in first line treatment, sorafenib, with only modest improvement in outcome (OS <11 mo). There are no second line options with all Phase III studies conducted so far showing negative results. Regorafenib is a multikinase inhibitor with activity across a spectrum of cancers and with promising preliminary results in second line HCC. The RESORCE study is a Phase
III randomized study with regorafenib (160 mg PO qd x 21 days /28 days) vs placebo in patients with HCC who progressed on sorafenib. mOS for regorafenib was 10.6 months vs 7.8 months in the placebo arm ($p < 0.001$).

mPFS was 3.1 months for regorafenib vs 1.5 months for placebo ($p < 0.001$). Response rate was 10.6% (mRECIST) and 6.6% (RECIST 1.1) for regorafenib, which is relatively intriguing in this setting and with this class of agents. AEs were relatively manageable.

**Impact on Clinical Practice**
Regorafenib is the new standard of care for advanced HCC patients who have progressed on sorafenib. The biggest challenge relates to the dosing strategy that is being assessed by the REDOS study (in mCRC). In the meantime, I would favor the standard 160 mg PO qd as a starting dose. Although not in planning, it would be interesting to examine the role of regorafenib in the first line setting. This agent succeeded where similar agents failed (sunitinib, linifanib, brivanib, etc), suggesting that there may be off targets specific to regorafenib.

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**Phase I/II safety and antitumor activity of nivolumab (nivo) in patients (pts) with advanced hepatocellular carcinoma (HCC): Interim analysis of the CheckMate-040 dose escalation study**

**Safety and antitumor activity of nivolumab (nivo) in patients (pts) with advanced hepatocellular carcinoma (HCC): Interim analysis of dose-expansion cohorts from the phase 1/2 CheckMate-040 study**

**A randomized, multicenter, phase 3 study of nivolumab vs sorafenib as first-line treatment in patients (pts) with advanced hepatocellular carcinoma (HCC): CheckMate-459**


**Dr O’Reilly**
The CheckMate 040 trial evaluated the safety and preliminary efficacy of nivolumab in hepatocellular carcinoma (HCC). The trial was conducted in 2 phases: in a dose escalation phase in virus-negative, HCV-positive and HBV-positive HCC, $N = 48$ patients, and a dose expansion phase involving $N = 214$ patients to further define the safety and efficacy. For the whole cohort the median age was 64 years, 80% were male and 47% were Asian. The recommended Phase II dose of nivolumab for all patients with HCC was 3 mg/kg q3wk. The major AEs were rash and pruritus, elevation of liver function tests (AST, ALT) and amylase. These latter side effects occurred at similar rates with HCC compared to other solid tumor patients.
In the dose expansion phase of N = 214, antitumor activity was observed in all groups, virus infected versus not and with/without PD-L1 positivity. Specifically, 35/214 (16%) had an objective response and the 9-month overall survival was 71%. The investigators concluded that nivolumab was safe and the level of oncologic activity was worthy of further evaluation. An ongoing Phase III trial, CheckMate 459, is evaluating the efficacy of nivolumab compared to sorafenib in untreated advanced HCC (N = 726). The primary endpoints are time to progression and overall survival. Other objectives include ORR, PFS and PD-L1 expression and outcome and quality of life analyses.

Dr Hecht

Hepatocellular carcinoma has a number of characteristics that would make it a potential target for immunotherapy. Most HCCs are associated with viral infection, some with viral integration. PD-L1 and -L2 expression has been associated with worse outcome after surgery.

These 2 abstracts report results from the CheckMate-040 trial with the anti-PD-1 antibody nivolumab. The first part was a dose escalation phase initially presented by El-Khoueiry in 2015, now updated. In this 48-patient study 3 CRs and 4 PRs were noted, one still ongoing. As liver failure is a competing cause of death in these patients with liver inflammation, safety is particularly important. The treatment was relatively well tolerated with some increase in LFTs, though all patients had a Child-Pugh score of 6 or less. The second abstract presents data from the large dose expansion phase that looked at 214 patients with sorafenib naïve, non-infected sorafenib progressing, HBV and HCV related HCCs. Tumor regression was seen in all groups, and 35 patients (16%) had responses, 30 of which are ongoing. Response rates were similar among groups, though perhaps slightly lower in HBV patients. Once again treatment was relatively safe and there did not seem to be a correlation between response and PD-L1 staining.

These results combined with anecdotal responses to other PD-1 inhibitors are truly groundbreaking considering that the only approved agent, sorafenib, has a RR of 2%, generally fairly short-lived. If the responses, which we have also seen, prove durable, this should be the new standard in HCC. Once again, there are no useful biomarkers and combinations with other standard treatments and immune therapies may improve RR. Also, safety in patients with higher Child-Pugh scores needs to be established. A Phase III trial discussed as a trial in progress is under way comparing nivolumab and sorafenib in first-line therapy as well as a second-line pembrolizumab trial.

Dr Bekaii-Saab

Patients with advanced HCC have only 1 option available to them in first line treatment, sorafenib, with only modest improvement in outcome (OS <11 mo) at the expense of significant toxicities. Given the strong rationale for immunotherapy in this disease, the role of PD-1 and PD-L1 inhibitors in HCC needs to be explored. CheckMate 040 is a Phase I/II study of nivolumab (Nivo) in patients with advanced HCC, with a dose escalation cohort analysis followed by an expansion phase analysis. In the dose escalation phase (N = 48), Nivo showed manageable toxicity with a disease control rate of 65%,
including 1 CR and 4 PR. The median OS was 15.1 months, which compares favorably to historical controls. Outcome was independent of viral infection.

The dose expansion cohorts at 3 mg/kg enrolled 214 patients. Four cohorts included uninfected sorafenib naïve/intolerant, uninfected sorafenib failure, HCV infected and HBV infected. AEs were consistent with expectations. ORR was 16% and did not seem to correlate with PD-L1 expression, with prior therapy or with infection vs no infection. It was too early to predict mOS. The study results were relatively interesting but worth exploring further with a follow-up randomized trial. CheckMate 459 is a Phase III trial of Nivo vs sorafenib in patients as first line treatment of HCC. Other smaller trials are exploring the role of PD-1 inhibitors with or without CTLA-4 inhibition in this disease. Until then, I recommend against the use of these agents in clinical practice outside a clinical trial, given the modest findings so far.
Melanoma

Talimogene Laherparepvec in combination with ipilimumab in previously untreated, unresectable stage IIIIB-IV melanoma


Dr Postow

T-VEC is a recently FDA approved oncolytic viral injectable therapy for melanoma. Approval was based upon results from a randomized study that showed a higher durable response rate with T-VEC than with the control treatment, GM-CSF, in patients with Stage III and IV melanoma. Ipilimumab is also FDA approved for patients with unresectable Stage III or IV melanoma.

This published study is a single arm, Phase 1B study testing the safety and preliminary efficacy of T-VEC in combination with ipilimumab. It showed that it is generally safe to combine T-VEC with ipilimumab and that the response rate of this combination appears preliminarily favorable.

Since this was not a randomized study, it remains unknown whether T-VEC increases the efficacy of ipilimumab or whether ipilimumab increases the efficacy of T-VEC. It is possible that the favorable response rate reported in this study reflects the earlier stage of disease (high percentage of Stage IIIB-IVA and ECOG PS 0) compared to prior studies of ipilimumab. The study is also limited by a low overall number of patients (n = 18 evaluable for efficacy). The earliest randomized data from the Phase II ipilimumab +/- T-VEC study are expected in October 2016 at the ESMO meeting.

Dr Luke

Ipilimumab was the first therapy shown to improve overall survival for melanoma in a randomized Phase III study, and T-VEC has recently been shown to improve the durable response rate for cutaneously injected lesions. There is a strong scientific rationale for combining T-VEC with immune-checkpoint blockade to increase treatment efficacy. This combination was previously shown to be safe with interesting preliminary activity. In this Phase Ib expansion cohort T-VEC was given as intratumoral injection in week 1 (10⁶ plaque-forming units/mL), then in week 4 and every 2 weeks thereafter (10⁸ plaque-forming units/mL) while ipilimumab was given per standard dosing at 3 mg/kg q3wk x 4 starting in week 6.

Treatment was reasonably well tolerated, with Grade 3-4 adverse events reported in 26% of patients (which is approximately the same as ipilimumab monotherapy). Whereas T-VEC is not associated with systemic response and ipilimumab is associated with a 10% RECIST response rate as monotherapy, the combination engendered a 50% response rate in this well selected patient population. This study raises the potential for combination use of intratumoral injection therapy and virotherapy with immune-
checkpoint blockade. The subsequent development plan for T-VEC is in combination with pembrolizumab, with which a preliminary report has also suggested an increased response rate and low toxicity.

While interesting from early clinical data series, the number of patients for which this is relevant is low, and it is unclear yet why this would be an advantageous approach for front-line patients. Should data be shown for synergy after initial failure of checkpoint blockade, then this approach may have more value.

**Dr Gonzalez**

Talimogene laherparepvec is an oncolytic immunotherapy that was evaluated in a randomized Phase III trial in combination with GM-CSF versus GM-CSF in the era before approval of the newer melanoma treatments. The primary endpoint was durable response rate, which was significantly higher with talimogene laherparepvec: 16% versus 2%, ORR was 26% versus 6%, OS improved by 4.4 months (HR 0.79; CI 0.62-1.00; p-value 0.051). Experimental data suggest that combination with ipilimumab may enhance efficacy.

The current study is a Phase Ib trial of talimogene laherparepvec in combination with ipilimumab. Patients had Stage IIIB-IV melanoma and no prior therapy except adjuvant >6 months before enrollment; CNS metastases and ocular and mucosal melanomas were excluded.

19 patients were enrolled. No DLTs occurred and no new safety signals were noted. 6 patients (31.6%) had Grade ≥3 AEs. ORR by immune-related response criteria (irRC) was 50%, 4 patients had confirmed CR, PFS at 12 and 18 months was 50%.

This study shows that these drugs can be safely combined. The authors suggest that the combination may have greater efficacy than monotherapy with either drug. However, this is a Phase I study with very small numbers of patients that are not comparable to recent immunotherapy trials. For example, 21% of patients had Stage IIIB or C, only 32% of patients (n = 6) had Stage IV M1c, 79% had normal LDH levels and only 1 patient had LDH >ULN — in 3 it was unknown (16%).

In conclusion, I agree that the combination has a tolerable safety profile and a Phase III trial is under way as is a combination with PD-1 blockade. However, I think it is premature to reach any conclusions regarding efficacy from the current data set.
Current and Future Use of Checkpoint Inhibitors

Three-year overall survival for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001

Robert C et al.
Proc ASCO 2016;Abstract 9503.

Dr Postow

This abstract demonstrated that 40% of patients with metastatic melanoma who received pembrolizumab in the Phase I study are alive after 3 years. This is a notable number and consistent with prior data from the nivolumab Phase I study. These 3-year overall survival rates appear more favorable than ipilimumab monotherapy long-term overall survival rates and support other trial data that suggest pembrolizumab improves overall survival compared to ipilimumab.

This abstract also demonstrated that of 61 patients who had a complete response and discontinued pembrolizumab for observation, 97% remain in complete response with approximately 10 months of follow-up.

While additional follow-up is needed, this provides some reassurance that patients with a complete response may be able to successfully stop ongoing PD-1 therapy and remain in complete response. Whether this durability after treatment cessation exists for patients with partial responses or long-term stable disease remains unknown. It is also unknown whether CT scans or PET scans are preferable to assess disease response.

Dr Luke

Anti-PD-1 antibody with pembrolizumab is a standard of care for advanced melanoma and has been shown to have a response rate of 30%-40% in pre-treated or naïve patients and improved overall survival relative to ipilimumab. Checkpoint immunotherapy is associated with durable disease control, and previous reports of nivolumab noted a 3-year survival of approximately 40% and, even more preliminary, 5-year survival of 34%. This data series summarized the long-term experience of pembrolizumab in advanced melanoma. Patients were aggregated from the KEYNOTE-001 study having been treated with doses ranging from 2 to 10 mg/kg every 2 or 3 weeks.

This was a relatively poor risk group, with 78% of patients having M1c Stage IV disease, 38% elevated LDH, 76% ≥1 prior therapy, and 52% prior ipi. As expected based on prior reports, the 3-year OS was 40% (median OS 24.4 months), with 3-year OS rates of 41% in both ipi-treated and naïve patients and 45% in treatment-naïve patients. These data are essentially identical to the results reported previously for nivolumab and reassuringly suggest that these 2 agents are interchangeable in clinical practice. Perhaps the important take-home point would be that it would not make scientific, biological or clinical sense to treat a patient with pembro or nivo and upon progression or severe toxicity then try the other agent as monotherapy.
Dr Gonzalez
This is an update of the study that led to the approval of pembrolizumab in melanoma. Patients were treated with 2 or 10 mg/kg q3wk or 10 mg/kg q2wk. Patients were enrolled in ipi-naïve and ipi-treated cohorts. 655 patients enrolled. At this data cutoff 36-month OS was 40% and similar across doses and across ipi-naïve and ipi-treated patients. Pembro continues to be well tolerated with continuing exposure. 61 (64%) of complete responders stopped pembro for observation and only 2 experienced disease progression. This is an important update, in particular the survival rate at 3 years and that responses are durable even after discontinuation.

These results support the notion that immunotherapy may be superior as front-line treatment over targeted agents for many patients as it seems possible that they can achieve an unmaintained CR.

Pembrolizumab versus ipilimumab for advanced melanoma: Final overall survival analysis of KEYNOTE-006


Dr Postow
This study provides longer-term follow-up on the Phase III study that showed pembrolizumab improves overall survival compared to ipilimumab. With longer follow-up, pembrolizumab continues to demonstrate improved overall survival compared to ipilimumab. This study secures pembrolizumab as a preferred treatment approach over ipilimumab monotherapy. There appeared to be greater numbers of patients with thyroid adverse events with pembrolizumab vs ipilimumab, but there were more instances of colitis in patients with ipilimumab vs pembrolizumab. The response rate to pembrolizumab was higher than ipilimumab, and the duration of response to pembrolizumab appears similar to the duration of response to ipilimumab. With longer follow-up of this study, the number of patients with complete responses continues to increase (in all treatment groups).

Notably, the doses of pembrolizumab in this study (10 mg/kg) are 5 times higher than the currently FDA approved dose (2 mg/kg). We technically do not know whether pembrolizumab at 2 mg/kg improves overall survival vs ipilimumab, but other studies of pembrolizumab have suggested there is no dose dependency. Therefore, it is expected that 2 mg/kg of pembrolizumab is a sufficient dose.

Dr Luke
Ipi was the first drug shown to improve OS in melanoma, while pembro was shown in the KEYNOTE-006 trial to improve survival further. This abstract updated the final OS report from that study. As previously reported, patients were randomized to either ipi 3 mg/kg q3wk x 4 or pembro at 10 mg/kg q2wk or q3wk. Within the 834 patients randomized, treatment groups were balanced. The median OS was not reached for pembro and was 16 months in the ipi group. The 2-year OS rates were 55% for pembro and 43% for ipi.
seen in other studies with these agents, the survival plot appeared to plateau with 2-year PFS at about 30% for pembro and 14% for ipi. For responding patients, 70% stayed in response longer than 72 weeks. Safety was as previously described.

These data confirm that anti-PD-1 is the front-line standard of care for immunotherapy treatment of melanoma. Based on this study there is no role for monotherapy ipilimumab in the front line. The trial results are the only data confirming an improvement in OS for anti-PD-1 vs ipi as the CHECKMATE 069 study of ipi-nivo vs ipi or nivo vs ipi has yet to report survival. Based on all other available data, however, it is assumed that the nivo vs ipi data will look essentially identical.

**Dr Gonzalez**

This is the final overall survival analysis of a landmark study of pembrolizumab at 10 mg/kg IV every 2 or 3 weeks x 2 years versus ipilimumab 3 mg/kg x 4 doses. Patients had Stage III or IV melanoma, ≤1 prior therapy excluding ipi or anti-PD-1 agents, no active brain metastases, ECOG PS 0-1. They were stratified by PS, PD-L1 status, prior treatment status. Primary endpoints were PFS and OS. Secondary endpoints were ORR, duration of response and safety. Primary assessment by central review using RECIST, treatment management investigator irRC.

Groups were well balanced. PFS (~30%) and OS (55%) at 24 months statistically superior in pembro arms versus ipi: HR 0.61 and 0.68. ORR 36% versus 13%. Results were consistent across all subgroups. Safety profile remained favorable to pembro.

This study was well designed and executed and confirms the superiority of pembrolizumab over ipilimumab in advanced melanoma. It establishes a new standard of care. Ongoing studies will try to further improve results using combination therapies with other immune modulators and targeted agents.

**Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: Early analysis of a non-randomised, open-label, phase 2 trial**


**Dr Postow**

This study was the first to report the efficacy of PD-1 therapy (pembrolizumab) for brain metastases in patients with melanoma and lung cancer. The overall number of patients in the study was small (n = 18 with melanoma and 18 with non-small cell lung cancer). No patients had symptoms related to their brain metastases or required steroids.

Pembrolizumab resulted in responses in the brain, both in patients with melanoma (22%) and non-small cell lung cancer (33%). Treatment was generally safe with an expected adverse event profile. Notably, there were some neurologic toxicities, but whether these were due to pembrolizumab or the brain metastases themselves remains unclear.
The preliminary efficacy reported with pembrolizumab appears better than ipilimumab in patients with brain metastases, although this was not a randomized study. This study does not provide information on whether it is safe to concomitantly administer SRS or whole brain RT in the context of concurrent pembrolizumab. Additional study is needed in much larger groups of patients and to help determine whether efficacy is seen in patients who are on steroids or who are symptomatic.

**Dr Luke**

PD-1 immunotherapy with pembrolizumab is a standard of care for both melanoma and lung cancer. The efficacy of PD-1 antibody therapy is not well defined in patients with brain metastases, however. In this non-randomized Phase II clinical trial, patients with untreated or progressive brain metastases of PD-L1+ lung cancer or melanoma of any PD-L1 status were given pembrolizumab at 10 mg/kg (q2wk) in open-label fashion. Treatment was well tolerated, similar to prior clinical trials of pembrolizumab. RECIST-quality responses were observed in 22% (4/18) patients with melanoma and 33% (6/18) patients with lung cancer. Those patients who achieved response generally maintained response for an extended period.

These data address likely the biggest ongoing problem area in melanoma medical oncology — namely brain metastases. While the data series presented here is hopeful, most physicians in clinical practice suggest that they have not seen substantial activity of anti-PD-1 monotherapy in brain metastases and the standard of care would still be to consider stereotactic radiation prior or concurrent to immune checkpoint blockade. For patients with small and asymptomatic disease, this series would suggest that deferring radiation with initial anti-PD-1 treatment would be reasonable, though I find it unlikely I would prefer to do so.

**Dr Gonzalez**

Brain metastases remain a significant problem in both lung cancer and melanoma. Treatment has most often consisted of local therapy directed at the brain. However, with progress in systemic therapies activity has been noted in the brain. This single institution Phase II trial is an attempt to systematically evaluate pembrolizumab 10 mg/kg every 2 weeks in untreated brain metastases. It enrolled 36 patients, 18 with melanoma and 18 with NSCLC. Key eligibility criteria were asymptomatic lesions between 5 mm and 20 cm, PD-L1 positivity for NSCLC patients and no leptomeningeal disease. Primary endpoint was brain metastasis response rate (RR) by modified RECIST.

There was good correlation between systemic and CNS response. 22% of melanoma patients and 33% of NSCLC patients had CNS response. I agree with the authors that the relatively lower CNS RR in melanoma might be due to vagaries of clinical trials in this group of patients, ie, 22% not evaluable in the brain because of rapid extra-cerebral progression coming off BRAF inhibition and bleeding in the target lesion in another patient. Also, pseudo-progression may occur in the brain and may be more problematic. Neurological toxicity was usually due to edema and responded to transient steroid use. After an episode of seizures all patients were given prophylaxis. No responses occurred in previously irradiated lesions.
This study provides early evidence of activity in selected patients with CNS metastases from melanoma or NSCLC. Its most important benefit might be in the prevention of development of clinical brain metastases.

**Clinical outcomes in metastatic uveal melanoma treated with PD-1 and PD-L1 antibodies**


**Dr Postow**

This was a multicenter, retrospective study evaluating the efficacy of PD-1/PD-L1 therapy for patients with metastatic uveal melanoma. The cohort size was reasonable (58 patients), and patients were heavily pre-treated.

Although treatment was well tolerated, as would be expected with single agent PD-1/PD-L1 therapies, the overall response rate was disappointingly low with only 2 responding patients. This raises questions whether uveal melanoma has a different immunobiology than cutaneous melanoma.

It is also possible that the predominant hepatic burden of disease in patients with uveal melanoma led to inferior responses in this group of patients as it is believed patients with hepatic metastases from cutaneous melanoma have lower responses to PD-1 agents than patients with metastases to lung or skin/soft tissue (data showing favorable ORR in patients with skin/soft tissue and lung metastases are from Ribas et al. JAMA 2016). Since responses are also infrequently observed with ipilimumab in patients with metastatic uveal melanoma, it remains unknown whether PD-1 or ipilimumab is a preferred treatment approach for this melanoma subtype. Questions remain about the efficacy of ipilimumab + nivolumab for metastatic uveal melanoma, which was not addressed in this study. Clinical trials remain important for this group of patients.

**Dr Luke**

Uveal melanoma is a rare subtype of melanoma arising from the uveal tract of the eye (choroid, ciliary body and iris) with an annual incidence of approximately 2,000 cases in the United States. Whereas BRAF and NRAS are commonly observed in cutaneous melanoma, uveal melanoma essentially never has these and instead is recurrently mutated in the G-coupled proteins GNAQ and GNA11. Therefore, targeted therapy in this disease has yet to be developed in a meaningful way. As part of standard of care, checkpoint immunotherapy is commonly given to these patients, but multiple reports have suggested very little efficacy for ipilimumab in this population.

In this retrospective analysis of PD-1/L1 blocking antibodies for uveal melanoma, the investigators documented that while safe to give, the treatment had near zero effectiveness (3.6% response rate, 9% stable disease lasting 6 months). These data highlight the lack of effective treatment options for these patients and argue strongly that all patients with uveal melanoma should be referred to a high-volume melanoma center and
recruited to clinical trials of novel approaches. Treatment with standard of care clinical therapeutics for melanoma has almost zero potential for effective disease palliation.

**Dr Gonzalez**

Uveal melanoma is a distinct entity from cutaneous melanoma. There is no standard treatment once the tumor has metastasized, and although data are limited, these tumors are generally refractory to treatments commonly used in melanoma.

This study is a retrospective look at 58 patients from several centers treated with a variety of anti-PD-1 agents at various doses and schedules. There were 2 PRs and no CRs for an ORR of 3.6%; 8.9% had SD for at least 6 months as best response.

Future studies will be needed to identify predictive biomarkers for response to immunotherapy and for better understanding of mechanisms of resistance to immunotherapy along with development of new agents. This is a population that should be prioritized for clinical trials.

**Avelumab in patients with chemotherapy-refractory metastatic Merkel cell carcinoma: A multicentre, single-group, open-label, phase 2 trial**


**Dr Postow**

Merkel cell carcinoma is an immunogenic tumor highly associated with the Merkel cell polyomavirus that has been shown to be responsive to PD-1/PD-L1 therapy. Prior published data suggest pembrolizumab has a high response rate in the first-line treatment setting (Ngheim et al. NEJM 2016). This Phase II study reports efficacy of the PD-L1 antibody avelumab in patients previously treated with chemotherapy. The response rate in this study was favorable (32%), and toxicity was low with very few Grade 3 events. Durability of responses was impressive. It did not seem that PD-L1 or Merkel cell polyoma viral status was obviously associated with responses.

Ongoing questions remain how well PD-1/PD-L1 treatment in Merkel cell would perform in a randomized study. Additionally, it remains unknown whether PD-1 (pembrolizumab) or PD-L1 (avelumab) is better. Nonetheless, these are impressive data and suggest PD-1/ PD-L1 agents are highly active in Merkel cell carcinoma both in the front-line and chemotherapy-refractory settings, although they are not yet approved by regulatory agencies.

**Dr Luke**

Merkel cell carcinoma is a rare neuroendocrine cutaneous malignancy that is extremely aggressive after the development of metastasis. Similar to small cell carcinoma of the lung, the disease is commonly responsive to front-line chemotherapy, but resistant disease develops quickly and patients have very short survival thereafter. Additionally, this tumor most commonly develops in patients of advanced age (high degrees of chronic sun
Radiographic responses to immunotherapy are often difficult to understand and may be different from responses to chemotherapy or targeted therapy. This study evaluated 600+ patients with advanced melanoma treated with pembrolizumab, and it addressed “atypical” response patterns, defined as progressive disease that was not subsequently confirmed as progressive disease at next assessment. Results indicated that only 7% of patients had atypical responses, which may even be an overestimation since patients continuing to be evaluated (and treated) after initial progression likely have more indolent disease or minimal progression at the time progression is first identified. RECIST was stricter than the immune-related response criteria in identifying progression. Two-year overall survival was lower in patients with RECIST progression yet non-progression by the immune-related response criteria than in patients with non-progression by both sets of criteria.

Dr Gonzalez

Merkel cell carcinoma (MCC) is an aggressive skin cancer associated with Merkel cell polyomavirus (MCPyV) and with no standard treatment. Avelumab is a PD-L1 IgG1 monoclonal antibody. This Phase II trial reports on 88 patients with Stage IV MCC progressing on at least 1 line of chemotherapy, not selected for PD-L1 expression or MCPyV status. Immune suppression was excluded. Primary endpoint was best overall objective response by RECIST; endpoints included PFS, OS, correlative studies. Objective RR, 31.8% (21.9-43.1). Median duration not reached, 82% ongoing. PFS at 6 months, 40%. Subgroup analysis shows activity in all subgroups. Avelumab may be more effective with less prior therapy.

Good tolerance. I think these are potentially game changing results for an aggressive tumor with no standard treatment. Breakthrough, fast track and orphan drug designation by FDA and EMA.

Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab

Hodi FS et al.

Dr Postow

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Good tolerance. I think these are potentially game changing results for an aggressive tumor with no standard treatment. Breakthrough, fast track and orphan drug designation by FDA and EMA.
Overall, this study confirms a very small number of patients will have atypical responses to immunotherapy with delayed benefits after initial progression. When other treatment options remain limited and patients are tolerating immunotherapy, continuing treatment beyond progression is reasonable, recognizing that most patients continue to progress. The immune-related response criteria are not yet accepted by regulatory authorities as standard, and most trials continue to report responses by RECIST.

**Dr Luke**

With the development of ipilimumab and immune-checkpoint blockade, the phenomenon of pseudoprogression or delayed response has been observed. This led to the development of the “immune-related response criteria (irRC)” which at their core suggest that progressive disease should be confirmed with a subsequent scan in patients who are otherwise biochemically intact and clinically well. Pseudoprogression with ipi was described as being present in approximately 10%-15% of patients. In this report the authors evaluated the incidence of pseudoprogression/delayed response and irRC upon treatment with the anti-PD-1 antibody pembrolizumab.

Similar to ipilimumab and as has been observed by most physicians who use these agents, this phenomenon was described in approximately 15% of patients treated with pembrolizumab (and nivolumab). Use of irRC is considered the standard approach in melanoma and should be considered in other diseases as well, though the utility is less clear (the rates of pseudoprogression in lung cancer may be lower). The key to use of the irRC is good internal medicine clinical practice in that the patient should be evaluated independently/in parallel with the scan results. Pseudoprogression should be considered if the patient is feeling well and there are no determining lab parameters, for example, decline in albumin, rise in creatinine or LFTs, etc.

Importantly, in patients who have clinical decline, confirmation of progression should not be considered standard as waiting to change treatment is likely to harm the patient.

**Dr Gonzalez**

This study is a retrospective analysis of responses in KEYNOTE-001 due to observation of immune response pattern in early development. Patients were treated based on investigator assessment of response by irRC. However, the primary endpoint was based on RECIST by central review. Analyses consisted of identification by central review of atypical responses by irRC and RECIST. Responses were considered atypical if disease progression was not confirmed by irRC by central review at next imaging assessment. OS was also evaluated in 3 groups with concordant or discordant responses. 327 of 655 patients were eligible for analysis of atypical response, which was noted in 7.3% of patients. Of 592 patients who had at least 2 assessments, 84 (14%) had PD by RECIST and non-PD by central irRC.

Survival for patients with discordant responses was between that of PD and non-PD concordant response assessment.

This study emphasizes what we already knew about responses to immunotherapy and that RECIST criteria probably underestimate the magnitude of responses and may lead to premature discontinuation of treatment.
Ipilimumab was approved by the FDA based on 2 randomized trials demonstrating benefit in overall survival for patients with metastatic melanoma. This study tested its role in the adjuvant setting of resected Stage III melanoma, compared to placebo. The dose of ipilimumab is 10 mg/kg, which is higher than the dose approved for metastatic melanoma, 3 mg/kg, because at the time of planning this study there was evidence that an increased dose of ipilimumab may be more efficacious. The study had previously demonstrated an improvement in recurrence-free survival, and with this new presentation there is now evidence of improvement in overall survival with the use of adjuvant high dose ipilimumab.

The rate of overall survival at 5 years was 65.4% in the ipilimumab group, as compared with 54.4% in the placebo group (HR 0.72; \( p = 0.001 \)). However, this was at the expense of a high rate of Grade 3/4 adverse events at 54.1% in the ipilimumab group, with 5 patients (1.1%) who died due to immune-related adverse events. This regimen is approved by the FDA for the adjuvant treatment of Stage III melanoma, and having longer follow-up and demonstration of improvement in overall survival allows better informed decisions on what adjuvant therapy to use for this disease.

It is well recognized that PD-L1 expression in solid tumors has limitations as a biomarker for response to PD-1/PD-L1 blockade. Some of these limitations are inherent to the test itself and have to do with the indirect measurement of induced tumor PD-L1 response to T-cell attack. Daud et al used digestion and flow cytometry on freshly isolated melanoma tissue to isolate and characterize CD4+ and CD8+ T cells. They showed that the fraction of CD8+ cells with the PD-1\textsuperscript{high}/CTLA-4\textsuperscript{high} phenotype predicted response to PD-1 treatment — tumors under 20% CD8+/PD-1\textsuperscript{high}/CTLA-4\textsuperscript{high} never responded while those greater than 30% always responded. In the 20%-30% range both responders and non-responders were present.
One of the interesting findings here is that CTLA-4 and PD-1 are highly co-expressed on exhausted antigen-experienced TILs, showing a potential mechanism for the high degree of effectiveness of combined ipilimumab and nivolumab (versus T-cell recruitment by ipilimumab followed by PD-1 effect on TIL). Several major limitations are apparent: one is the need for fresh tumor biopsy samples, which is clearly not possible in a large multi-site trial. Additionally, we don’t know if this phenotype is predictive in other tumors; we also do not know how reproducible this assay is. (Full disclosure: I am the first author of this paper.)

**Dr Weber**

The investigators performed a complex analysis of immune cells within the tumor microenvironment (TME) by assessing the phenotype of tumor-infiltrating T cells extracted from tumors from patients prior to and after treatment with the PD-1 antibody pembrolizumab. They found that in a small cohort of patients, T cells that were double positive for the checkpoints PD-1 and CTLA-4 and thus were “exhausted” dysfunctional effector cells were associated with response and progression-free survival. The functional measurement of those cells showed that they were not completely dysfunctional but were partly able to make cytokines upon stimulation. Within the TME, the levels of activated T cells that expressed HLA DR rose with treatment, whereas the T regulatory cells within the tumor did not change.

This was confirmed in a small validation cohort of patients. This work suggests that T-cell activation state and function may be both predictive and prognostic markers for the efficacy of PD-1 blockade. While this assay is not practically translatable to a clinically useful test, it may lead to assessment of a subset of the circulating T cells to see if they may be interrogated to determine if their activation markers might provide useful predictive information.

**Dr Ribas**

The authors performed flow cytometric analysis of single cells obtained from processed biopsies from patients with metastatic melanoma before they received anti-PD-1 therapy. Consistent with prior studies using pathological analyses, the pre-existence of CD8+ T lymphocytes in the tumor was correlated with response to therapy. This is because PD-1 blockade therapy releases a negative immune checkpoint that is active when antitumor CD8+ T cells infiltrate cancers, and the cancer cells protect themselves through the reactive surface expression of PD-L1.
Sequential administration of nivolumab and ipilimumab with a planned switch in patients with advanced melanoma (CheckMate 064): An open-label, randomised, phase 2 trial

Weber JS et al.

Dr Daud
This is a very important study that sheds light on the potential mechanism of synergy between ipilimumab and nivolumab. The study investigators randomized patients to either ipilimumab followed by nivolumab or nivolumab followed by ipilimumab. While the null hypothesis is not stated, I would have expected the ipi followed by nivo arm to be at least as good as the nivo followed by ipi arm. However, the authors show the exact opposite — the nivo followed by ipi arm was markedly superior, and surprisingly the ipi followed by nivo arm underperformed compared to the historic response rates seen in patients treated with nivo alone. The side effect profile was similar but somewhat worse for patients treated with nivo first.

This trial illuminates several pieces of data in the clinical and experimental literature that were previously unclear. One is the low response rate of PD-1 in patients pretreated with ipilimumab (20%-30% for pembrolizumab in ipi-pretreated patients). Another is reopening the debate on exactly how ipilimumab works and what the mechanisms of synergy between ipilimumab and nivolumab are.

Dr Weber
In this study, the investigators sought to test whether sequential immunotherapy with an anti-PD-1 antibody followed by a planned switch to CTLA-4 blockade or vice versa, with nivolumab maintenance following both regimens, was associated with less toxicity than concurrent combination immune checkpoint blockade, and whether the high level of efficacy seen with the concurrent regimen was preserved. Surprisingly, response rate and toxicity were quite a bit higher in the nivolumab then ipilimumab planned switch group than the converse, and the toxicities overall after 2 cycles of therapy with the switch were no better than those seen with concurrent therapy. Neither sequential regimen had a superior toxicity rate to concurrent therapy.

Estimated 2-year survival with nivolumab then ipilimumab followed by nivolumab maintenance was similar to that seen with concurrent treatment at 62%. This work suggests that if monotherapy is planned, nivolumab should be administered first, then ipilimumab if needed. Future work will revolve around immune determinants of the inferior outcome with the ipilimumab then nivolumab sequence.

Dr Ribas
This Phase II randomized study tested sequential therapy with nivolumab first for 6 doses every 2 weeks, then ipilimumab for 4 doses every 3 weeks, and then maintenance with nivolumab (68 patients), or starting with ipilimumab and then switching
to nivolumab (70 patients). The goal was to explore whether either sequence would have a response rate that was similar to the concurrent administration of nivolumab and ipilimumab but with a more favorable toxicity profile. This study suggests that the sequence starting with nivolumab and then switching to ipilimumab was more favorable compared to the opposite sequence, with a response rate of 56%.

The nivolumab to ipilimumab regimen had a Grade 3/4 toxicity rate of 50%, while the opposite sequence had a toxicity rate of 43%. Overall, this study defined the nivolumab to ipilimumab sequence as a regimen that could be used to slightly lower toxicities while having a reasonably high response rate.

Updated results from a phase III trial of nivolumab combined with ipilimumab in treatment-naive patients with advanced melanoma (CheckMate 067)

Wolchok JD et al.
Proc ASCO 2016;Abstract 9505.

Dr Daud
This is an update from 2015 when this study was presented and published. The trial compared ipilimumab + nivolumab to nivolumab alone or to ipilimumab alone. The updated PFS for the ipi + nivo arm was 11.5 months vs 6.9 months for nivo vs 2.9 months for ipi alone. These are not significantly changed. The major piece of data presented was the duration of response. The median DoR was 22.3 months for nivolumab and 14.4 months for ipilimumab but has not been reached for the combination. The other data, including AE data, have been updated and are slightly higher but not meaningfully changed. The overall survival data were (surprisingly) not presented (still immature), even though there has been a significant period of follow-up.

Dr Weber
The investigators provide updated clinical results from the 3-arm randomized Phase III trial of concurrent nivolumab/ipilimumab compared with either drug alone. They show that the advantage in progression-free survival for the concurrent cohort is maintained with a minimum follow-up of 18 months and a median follow-up of over 20 months, and that over 70% of patients in the concurrent cohort and the PD-1 alone cohort remain in remission. Survival data remain immature. For all prognostic subgroups, especially those with elevated LDH, the concurrent cohort had a better response rate and superior progression-free survival compared to the single-agent groups, although both response and PFS were excellent at all levels of LDH with concurrent therapy.

Immune related adverse events remain high in the concurrent cohort at over 50% for those of Grade 3-4. PD-L1 tumor staining greater than 5% did not distinguish those who would do well with either concurrent treatment or PD-1 blockade alone, with superior response and PFS for those in the concurrent group regardless of PD-L1 staining. These data continue to support the widespread use of the concurrent combination, although the toxicity rates of this regimen remain a significant concern.
**Dr Ribas**

This presentation updated the PFS of nivolumab combined with ipilimumab compared to either agent alone but did not provide new information on the eagerly anticipated overall survival results with these 3 study arms. In this update, the median PFS with the combination continued to be significantly improved compared to ipilimumab and numerically improved over nivolumab.

**Pembrolizumab (pembro) plus ipilimumab (ipi) for advanced melanoma: Results of the KEYNOTE-029 expansion cohort**

Long GV et al.  
*Proc ASCO* 2016;Abstract 9506.

**Dr Daud**

While ipilimumab + nivolumab is certainly the most active immunotherapy currently, it is also toxic, with a 56.5% Grade 3-4 toxicity rate. Given that ipilimumab 3 mg/kg is used in this combination, and given that the nivolumab is dose reduced, an obvious question is whether we should combine full-dose PD-1 with reduced-dose ipilimumab. This was the question addressed in this study. Long et al combined pembrolizumab 2 mg/kg with ipilimumab 1 mg/kg x 4 cycles, continuing with pembrolizumab. The most notable finding was the reduced Grade 3-4 toxicity, which was 42%. The ORR was 57%, which is very respectable and almost identical to the ipilimumab-nivolumab RR.

This is a smaller study and these numbers may change, but this study validates the CTLA-4 + PD-1 combination strategy and, along with the other regimens being tested in lung cancer where ipilimumab doses are being used q6 weeks, may be the future.

**Dr Weber**

The authors presented the early clinical results of a Phase I/II trial of concurrent pembrolizumab and ipilimumab in which the ipilimumab dose had been lowered to 1 mg/kg from the 3-mg/kg dose used during induction in the CheckMate 067 and 069 trials. 153 patients were enrolled, and an impressive 72% completed all 4 induction doses. Only 10% of patients discontinued therapy due to toxicity, which is quite favorable compared to concurrent ipilimumab/nivolumab. Of the 64 Grade 3-4 treatment-related adverse events, 22 consisted of elevations of lipase. The 57% response rate and 10% CR rate compare favorably with concurrent nivolumab/ipilimumab.

The 6-month overall survival rate of 93% is immature to base any firm conclusions on but seems excellent. These data suggest that lowering the dose of ipilimumab does not compromise early efficacy assessment but does markedly reduce the toxicity of a concurrent PD-1/CTLA-4 blockade combination. These data support the continued assessment of combination immune checkpoint regimens in which the dose of ipilimumab may be lowered, its interval lengthened, or both.
Dr Daud
With this update of the dabrafenib/trametinib trial that led to the approval of this combination in melanoma. The authors extended the follow-up and also analyzed prognostic factors for response to the BRAF-MEK regimen. They found that LDH and number of metastatic disease sites were predictive of response (LDH ≤ULN and <3 metastatic sites have HRs of 0.21 and 0.34 respectively). The updated median OS was 27.4 months and 25 months in parts B and C of the study. The PFS at 1, 2 and 3 years was 44%, 22% and 18% respectively. Overall there appeared to be a flattening of the PFS curve at 20 months, although the events after that were limited, so it’s hard to say for sure. There is also a suggestion in the BRIM-7 data that this may be the case with the vemurafenib/cobimetinib combination as well.

Dr Weber
In this presentation, the authors update the published experience with the Phase II studies of the combination of dabrafenib and trametinib that led to the approval of this regimen. Three year survivals are excellent, with rates ranging from 38% to 47%, although follow-up did not reveal a clear plateau of survival beyond 3 years. Factors that were associated with superior long term survival included achieving a complete response and having a low baseline tumor burden with 3 or fewer sites of disease and a normal LDH value. No changes were observed in toxicity patterns on long term follow-up, with pyrexia and fatigue as potential dose limiting side effects of the combination.

These data suggest that the cohort of patients who are BRAF mutated with a baseline low tumor burden may have long term survival with front line BRAF + MEK inhibition, and may do as well as patients receiving front line immunotherapy.

BRAF V600-Mutant Disease

Overall survival and durable responses in patients with BRAF V600-mutant metastatic melanoma receiving dabrafenib combined with trametinib

Long GV et al.

Dr Ribas
With the goal of improving the safety but hoping to maintain the high response rate of the combination of nivolumab and ipilimumab, this study combined pembrolizumab with ipilimumab but with ipilimumab given at one third of the FDA approved dosing, 1 mg/kg instead of 3 mg/kg. Among 107 treated, the drug-related Grade 3-4 adverse event rate was 38%, which compares favorably to the data with concurrent nivolumab plus ipilimumab (at 3 mg/kg), with which the objective response rate was similar to this combination at 57%.
Dr Ribas
This is a pooled analysis of long term survival in patients treated within different cohorts of the Phase I trial with dabrafenib and trametinib for patients with BRAF V600 mutated metastatic melanoma. This study provided evidence of a median overall survival of 27 months, which demonstrates the remarkable beneficial effect that the use of BRAF and MEK inhibitor combination therapy has brought to patients with melanoma. Certain subgroups of patients have very good outcomes, such as patients with a baseline normal LDH, for whom the 3-year survival rate is 62%.

Genomic analysis and 3-y efficacy and safety update of COMBI-d: A phase 3 study of dabrafenib (D) + trametinib (T) vs D monotherapy in patients (pts) with unresectable or metastatic BRAF V600E/K-mutant cutaneous melanoma

Flaherty K et al.
Proc ASCO 2016;Abstract 9502.

Dr Daud
This was an interesting presentation of analysis of a previous Phase III clinical trial. While several analyses were presented, the numbers were low (only a subset of patients was included). The overall conclusions were that patients with BRAF V600K mutation-positive disease had a higher mutation burden compared to the V600E-positive melanoma patients. However, one interesting finding was the linking of mutation burden with overall survival. This has to be considered preliminary because the numbers were small and it wasn’t clear what types of treatment patients were put on after the targeted therapy (so it’s possible that immunotherapy may be responsible for the effect seen).

Dr Weber
In this updated analysis of outcomes for BRAF mutated patients who were treated in a Phase III randomized trial of dabrafenib and trametinib compared to dabrafenib plus placebo, the authors demonstrate an excellent PFS of 11 months and a median overall survival of 25.1 months for the combination. Landmark 3-year survival was 44% for the combination versus 32% for dabrafenib alone, with a hint of a survival plateau beyond 3 years. For patients with elevated LDH, the advantage in survival still lay with the combination, although survival was worse with elevated LDH than for the overall group for both regimens, with 3-year survival of 25% versus 14%. For the cohort of patients with normal LDH and 3 or fewer sites of disease, the 3-year survival was an excellent 62%. In a genomic sequencing analysis of a portion of all patients, CDKN2A mutations or deletion were associated with a worse outcome with combination treatment, and overall mutational load added to normal LDH levels distinguished patients with excellent survival. These data provide new information on the importance of mutational load and disease burden in patients treated with BRAF + MEK inhibition and suggest that some select BRAF mutated patients may do as well with front line targeted therapy as with immunotherapy.
These are updated results from the coBRIM trial, which has been presented previously. The median OS for the combination arm is 22.3 months, which is markedly superior to the vemurafenib monotherapy arm. No new AEs were noted. Probably the most significant result here was the suggestion of a flattening of the PFS and OS curves at around 15-18 months, although there were very few events seen and many patients were censored.

**Dr Weber**

The investigators present the first data from a randomized Phase III study of the BRAF + MEK inhibitors vemurafenib and cobimetinib compared to vemurafenib and placebo. An excellent response rate of 70% for the combination was observed, and with over 18 months of median follow-up median survival was 22.3 months versus 17.4 months for the single-agent BRAF inhibitor. Two-year overall survival was 48% versus 51% for the dabrafenib + trametinib combination. Elevated LDH levels were associated with a poor outcome, with a median overall survival of 14.8 months with the combination with elevated LDH compared to beyond 23 months with normal LDH.

Skin toxicity was lower in the combination group, most likely due to suppression of paradoxical MAP kinase activation, and side effects typical for MEK inhibitor treatment alone were also observed in the combination arm. The overall efficacy of the combination of cobimetinib and vemurafenib was similar to that observed in studies that compared the combination of dabrafenib and trametinib with BRAF inhibition alone in 2 randomized Phase III trials. These data support the use of cobimetinib and vemurafenib as an acceptable and effective regimen for BRAF mutated melanoma.

**Dr Ribas**

This presentation provided updated results of the coBRIM trial, which was the pivotal trial leading to the approval of the combination of vemurafenib and cobimetinib by demonstrating an improvement in PFS over single agent vemurafenib in patients with BRAF mutant metastatic melanoma. At the time of the protocol-specified events for the analysis of overall survival, the median overall survival is statistically significantly better for patients with the combination than with single agent therapy (22.3 vs 17.4 months, HR 0.70, \( p = 0.005 \)). The updated follow-up did not change the toxicity rates or risks of the therapy. This study confirms the clinical benefit of the combination of vemurafenib and cobimetinib.
Targeting NRAS

Results of NEMO: A phase III trial of binimetinib (BINI) vs dacarbazine (DTIC) in NRAS-mutant cutaneous melanoma


Dr Daud
This study randomized 402 patients to either binimetinib (a MEK inhibitor) or DTIC in a 2:1 randomization. While the ORR and PFS favored binimetinib, the clinical differences were underwhelming: the ORR and PFS were 15 and 2.8 months, respectively. The overall survival was not statistically significant, and given the overall results, it seems that MEK inhibition per se is not likely to be used in NRAS mutant melanoma.

Dr Weber
The investigators tested a MEK inhibitor, binimetinib, compared to dacarbazine in a Phase III study in patients with NRAS mutated BRAF wild type melanoma. The development of targeted drugs for the BRAF wild type melanoma patient is a major unmet need, and this trial was the first definitive attempt to show benefit with a new drug in that population. Median progression-free survival was minimally improved from 1.5 to 2.8 months, although interestingly, patients who received prior immunotherapy had a greater relative benefit with binimetinib, with an increase from 1.6 to 5.5 months. Response rates were 15% for binimetinib and 7% for dacarbazine, while there was no difference in overall survival, with a hazard ratio of 1.0.

Grade 3-4 side effects were significantly more frequent in the binimetinib arm compared to dacarbazine. These data suggest that single-agent MEK inhibition provides little clinically significant benefit to patients with melanoma with NRAS mutations and that development of new combination targeted regimens for this population should be a high priority. The intriguing data on the benefit with targeted therapy in those patients who had received prior immunotherapy merit follow-up.

Dr Ribas
There is no approved targeted therapy for patients with NRAS mutated metastatic melanoma. Previous data suggested the potential benefit of a MEK inhibitor in this setting, and this randomized trial compared the MEK inhibitor binimetinib with what was the standard of care therapy with dacarbazine. The study was planned for front line therapy but was amended to allow prior immunotherapy. The study demonstrated an improvement in median PFS of 2.8 versus 1.5 months (HR 0.62, p < 0.0001), which was the primary endpoint of the study, but overall survival was overlapping between the 2 groups.
Dr Oh
The most important advance in the management of metastatic prostate cancer in the past 2 years has been the use of docetaxel for metastatic hormone-sensitive prostate cancer, based on the results from CHAARTED and STAMPEDE, presented in this paper. The paradigm shift is based on the magnitude and consistency of benefit in these 2 large Phase III trials and is despite negative results from the smaller GETUG 15 study. STAMPEDE randomized 2,962 men with metastatic and locally advanced prostate cancer embarking on ADT to docetaxel or zoledronic acid or both. Zoledronic acid had no effect, but with docetaxel, overall mortality in the entire cohort was reduced by 22% and OS increased from 71 to 81 months.

For the metastatic patients, mortality was reduced by 24% and survival increased from 45 to 60 months, an astonishing result. Absolute 5-year survival in M+ patients increased from 39% to 50%, an 11% increase. Delays in cancer progression were noted in the non-metastatic cohort, but OS was not yet different. So should all patients with metastatic disease receive 6 cycles of docetaxel chemotherapy? Considering the risks of chemotherapy, the answer is probably not. However, the standard of care in 2016 is indeed to consider docetaxel for most fit patients, especially considering the magnitude of the benefit.

Dr Antonarakis
The STAMPEDE trial, in conjunction with the previous CHAARTED study, provides strong evidence to use upfront docetaxel in men with metastatic hormone-sensitive prostate cancer. STAMPEDE is an ongoing multi-arm multi-stage trial design with at least 8 arms comparing standard androgen deprivation therapy (ADT) alone to multiple other arms of combination therapies. In this paper, the authors report on a randomized comparison (2:1:1:1) of ADT alone vs ADT plus zoledronic acid vs ADT plus docetaxel vs ADT plus zoledronic acid and docetaxel. Eligible patients included those with metastatic (61%) as well as nonmetastatic (39%) hormone-sensitive prostate cancer. The addition of zoledronic acid did not contribute to any survival prolongation in either arm and should not be incorporated in this setting. However, compared to ADT alone, overall survival was superior with the addition of docetaxel (HR 0.78, \( p = 0.006 \)) as well as the addition of both docetaxel and zoledronic acid (HR 0.82, \( p = 0.022 \)). In subset analyses, the survival improvement with docetaxel was preserved in
the M1 subset but was not observed in the M0 subset due to fewer deaths to date, reflecting an underpowered study. Grade ≥3 adverse events were more common in the docetaxel-containing arms (52% vs 32%), and this was mainly driven by grade 3 neutropenia (including febrile neutropenia). Based on the results of CHAARTED and STAMPEDE, my practice is to offer up-front chemohormonal therapy to chemo-fit patients with metastatic (but not nonmetastatic) hormone-sensitive prostate cancer and particularly to men with high-volume disease as defined by the CHAARTED study.

Dr Quinn

The docetaxel version of the STAMPEDE sequence where patients are treated with agents in addition to ADT is a practice changing clinical trial that needs to be placed in context with the CHAARTED study.

In this trial patients with M1 prostate cancer were treated with either ADT alone or ADT + docetaxel, with the primary endpoint of survival. Overall survival was improved by 22 months at the median in the docetaxel group. Unfortunately, there was no stratification for low- versus high-risk cancer at baseline, so comparing these groups with the CHAARTED trial, where there was major benefit in high-risk patients but none in low-risk patients, is difficult.

The 2 trials have provided a base for offering docetaxel to patients with hormone naïve metastatic prostate cancer at the development of first metastases. Such therapy provides high efficacy value in terms of life extension for cost of 6 cycles of docetaxel, but it is not without toxicity. Notably, we do see higher rates of neutropenia, skin toxicity and nail loss in the HNPC group compared to patients in the CRPC disease state.

In addition, in this report on the STAMPEDE trial, zoledronic acid was given to half the patients, with no improvement in survival but some evidence of efficacy in slowing the development of bone metastases. A cohort of M0HNPC (PSA only) was also included, with evidence of some benefit from docetaxel but no definitive overall survival advantage.

When combined with Matthew Smith’s CALGB trial in HNPC, where there was no survival or other advantage, the use of antiresorptive agents in HNPC needs to be limited to regimens showed to ameliorate decrease in BMD from ADT.

Cabazitaxel vs docetaxel in chemotherapy-naive (CN) patients with metastatic castration-resistant prostate cancer (mCRPC): A three-arm phase III study (FIRSTANA)


Dr Oh

After cabazitaxel was approved in 2010 for second-line treatment of mCRPC, at least 2 critical questions arose. First, could cabazitaxel be superior to docetaxel in the first-line setting? Second, is the dose of 25 mg/m² too high given the myelosuppression that was seen? Both of these were addressed in FIRSTANA, a Phase III study...
comparing docetaxel 75 mg/m² to cabazitaxel at either 20 or 25 mg/m². 1,168 mCRPC patients were randomized; no superiority was seen for either C20 or C25 compared with docetaxel. OS was ~25 mo in each arm and PFS was also not different between the arms. Tumor response was greater for C25 compared with docetaxel, but no other secondary endpoints were different. Toxicity was different between the 2 taxanes, with increased febrile neutropenia and diarrhea in the C25 arm and increased edema, neuropathy and alopecia in the docetaxel arm.

This study shows no survival advantage to cabazitaxel over docetaxel in the first line — the Kaplan-Meier curves could not be more superimposable. However, we do note that a lower dose of cabazitaxel (20 mg/m²) is also active and comparable to docetaxel, and we see the first direct comparison of these important prostate cancer therapies in terms of toxicities. The differences in neuropathy, alopecia and edema could be useful in managing patients with cytotoxic chemotherapy. The higher rates of febrile neutropenia seen in FIRSTANA and also TROPIC suggest that cabazitaxel at 25 mg/m² should generally be used with growth factor support in most patients.

**Dr Antonarakis**

Based on the results of the TROPIC trial, cabazitaxel 25 mg/m² has been FDA-approved since 2010 specifically for metastatic CRPC patients who have already received prior docetaxel chemotherapy. In FIRSTANA, cabazitaxel and docetaxel were compared in a head-to-head randomized trial designed to show superiority of cabazitaxel over docetaxel with respect to overall survival. In addition, a lower dose of cabazitaxel (20 mg/m²) was also included as a third arm. Patients (n = 1168) were randomized equally to one of three arms: cabazitaxel 25 mg/m², cabazitaxel 20 mg/m² or docetaxel 75 mg/m². The trial failed to meet its primary endpoint: Neither of the cabazitaxel arms produced superior survival than the docetaxel arm (24-25 months median overall survival in all arms).

The only secondary endpoint that favored cabazitaxel was the objective response rate, which was superior for cabazitaxel 25 mg/m² compared to docetaxel (42% vs 31%, p = 0.037). Febrile neutropenia, diarrhea and hematuria were more frequent in the cabazitaxel 25 mg/m² arm; peripheral neuropathy, peripheral edema, alopecia and nail dystrophy were more frequent in the docetaxel arm. Based on this negative trial, cabazitaxel should not be used as first-line chemotherapy in men with metastatic CRPC, and docetaxel remains the chemotherapy standard of choice.

One potential caveat is that cabazitaxel chemotherapy can be considered for patients newly developing CRPC who have previously received docetaxel-based chemohormonal therapy for metastatic hormone-sensitive prostate cancer as suggested by the results of the CHAARTED and STAMPEDE trials.

**Dr Quinn**

This study compared 3 taxane regimens as the first chemotherapy given in mCRPC: docetaxel 75 mg/m² every 3 weeks, cabazitaxel 25 mg/m² every 3 weeks or cabazitaxel 20 mg/m² every 3 weeks, each regimen being given with prednisone 10 mg per day orally. The 3 regimens produced similar overall survival although there was some
difference in PSA and radiographic response. Caba20 produced less neutropenia than Caba25, and the cabazitaxel arms were associated with less neuropathy.

Coming out of this study docetaxel remains the standard agent in the mCRPC space. However, a case can be made for using cabazitaxel in patients with pre-existent symptomatic (Grade 2) peripheral neuropathy. When these results are combined with similar data from the PROSELICA trial, practice will be to give Caba20 rather than Caba25 because of less toxicity, similar OS and a cost saving of 20% on the average per dose.

Radium-223 and concomitant therapies in patients with metastatic castration-resistant prostate cancer: An international, early access, open-label, single-arm phase 3b trial


Dr Oh

Radium-223 was approved in 2013 on the basis of the ALSYMPCA trial, a randomized Phase III trial that demonstrated a survival benefit with radium-223 compared to placebo in patients with symptomatic, metastatic CRPC involving bone. Patients were allowed to receive non-cytotoxic concurrent therapies, but currently approved AR targeted therapies such as abiraterone and enzalutamide were not yet available. In this international, early access, single arm trial, 839 patients with mCRPC were treated with radium-223 but could also receive drugs such as enzalutamide, abiraterone and denosumab (but not chemotherapy). The results confirmed the general safety profile of radium-223, with low rates (1%-5%) of hematologic toxicities.

In addition, patients were allowed to receive radium-223 even if asymptomatic, providing an earlier population of patients than that enrolled in ALSYMPCA. Finally, though the trial was not randomized, there was a suggestion that radium-223 could be safely combined with abiraterone or enzalutamide and in combination might be associated with a survival benefit compared to survival for patients who did not receive combined therapy. While we await results of randomized trials addressing these questions, this study suggests that such combinations may be the future of therapy for mCRPC.

Dr Antonarakis

Radium-223 was previously approved by the FDA in 2013 based on the results of ALSYMPCA (n = 921), a placebo-controlled randomized (2:1) trial of radium-223 vs best supportive care in men with symptomatic castration-resistant prostate cancer with 2 or more bone metastases. The current study is a single-arm phase IIIb early-access trial (n = 696) of radium-223 in a similar patient population. However, asymptomatic men were included here, as were those receiving concurrent abiraterone or enzalutamide or denosumab. The trial showed acceptable safety (grade 3 anemia/thrombocytopenia/leukopenia in 5%/2%/1%, respectively) and an overall survival of 16 months, similar to the 15-month survival in ALSYMPCA.
Survival was higher in men with baseline alkaline phosphatase levels less than the upper limit of normal, hemoglobin levels ≥10 g/dL, ECOG performance status of 0, and absence of baseline bone pain. In an exploratory analysis, survival was also greater in men receiving concurrent abiraterone or enzalutamide or both, as well as in those concurrently receiving denosumab. Therefore, this study demonstrates the safety of combining these agents with radium-223. However, whether the addition of abiraterone or enzalutamide to radium-223 improves survival is unknown because this was a single-arm study, and there are ongoing phase III trials to answer this question (NCT02043678 and NCT02194842, respectively).

Finally, despite the fact that this early-access study allowed enrollment of asymptomatic patients (and even suggested better survival in these men), the current FDA label for radium-223 requires symptomatic bone metastases.

Dr Quinn
This is called a Phase IIIb trial but is actually a Phase IV expansion trial looking at radium-233 given in the FDA label space with either concurrent enzalutamide or abiraterone and/or other antiresorptive agents permitted. The primary objective of the study was to demonstrate the safety of radium-223 in combination with these agents. There are NO statistical assumptions for this — not even the experimental (radium-223) arm of the ALSYMPCA trial — something that would cause conniptions and grave rolling in every clinical trials tutor who ever had the burden of trying to teach me in the last 25 years. The cohort does allow delineation of alkaline phosphatase, hemoglobin, ECOG status, pain severity and other clinical parameters as predictors of outcome.

This is comfort food for those of us that are combining these drugs with very little evidence base. There is reference to the randomized studies that are in process to address these questions in a more robust fashion.

Enzalutamide versus bicalutamide in castration-resistant prostate cancer: The STRIVE trial


Dr Oh
Enzalutamide was first approved in mCRPC based on the results of the AFFIRM Phase III trial in post-docetaxel patients. Then, based on PREVAIL, which enrolled mCRPC patients prior to the use of chemotherapy, enzalutamide again showed an OS and PFS benefit (compared to placebo), which led to an expansion of its indication. Based on the hypothesis that AR-targeted therapies may have even greater benefit if used earlier in the disease course of mCRPC, the current Phase II trial, STRIVE, randomized 396 patients with non-metastatic and metastatic CRPC to enzalutamide (160 mg/day) or bicalutamide (50 mg/day). With a primary endpoint of PFS, STRIVE demonstrated a 76% reduction in risk of progression or death with enzalutamide compared to bicalutamide (19.4 vs 5.7 mo; \( p < 0.001 \)).
Significant differences were seen in secondary endpoints, including 50% PSA declines (81% vs 31%) and radiographic PFS (0.31) in metastatic patients. Toxicity was not significantly different from that reported in PREVAIL. Overall, this study demonstrated that enzalutamide was superior to bicalutamide in CRPC with or without mets. This is not a surprise considering that bicalutamide has never been shown to have a clinical benefit in mCRPC and given the mechanistic superiority of enzalutamide to bicalutamide.

What remains unclear even with these results is whether enzalutamide should be used in non-metastatic CRPC, an important question that awaits the results of PROSPER, which was designed to address this better.

**Dr Antonarakis**

Enzalutamide is FDA-approved for men with metastatic castration-resistant prostate cancer (CRPC) in both the pre-docetaxel and post-docetaxel settings based on the placebo-controlled PREVAIL and AFFIRM studies. Here, enzalutamide and bicalutamide were compared in the head-to-head randomized phase II STRIVE trial (n = 396) in men with nonmetastatic or metastatic CRPC, using a primary endpoint of progression-free survival (incorporating PSA progression, radiographic progression, or death).

The results showed that enzalutamide was superior to bicalutamide with respect to progression-free survival (19.4 vs 5.7 months; HR 0.24, P<0.001), as well as PSA response rate (81% vs 31%, P<0.001), PSA progression (HR 0.19, P<0.001), and radiographic progression (HR 0.32, P<0.001), although overall survival was not assessed. Adverse events appeared numerically more frequent with enzalutamide compared to bicalutamide in terms of fatigue (38% vs 28%), hot flashes (16% vs 10%), falls (14% vs 8%), hypertension (12% vs 5%), dizziness (12% vs 7%), and anorexia (12% vs 9%), and more patients came off study due to adverse events in the enzalutamide arm (8% vs 6%).

At this time, the FDA label of enzalutamide does not permit its use in nonmetastatic CRPC patients, and this reflects my own practice. This study also did not address the benefit of sequential therapy with bicalutamide followed by enzalutamide, nor did it evaluate the cost-effectiveness of this approach. Finally, the use of enzalutamide in the nonmetastatic CRPC setting is being tested in the placebo-controlled PROSPER study (NCT02003924), which will evaluate metastasis-free survival as its primary endpoint (n = 1560).

**Dr Quinn**

STRIVE was an extended randomized Phase II study comparing enzalutamide to bicalutamide in 2 cohorts of CRPC: M0 and M1. Enzalutamide was proven superior for PSA response and time to progression (hazard ratios of 0.19-0.32 in favor of enzalutamide) in both cohorts but was associated with more all-grade fatigue and falls. Enzalutamide is a very much more potent AR inhibitor in CRPC at the cost of a mild increment in Grade 1-2 toxicity side effects.
Dr Oh

Like PREVAIL, the TERRAIN trial sought to investigate an early population of patients with asymptomatic or minimally symptomatic mCRPC. However, instead of randomizing to placebo, 375 patients in TERRAIN were randomized to enzalutamide versus bicalutamide (50 mg/day). The HR for disease progression was 0.44 (15.7 vs 5.8 mo; \( p < 0.0001 \)), strongly favoring the enzalutamide group. More fatigue was seen in the enzalutamide group (28% vs 20%), but most of it was low grade. SAEs were also slightly more frequent in the enzalutamide group (31% vs 23%). In conclusion, TERRAIN demonstrated that enzalutamide was superior to bicalutamide in asymptomatic or minimally symptomatic mCRPC, results similar to those for metastatic disease in the STRIVE trial.

Why compare enzalutamide to bicalutamide in this clinical setting? Many clinicians in different countries continue to use bicalutamide, including in some patients with mCRPC. There may be several reasons for this, including cost, availability and/or concerns about toxicity. At the very least, TERRAIN directly addresses the issues of efficacy and safety and unequivocally demonstrates the superiority of enzalutamide to bicalutamide in delaying progression of mCRPC.

Dr Antonarakis

Similarly to the STRIVE study, the TERRAIN trial was a double-blind randomized study of enzalutamide vs bicalutamide, but this trial only included metastatic CRPC patients. The primary endpoint was progression-free survival (incorporating radiographic progression, clinical progression or death), and this definition did not include PSA progression as in STRIVE. The study showed that enzalutamide was superior to bicalutamide with respect to progression-free survival (15.7 vs 5.8 months; HR 0.44, \( P<0.0001 \)), as well as PSA response (82% vs 21%, \( P<0.001 \)), PSA progression (HR 0.28, \( P<0.001 \)), and radiographic progression (HR 0.51, \( P = 0.0002 \)), although overall survival was also not assessed here.

Adverse events appeared numerically more frequent with enzalutamide compared to bicalutamide in terms of fatigue (28% vs 20%), hot flashes (15% vs 11%), hypertension (14% vs 7%), and grade 3 cardiac events (5% vs 2%), and total serious adverse events were greater in the enzalutamide arm than in the bicalutamide arm (31% vs 23%). Based on the results of STRIVE and TERRAIN, the immediate use of enzalutamide is reasonable in men with metastatic (but not nonmetastatic) CRPC, while the initial use of bicalutamide followed by enzalutamide upon progression is an alternative strategy that may mitigate some physical and financial toxicities.
Dr Quinn

TERRAIN was a randomized Phase II trial comparing enzalutamide to bicalutamide in mCRPC. In a generally more advanced mCRPC cohort than accrued to STRIVE, the study showed a major PFS advantage with enzalutamide (HR 0.44). QoL as measured by FACT-P improved on therapy with enzalutamide to a greater degree than with bicalutamide. Enzalutamide produced more fatigue and hypertension than bicalutamide, while nausea and arthralgias were more common with bicalutamide.

Dr Oh

We are able to predict those patients with localized disease who are most likely to recur and die. These high-risk patients seem ideal candidates to treat with newer therapies developed in the mCRPC setting. In this randomized Phase II trial, 65 patients with high-risk localized prostate cancer were randomized 2:1 to receive 24 weeks of neoadjuvant therapy with either enzalutamide + abiraterone acetate or abiraterone alone, followed by radical prostatectomy. The primary endpoint was pathologic stage, and this was not different between the arms (though a trend favored the combination arm). Paradoxically, however, residual tumor quantification was actually less in the abiraterone alone arm, suggesting that the addition of enzalutamide did not improve eradication of residual cancer.

Indeed, pCR was seen in only a single patient in each arm, and other traditional measures of disease burden, such as nodal involvement and margin positivity, were no different, despite complete PSA suppression in ~90% of both groups. Intriguingly, certain molecular clues to resistance were seen, including increased AR-V7 expression in the combination arm. Bottom line: 2 AR targeted therapies are not necessarily better than 1, at least in localized prostate cancer.

Dr Antonarakis

This is a neoadjuvant randomized (2:1) trial of androgen deprivation therapy (ADT) plus the combination of abiraterone and enzalutamide vs ADT plus abiraterone alone in 65 men with high-risk localized prostate cancer (Gleason ≥8, or Gleason ≥7 and PSA ≥10 ng/mL). Patients were treated with systemic therapy for 24 weeks followed by radical prostatectomy. This same group from MD Anderson had previously conducted a study combining abiraterone plus enzalutamide in men with metastatic CRPC, suggesting high efficacy with this combination in that setting. Contrary to the authors’ hypothesis, pathologic downstaging (to ≤pT2 N0) did not occur more frequently in the abiraterone plus enzalutamide group compared to the abiraterone alone group (13/44 = 30% vs 11/21 = 52%).
In addition, complete PSA responses (≤0.1 ng/mL) were similar between arms (89% vs 90%), as were other measures of residual tumor volume/cellularity. Interestingly, the chance of achieving pathological downstaging (to ≤pT2 N0) was associated with a canonical AR signaling signature (high AR-FL, high CYP17 expression) but not baseline PSA. In addition, ARV7 protein was detected more frequently in the combination therapy arm (abiraterone plus enzalutamide). A separate neoadjuvant trial (n = 75) is currently evaluating ADT plus enzalutamide vs ADT plus enzalutamide and abiraterone in men with high-risk prostate cancer before prostatectomy (NCT02268175). In addition, the phase III A031201 trial (NCT01949337) of enzalutamide vs enzalutamide plus abiraterone in men with metastatic CRPC has completed enrollment of 1224 patients and is awaiting its overall survival outcomes.

Dr Quinn

This trial compared neoadjuvant LHRH therapy with abiraterone and enzalutamide to LHRH therapy and abiraterone before radical prostatectomy. The addition of enzalutamide resulted in more fatigue and hot flashes. Patients given the 3 agents had a higher rate of <pT2 stage tumor (p = 0.08) but a higher rate of positive margins and LN involvement. PSA nadir to less than 0.1 ng/mL occurred in 89% and 90% of patients. Calculated tumor volume was lower in 2-drug treated patients (p = 0.045). Steroid metabolites were similar between arms. On molecular analysis AR-V7 was found more commonly in residual tumor tissue of patients in the enzalutamide arm.

Patients with tumors less than pT2N0 were characterized by higher protein expression of AR, PTEN, RB and CYP17A where AR and PTEN were associated in a multivariate model. These results suggest that adding more drugs targeting AR pathways may not bring better responses than fewer drugs. However, this needs testing in other prostate cancer disease states such as mCRPC, where the Alliance trial A has just completed accrual testing the addition of enzalutamide alone or in combination with abiraterone in early mCRPC.

Association of AR-V7 on circulating tumor cells as a treatment-specific biomarker with outcomes and survival in castration-resistant prostate cancer


Dr Oh

AR-V7 is a biomarker that appears to be a mechanism of resistance to AR-targeted therapies (ARTs), such as abiraterone and enzalutamide, in mCRPC. Since it was first described by Antonarakis et al in NEJM to be predictive of non-response to these agents, a follow-up paper suggested that taxanes may work in mCRPC independent of AR-V7 status. This paper from MSKCC evaluated 191 patients receiving ARTs versus taxanes and found several interesting findings: (1) only a total of 18% had AR-V7 detected, but it was strongly influenced by line of therapy (3% first line, 18% second line, 31% third or later line) and (2) survival was superior with taxane therapy compared with ARTs in patients with AR-V7(+) CTCs but not in AR-V7(-) patients. This suggests that the EPIC CTC platform could be useful to decide who should receive taxane chemotherapy.
Dr Antonarakis

There is accumulating evidence that the detection of the AR splice variant AR-V7 in circulating tumor cells (CTCs) from CRPC patients may be associated with lack of benefit from abiraterone and enzalutamide but retained sensitivity to taxane chemotherapy. Previous AR-V7 assays have used cell-surface markers to capture CTCs and have focused on PCR-based approaches to detect AR-V7 mRNA. The current study used immunofluorescence to detect nuclear AR-V7 protein in CTCs from 161 men with mCRPC. An AR-V7+ CTC was defined as one with nuclear-localized AR-V7 protein using their immunofluorescence assay.

The results showed that prevalence of AR-V7-positive CTCs increased with more lines of systemic therapy for CRPC and that detection of AR-V7-positive CTCs was associated with primary resistance to AR-signaling inhibitors (lower PSA response rates, shorter progression-free and overall survival) but that AR-V7 detection was not associated with primary chemotherapy resistance. Moreover, in AR-V7+ patients, taxane treatment appeared to produce superior survival compared to AR-directed therapy (HR 0.24, P=0.035). This study, together with the previous studies, adds to the growing evidence that CTC-specific AR-V7 detection may be a treatment-specific biomarker indicating better outcomes with taxanes in this setting. Prospective studies (NCT02269982) are ongoing to further validate the clinical utility of AR-V7 testing in men with metastatic CRPC receiving AR-directed agents and taxane chemotherapies.

Dr Quinn

This manuscript describes experience with assays of AR-V7 in CTCs in 161 men prior to therapy for mCRPC. Using an immunofluorescence assay they report that nuclear expression of AR-V7 is associated with poorer response to androgen receptor signaling inhibitors. A multivariate analysis showed that patients with nuclear AR-V7 have better survival when treated with taxanes versus ARSI drugs (hazard ratio, 0.24; 95% CI, 0.10-0.57; p = .035).

This study validates CTC nuclear expression of AR-V7 as clinically meaningful. It also suggests that this may form a basis for therapeutic choice between ARSI drugs and taxanes in mCRPC. This later finding was exploratory in the current study and therefore hypothesis generating, with need for prospective validation in follow-up trials.

Inherited DNA-repair gene mutations in men with metastatic prostate cancer

Pritchard CC et al. 

Dr Antonarakis

The incidence of germline (ie, heritable) mutations in genes governing DNA repair pathways was previously thought to be low in men with prostate cancer, unlike in patients with breast and ovarian cancers. In this study, the authors sequenced germline DNA from 692 men with metastatic prostate cancer, unselected for positive family
history or age at diagnosis. They focused on a set of 20 genes known to be associated with a variety of familial cancer-predisposition syndromes. They found that 11.8% of men with metastatic prostate cancer harbor one or more inherited DNA-repair gene mutations and that this incidence was higher than in men with localized prostate cancer (4.6%) or in the general population (2.7%).

The most commonly mutated genes were BRCA2 (5.3%), CHEK2 (1.9%), ATM (1.6%), and BRCA1 (0.9%). All of these are involved in the homologous recombination DNA repair pathway. Intriguingly, the frequency of these germline DNA-repair mutations in men with metastatic disease did not differ significantly according to family history of cancer or age at diagnosis. In addition to obvious family implications, these results may have direct therapeutic value for such patients who might be more sensitive to platinum chemotherapies, PARP inhibitors or immune checkpoint blockade strategies. Moreover, testing can be done from a simple blood or saliva sample.

**Dr Quinn**

This study assessed the germline DNA of 692 patients with advanced prostate cancer. Inherited DNA repair enzyme mutations presumed to be deleterious were identified in 82 men (11.8%); mutations were found in 16 genes, including BRCA2 (37 men [5.3%]), ATM (11 [1.6%]), CHEK2 (10 [1.9% of 534 men with data]), BRCA1 (6 [0.9%]), RAD51D (3 [0.4%]), and PALB2 (3 [0.4%]). These frequencies did not differ based on family history of prostate cancer or age at diagnosis or non-Hispanic white racial group. There was an association between having a family member with another (nonprostate) cancer and germline mutation. There was an association of germline DNA-repair gene with a Gleason score of 8 through 10 versus 7 or lower (odds ratio, 1.8; 95% confidence interval [CI], 1.0 to 3.5; \( p = 0.04 \)).

The incidence of these mutations was higher than in a project that found them in 4.5% of men with clinically localized prostate cancer (\( p < 0.001 \)). In a subset of 61 patients, tumor DNA was available for analysis and a somatic alteration was found in the second allele corresponding to the germline loss in 59% of tumors.

This study defines the germline mutation rate of around 12% in patients with advanced prostate cancer and defines the need for a family history assessment beyond that of prostate cancer occurrence for these patients. The finding of a second somatic hit in 59% of a subset of patients with tumor tissue compares the genetic basis of prostate cancer in an important subset of patients.

Given the potential therapeutic benefit of targeting these genes with PARP inhibitors, ATM inhibitors and other putative agents, screening of patients with prostate cancer and family history of cancers apart from prostate cancer may be appropriate.
Dr Antonarakis

The use of poly(ADP) ribose polymerase (PARP) inhibitors in unselected patients with metastatic CRPC has not been a very fruitful approach. In the current study, the authors performed a phase II trial using oral olaparib (400 mg twice daily) in 49 men with heavily pretreated metastatic CRPC. While the response rate to olaparib was only 33% in the overall population, the authors found an 88% response rate in patients with mutations in one or more DNA-repair genes. These mutations were detected from metastatic tumor biopsies and involved genes such as BRCA1/2, ATM, CHEK2 and FANCA (most of which are involved in homologous recombination DNA repair) and are thought to be present in about one-quarter of metastatic CRPC patients.

In addition, progression-free survival and overall survival were superior with olaparib in the biomarker-positive patients compared to biomarker-negative patients. Based on the results of this study, the FDA has granted olaparib “breakthrough therapy” status for the treatment of patients with taxane-refractory metastatic CRPC who have received either enzalutamide or abiraterone and have mutations in BRCA1/2 or ATM. Randomized phase III studies of olaparib in metastatic CRPC patients with mutated BRCA1/2 or ATM genes are currently being launched.

Dr Quinn

50 heavily pretreated mCRPC patients were enrolled on this Phase II study of the PARP inhibitor olaparib with mandated tumor biopsies for NGS to assess for somatic DNA repair enzyme gene mutations. 16 patients had such mutations and 14 (88%) of these had responses to olaparib therapy as measured by radiographic, PSA or CTC count response. In those patients who were marker negative the response rate was 6%. Several of the responses to olaparib, albeit with short follow-up, have been durable.

Grade 3-4 toxicities with olaparib included anemia (20%) and fatigue (12%). Olaparib is a therapeutic option for patients with somatic germ alterations in DNA repair enzyme genes. This may form the basis for undertaking tumor tissue biopsy and analysis to personalize the use of this therapeutic. Further studies with PARP inhibitors and other agents such as ATM/ATR inhibitors are warranted.
Dr Oh
Patients receiving docetaxel chemotherapy often complain of cumulative adverse events, including fatigue, weakness, decreased appetite, and alopecia. Docetaxel is usually given continuously until progression for up to 10 cycles. Similar to the approach taken for intermittent ADT for hormone-sensitive prostate cancer, some investigators have hypothesized that intermittent docetaxel might have comparable efficacy with less toxicity and perhaps less chemoresistance. A planned Phase III trial of continuous vs intermittent docetaxel was conducted in Germany but failed to fully accrue. 187 patients (<45% planned) were eventually accrued to this randomized trial — the results suggested that intermittent docetaxel was non-inferior to continuous therapy when evaluating 1-year survival.

However, when looking at overall survival, the endpoint of non-inferiority was not reached, as the study was underpowered. Toxicity was not different, and there were no QoL data. There was certainly no suggestion that intermittent therapy was more effective.

So the general approach to using docetaxel chemotherapy has not really changed — try to give up to 10 cycles if possible, but stop sooner if the risk/benefit ratio does not favor continuing. Consider resuming docetaxel in the future if the patient was still benefiting at the time of discontinuation.

Renal Cell Carcinoma

CABOzantinib versus SUNititinib (CABOSUN) as initial targeted therapy for patients with metastatic renal cell carcinoma (mRCC) of poor and intermediate risk groups: Results from ALLIANCE A031203 trial

Choueiri TK et al.
Proc ESMO 2016;Abstract LBA30_PR.

Dr Quinn
Alliance newsletter Aug 2016: POSITIVE TRIAL RESULTS FOR PATIENTS WITH PREVIOUSLY UNTREATED ADVANCED RENAL CELL CANCER

“Alliance researchers recently announced positive top-line results from Alliance A031203 (the CABOSUN study), a randomized phase II trial of cabozantinib in patients with previously untreated advanced renal cell carcinoma (RCC). The trial has met its
Dr Petrylak
The standard treatment for poor risk renal cell carcinoma is either intravenous temsirolimus or oral sunitinib. Since there is a survival benefit in second line renal cell carcinoma with cabozantinib, it would be reasonable to move this treatment up front in this group of patients. This was a randomized Phase II trial in which 157 patients with untreated clear-cell metastatic renal cell carcinoma of intermediate or poor risk were randomized either to oral cabozantinib (60 mg once daily) or sunitinib (50 mg once daily, 4 weeks on, 2 weeks off). A 31% reduction in the median rate of disease progression or death was noted when cabozantinib-treated patients were compared to those treated with sunitinib (8.2 months vs 5.6 months, \( p = 0.012 \)).

The objective response rate was also significantly higher in the cabozantinib arm compared to the sunitinib arm (46% vs 18%). Adverse events were similar between the 2 arms of the study, with the incidence of Grade 3 or higher adverse events being 65% in the cabozantinib arm and 68% in the sunitinib arm. The most common adverse events for both treatments included diarrhea, fatigue, hypertension, palmar-plantar erythrodysesthesia, and hematologic events, and 16 patients in each arm terminated their treatment early due to toxicity. Clearly more data need to be generated, and the study needs to mature for survival. It is also unclear whether this can be generalized to good risk patients.

**Cabozantinib versus everolimus in advanced renal cell carcinoma (METEOR): Final results from a randomised, open-label, phase 3 trial**


Dr Drake
This published article describes the final results of the METEOR study of cabozantinib (versus everolimus) in metastatic renal cell carcinoma, essentially updating a prior study published in *The New England Journal of Medicine* in 2015. That first report focused on progression free survival (PFS) in the first 375 randomized patients; this report includes the entire 658-patient study population. Unsurprisingly, the PFS data mirror those of the first publication, with a PFS for cabozantinib of 7.4 months versus 3.9 for everolimus. It should be noted that PFS in the first 375 patients was the primary endpoint of the study. These updated data included an unplanned second interim analysis of overall survival (OS), which showed an OS of 21.4 months in the cabozantinib group versus 16.5 months for everolimus.
As was the case in the NEJM manuscript, both regimens were associated with significant toxicity — Grade III/IV AEs occurred in approximately 70% of the cabozantinib-treated patients versus 60% for the everolimus group. ORR was also greater in the cabozantinib arm as compared to the everolimus arm (17% versus 3%) — leading to the conclusion that cabozantinib is the first agent to beat everolimus on 3 counts, OS, ORR and PFS. The clinical relevance of that 3-pronged victory remains unclear — with an all-grades AE rate of 100% it is unlikely that cabozantinib will come before nivolumab in the RCC treatment paradigm. What is clear is that everolimus is likely to fall out of favor, showing relative inferiority in at least 3 recent trials.

Dr Quinn

METEOR accrued mRCC patients previously treated with VEGFR-directed therapies. In the initial iteration in the NEJM there was a significant PFS benefit for cabozantinib over everolimus. Dose reduction was common with cabozantinib so that most patients ended up on 40 mg per day compared to the starting dose of 60 mg. Dose reduction occurred most often for gastrointestinal and general constitutional symptoms. Subsequently cabozantinib demonstrated an overall survival advantage compared with everolimus. In the later analysis (n = 658): ORR 17% vs 3%, PFS 7.4 vs 3.9 months, OS 21.4 vs 16.5 months (HR 0.66 [95% CI 0.53-0.83], p = 0.0003).

In subgroup analysis all groups benefited from cabozantinib, but interestingly patients with visceral mets (HR 0.66), bone mets (HR 0.54) and higher MET expression (HR 0.55) appeared to have better OS.

Dr Plimack

Cabozantinib and lenvatinib + everolimus were both FDA approved in the past year for the treatment of renal cell carcinoma after first line TKI therapy. Cabozantinib was approved based on a randomized Phase III trial of cabozantinib vs everolimus showing a 5-month overall survival benefit and a response rate of 17% vs 3% with everolimus. Notably, 62% of patients required a dose reduction for a median daily dose of 43 mg. However, only 12% discontinued due to an adverse event. Cabozantinib is now considered a new standard of care in this setting.

Dr Petrylak

Everolimus, an mTOR inhibitor, was the second line standard of care for patients with metastatic renal cell carcinoma. Cabozantinib is a small molecule inhibitor of the tyrosine kinases c-MET and VEGFR2 and has been shown to reduce tumor growth, metastasis, and angiogenesis. It is FDA approved for the treatment of metastatic papillary carcinoma of the thyroid and has been evaluated in prostate cancer. The METEOR trial compared cabozantinib to everolimus in 658 patients with metastatic renal cell carcinoma. The final results of this trial were reported with a median follow-up of nearly 19 months. Objective response rates were 17% in patients treated with cabozantinib versus 3% in those treated with everolimus.

The median overall survival was 21.4 months and 16.5 months for patients treated with cabozantinib and everolimus, respectively. An analysis of progression free survival (PFS)
in patient subgroups demonstrated that those patients with more favorable characteristics derive more clinical benefit. PFS for those patients who had favorable or intermediate prognostic factors was 7.5 months compared to 5.4 months for those patients with poor prognostic factors. Cabozantinib had more activity in patients with bone metastases. This is an observation that was noted previously in patients with metastatic prostate cancer. Approximately half of the patients went on to receive further therapy after disease progression on everolimus or cabozantinib.

Grade 3 or 4 adverse events observed in the cabozantinib treated patients included hypertension (15% versus 4%), diarrhea (13% versus 2%), fatigue (11% versus 7%), palmar-plantar erythrodysesthesia syndrome (8% versus 1%), anemia (6% versus 17%), and hypomagnesemia (5% versus 0%). This study led to the approval by the FDA of cabozantinib for second line metastatic renal cell carcinoma.

**Lenvatinib, everolimus, and the combination in patients with metastatic renal cell carcinoma: A randomised, phase 2, open-label, multicentre trial**


**Dr Drake**

Combination chemotherapy can be curative for a few cancer types (testicular cancer, lymphoma); based on that paradigm the notion of combining anti-cancer drugs with different mechanisms of action and/or resistance has been widely explored. In RCC, the proven efficacy of VEGF-targeted agents (sunitinib, sorafenib, pazopanib, axitinib) has led to a number of trials combining those drugs with mTOR inhibitors. Those studies have been uniformly disappointing, mostly showing increased toxicity without much evidence for additive, let alone synergistic, increase in efficacy. This study, comparing the combination of the mTOR inhibitor everolimus with the novel VEGF-TKI lenvatinib to either monotherapy represents the first successful combination of those 2 modalities in RCC.

The results from this relatively small (153-patient) randomized trial showed an improved PFS with the combination regimen as compared with everolimus (14.6 versus 5.5 months, HR = 0.40, \( p < 0.0005 \)), although the combination arm did not fare statistically significantly differently than lenvatinib monotherapy (14.6 versus 7.4 months, HR = 0.66, \( p = 0.12 \)). Combination VEGF/mTOR inhibition was reasonably toxic as well, with Grade 3/4 AEs occurring in 71% of treated patients. The combination regimen was associated with Grade 3/4 diarrhea in 20% of treated patients, whereas everolimus Grade 3/4 AEs were dominated by anemia (12%). Two deaths were attributed to the study drug. What was impressive, however, was the ORR, which was 43% in the combination arm versus 6% for everolimus alone and 27% for lenvatinib monotherapy.

Clinically, these data suggest improved activity for the combination of lenvatinib + everolimus, but since small patient numbers were involved, a larger confirmatory study is in order to better quantify both clinical activity and toxicity.
**Dr Quinn**

This study was a randomized Phase II in RCC patients who had received prior VEGF-directed therapy. Patients were randomized to either single-agent everolimus (control arm) or lenvatinib or a combination of both drugs (each of the agents was dosed lower in the combination). The combination resulted in a better ORR (43%), PFS (14.6 months) and OS (median 25.5 months) at the cost of an increase in side effects over single-agent treatment. These data were presented to the FDA, who approved the combination of lenvatinib and everolimus based on improvement in outcomes over everolimus alone. Subsequently the manufacturers of the 2 drugs agreed to co-market the combination. Where do we fit this combination? Second line versus Nivo or Cabo? Later where you might give axitinib or everolimus?

Trials are planned, potentially in the first line vs sunitinib or other standard of care.

**Dr Plimack**

Lenvatinib + everolimus as a standard of care is more controversial. The FDA approval is based on a randomized Phase II trial, not Phase III. While the study shows a statistically significant PFS and OS benefit of the L + E combination as compared to everolimus, the comparison of L + E to lenvatinib alone does not show a statistically significant advantage, calling into question whether the combination is truly better than sequential second line VEGF therapy followed by mTOR inhibition or the reverse. Giving both drugs in combination compounds both toxicity and cost. So while these results aren’t as impressive or impactful clinically, this combination would be reasonable to consider once both checkpoint and single agent TKI therapy have been exhausted and the next reasonable option left is an mTOR inhibitor, as the addition of lenvatinib does seem to boost the efficacy of everolimus alone.

**Dr Petrylak**

Lenvatinib is a receptor tyrosine kinase inhibitor that inhibits the kinase activities of the vascular epithelial growth factor (VEGF) receptors VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4). Lenvatinib also inhibits other receptor tyrosine kinases implicated in pathogenic angiogenesis, tumor growth, and cancer progression in addition to their normal cellular functions, including the fibroblast growth factor (FGF) receptors FGFR1, 2, 3, and 4; platelet-derived growth factor receptor alpha (PDGFRα); KIT; and RET.

The combination of lenvatinib and everolimus exhibited anti-angiogenic and antitumor activity, as demonstrated by decreased human endothelial cell proliferation, tube formation, and VEGF signaling in vitro and tumor volume in mouse xenograft models of human renal cell carcinoma, greater than that observed with each drug alone.

In this randomized Phase II study, 153 patients with advanced or metastatic renal cell carcinoma who previously received anti-angiogenic therapy were randomized to receive lenvatinib at 18 mg plus everolimus at 5 mg (n = 51), lenvatinib at 24 mg (n = 52), or everolimus at 10 mg (n = 50) once daily.

The major efficacy outcome measure was investigator-assessed progression-free survival evaluated according to RECIST (Response Evaluation Criteria in Solid Tumors).
v1.1. Among the 101 patients in the lenvatinib plus everolimus group and the everolimus monotherapy group, 72% were male, median age was 60 years (31% >65 years), 96% were white, metastases were present in 95%, and unresectable advanced disease was present in 5%. All patients had ECOG PS 0 (54%) or 1 (46%), and Memorial Sloan Kettering Cancer Center (MSK) risk categories were favorable, intermediate, and poor in 24%, 37%, and 39% of patients in the lenvatinib plus everolimus group and 24%, 38%, and 38% of patients in the everolimus group, respectively.

Median progression-free survival was 14.6 months (95% confidence interval [CI] = 5.9–20.1 months) in the lenvatinib plus everolimus group versus 5.5 months (95% CI = 3.5–7.1 months) in the everolimus group, with a hazard ratio of 0.37 (95% CI = 0.22–0.62). The treatment effect was supported by a retrospective independent radiographic review, which yielded a hazard ratio of 0.43 (95% CI = 0.24–0.75). The hazard ratio for a post-hoc, updated comparison of overall survival between the lenvatinib plus everolimus and the everolimus group was 0.67 (95% CI = 0.42–1.08). Comparison between the lenvatinib and everolimus monotherapy groups supported the activity of lenvatinib.

The combination showed numerically superior progression-free survival, objective response rate, and overall survival versus lenvatinib monotherapy.

**Long-term overall survival with nivolumab in previously treated patients with advanced renal cell carcinoma (aRCC) from phase I and II studies**


**Dr Drake**

This abstract tabulated long-term data from RCC patients treated with the anti-PD-1 antibody nivolumab, combining data from Phase I/II trials. There are 2 noteworthy aspects of these data: first is an impressive long-term OS, with approximately 30% of patients alive at 4 years and a survival curve showing a flattening shape, suggesting the possibility of long-term non-progression in some treated patients. Second, the data show no evidence for accumulating autoimmune toxicity; indeed, the majority of treatment-related AEs occur relatively early (within the first 6 months) of treatment. Although the numbers of patients involved is relatively small, these data provide clinical confidence for treating physicians in that at least some fraction of nivolumab-treated RCC patients are likely to enjoy long-term survival.

**Dr Quinn**

This was a composite of several Phase I and II studies in mRCC with nivolumab to look at long-term outcomes for patients followed for more than 4 years. In 167 patients the ORR was 21.6%, median time to response was 2.8 months, median duration of response 23 months and median overall survival was 23 months. Around one third of patients were alive at 4+ years. Of patients alive for more than 4 years, 17% were MSKCC poor risk, 33% SD as best response and 19% PD as best response. Most treat-
ment-emergent adverse events occur in the first 6 months of treatment with diminishing occurrence thereafter. Most toxicity types resolved with therapy and time, but endocrinopathies tended to be more persistent. It would be of great interest whether PD-L1 expression predicts long-term survival — this may allow us to select patients for single immunotherapy against combinations as in melanoma, for example.

**Atezolizumab, an anti-programmed death-ligand 1 antibody, in metastatic renal cell carcinoma: Long-term safety, clinical activity, and immune correlates from a Phase Ia study**


**Dr Drake**

This paper reports on 63 RCC patients treated with the anti-PD-L1 antibody atezolizumab in a Phase Ia study. The ORR in evaluable patients was 15%, consistent with data from the Phase III trial of nivolumab (to be discussed next). Tolerability was excellent, with no Grade 4 AEs and 17% Grade 3 AEs. ORR did not correlate with PD-L1 expression on immune cells (IC). This study included some additional biomarker work, which showed that at baseline, the effector to regulatory T-cell ratio might carry some predictive value. Overall this study confirms the concept that PD-1/PD-L1 blockade is active in RCC.

However, given the recent approval of nivolumab in RCC, interest in atezolizumab monotherapy is perhaps less acute than interest in the combination of atezolizumab + bevacizumab, which is being evaluated in an ongoing Phase III first-line trial.

**Dr Quinn**

Phase I dose-escalation experience with atezolizumab in RCC: 70 patients (63 ccRCC, 7 non clear cell). MTD was not reached. Variety of prior lines of therapy for RCC. In 63 ccRC patients, median OS 28.9 months (median OS 20.7 months in patients with prior VEGF therapy), PFS 5.6 months, toxicity modest. ORR 15%; by PD-L1 IC 1/2/3 18% vs 9% IC 0 — note, SP142 antibody IHC on tumor cells rather than immune cells. All RECIST responses were in patients with ccRCC but 1 non clear cell patient experienced response by irRC. Interestingly, patients with Grade 4 by nuclear grade or sarcomatoid differentiation (n = 18) had a response rate of 22% with median OS 26.2 months and MSKCC poor risk patients (n = 20) ORR 25% and median OS 20.7 months. Interesting activity overall but especially in some groups with poorer outcomes.

Future studies: Bev + atezo vs sunitinib in first line ccRCC recently completed accrual.
Nivolumab versus everolimus in advanced renal-cell carcinoma\(^1\)

Treatment beyond progression with nivolumab (nivo) in patients (pts) with advanced renal cell carcinoma (aRCC) in the phase III CheckMate 025 study\(^2\)

\(^1\) Motzer RJ et al. 

\(^2\) Escudier BJ et al. 
*Proc ASCO* 2016;Abstract 4509.

**Dr Drake**

This *NEJM* paper relays data from the pivotal Phase III (CheckMate 025) trial of nivolumab in second-line (and beyond) RCC. This trial was positive for its primary OS endpoint: 25 months for nivolumab vs 19.6 months for everolimus (HR 0.73, \(p = 0.002\)). ORR was also improved in the nivolumab arm (25% versus 5%). What was not improved was PFS, which was similar between arms at approximately 4.5 months. There was a fairly extensive analysis of PD-L1 staining as a predictive biomarker, which surprisingly showed no correlation with OS. As in prior studies, nivolumab was well tolerated, with a Grade 3/4 AE rate of 19%, which compared favorably with everolimus (37%).

One often overlooked aspect of these data is the admittedly underpowered but hypothesis-generating subgroup analyses; consistent with prior data from the Phase Ib trial, these data hint that patients in a worse MSKCC prognostic group may actually be more likely to benefit: Poor-risk patients had an unstratified HR for death (versus everolimus) of 0.47 (CI 0.30-0.73), whereas favorable patients had a HR of 0.89 (CI 0.59-1.32). Overall, these data strongly support nivolumab as a second-line agent in RCC but provide little guidance for patient selection. And although impressive, the 25% ORR reported here leaves significant room for improvement via combination regimens like ipilimumab/nivolumab, which is being evaluated in the first-line setting in RCC.

**Dr Quinn**

Nivolumab was compared to everolimus in RCC patients previously treated with VEGF-directed therapy. Nivolumab was superior for ORR (25% vs 5%), OS and adverse events but not PFS. In addition, quality of life was significantly better on nivolumab. Of note, only about 1% of patients in each arm achieved CR — this was considered disappointing in the context of complete response being the first step with “paleo” immunoncology — high-dose IL2.

These data were key in the FDA decision to approve nivolumab for use in advanced kidney cancer progressing after prior VEGF-directed therapy. Post hoc analysis shows that patients who continued nivolumab had a better survival: 28.1 vs 15 months; HR 0.41, \(p < 0.001\). This is hypothesis generating and subject to major selection bias in that patients who are asymptomatic or who have low-volume cancer and/or fewer side effects are likely to be selected to stay on therapy. Notable, however, is that 50% of
patients selected to continue therapy after progression and that there are patients that have durable responses after progression who likely have benefit from ongoing therapy.

**Dr Plimack**

CheckMate 025 established nivolumab as a standard of care for metastatic RCC after prior first line TKI therapy, based on a 5-month overall survival benefit compared to everolimus. Notably, the median overall survival in this group was 25 months. The significance of this positive trial is that it establishes a new treatment modality — checkpoint inhibition — as opposed to the other trials, which evolve the previously established TKI and mTOR therapies.

Treatment beyond progression is a new paradigm that has emerged with the checkpoint inhibitors. We know that initial RECIST progression can be followed by a response, and long term survival can occur for patients who initially progress, as noted above. However, knowing when to treat beyond progression (TBP) versus switching therapies is somewhat of an art.

There are 2 scenarios where I typically favor TBP rather than a switch. The first is if the patient looks and feels well but the first scan shows some minimal progression. The second is for a patient who has already achieved disease control and then many months to years into therapy progresses in a solitary site. In this latter scenario we often treat the new lesion focally with surgery or radiation and then continue with the checkpoint inhibitor.

**Dr Petrylak**

This international trial randomized 821 previously TKI treated metastatic clear cell renal cancer patients to receive nivolumab at 3 mg/kg intravenously every 2 weeks or everolimus at 10 mg orally once a day. The hazard ratio (HR) for death (from any cause) with nivolumab versus everolimus was 0.73 ($p = 0.002$). Objective response rates were almost fivefold higher with nivolumab, 25% versus 5% ($p < 0.0001$). In each arm, complete responses were observed in 1% and the median duration of response was 12 months. Median progression-free survival was 4.6 months with nivolumab and 4.4 months with everolimus ($HR = 0.88; p = 0.11$).

Nivolumab was effective irrespective of the expression of the PD-1 ligand, PD-L1, suggesting that PD-L1 expression should not be used to select patients for this treatment, Dr Sharma said. Hazard ratios were 0.79 for patients with PD-L1 expression $\geq 1\%$ and 0.77 for those with PD-L1 expression $< 1\%$. Treatment-related adverse events of any grade were observed in 79% of those who received nivolumab and 88% of those who received everolimus; Grade 3-4 events occurred in 19% and 37%, respectively. The most common Grade 3-4 events were fatigue with nivolumab (2%) and anemia with everolimus (8%). Toxicities led to treatment discontinuations in 8% and 13%, respectively, and 2 patients taking everolimus died as a result of toxicity. There were no treatment-related deaths on the nivolumab arm.

The issue of continued treatment was addressed in this paper as well as the paper presented by Escudier at ASCO. The Motzer study included an ad hoc sensitivity analysis among patients who did not experience disease progression or death by 6 months.
Genitourinary Cancer

(35% with nivolumab and 31% with everolimus). In this analysis, median progression-free survival was 15.6 months with nivolumab versus 11.7 months with everolimus (HR = 0.64). The observation that the curves diverged after the median was reached suggests a potential delayed treatment effect with immunotherapy. Escudier et al found that of 406 nivolumab patients, 38% were treated beyond progression (TBP); 36% were not TBP.

Median overall duration of treatment was 8.8 (TBP) and 2.3 months (NTBP). From randomization to progression, objective response rate was 20% and 14%; median time to response was 1.9 and 3.7 months; duration of response was 5.6 and 7.0 months for TBP and NTBP patients, respectively. Treatment-related adverse events occurred in 71% of patients TBP and 70% of patients NTBP before first progression. The median duration of TBP was 3.4 months. Of 140 patients TBP with tumor measurements before and after progression, 14% had ≥30% tumor burden reduction from first progression. Median overall survival was 28.1 (TBP) versus 15.0 months (NTBP); p < 0.001. The percentage of patients who had tumor burden reduction past progression is similar to that seen with atezolizumab in bladder cancer.

Adjuvant sunitinib or sorafenib for high-risk, non-metastatic renal-cell carcinoma (ECOG-ACRIN E2805): A double-blind, placebo-controlled, randomised, phase 3 trial


Dr Drake

VEGF tyrosine kinase inhibitors show clear activity in metastatic RCC, as well as in the pre-surgical setting, where TKI treatment is occasionally utilized to “debulk” patients in preparation for definitive primary therapy. What was not known was whether these agents would have activity in the adjuvant setting — after surgery a significant fraction of patients with high-risk disease eventually relapse and succumb to metastatic RCC. Biologically, this is thought to occur when ‘micrometastatic’ disease, already present at the time of surgery, evolves and progresses. However, it should be noted that very little is known about the location or phenotype of these elusive ‘micromets,’ especially in humans.

Nevertheless, the success of early adjuvant therapy in other cancers — breast cancer is a good example — has led to interest in testing whether therapies that are effective in advanced disease could prevent recurrence. ECOG-E2805 tested this concept by randomizing a very large number of patients (1,943) to sorafenib versus sunitinib versus placebo, with treatment commencing post-surgery and continuing for 1 year. The results were overwhelmingly negative, with no suggestion of benefit for either TKI. Additionally, both agents seemed to be potentially less well tolerated in this adjuvant setting, with a large number of patients discontinuing treatment for toxicity, even with dose reductions. Clinically, then, adjuvant treatment of RCC with TKI is not likely to occur in the near term.
Perhaps more intriguingly, these data suggest that the biology of micrometastatic RCC may be different from the larger lesions apparent in either the primary or recurrent setting.

**Dr Quinn**

ECOG-ACRIN E2805, otherwise known as the ASSURE trial, is the first adjuvant trial of targeted therapy for high-risk RCC treated with nephrectomy. The trial compared a year of placebo, a year of sorafenib and a year of sunitinib. The course of the trial was notable for patients requiring dose reduction and dropping out of the trial, requiring an amendment to increase numbers accrued. Despite this the trial failed to demonstrate any difference between the arms for PFS or OS.

While this trial produced a pause in the adjuvant targeted therapy field (we have adjuvant trials of sorafenib [SORCE], pazopanib [PROTECT], axitinib [ATLAS] and everolimus [EVEREST – SWOG S0931] accrued and to report in the next 3 years), news emerged that the STRAC trial with sunitinib has met its DFS endpoint.

**Dr Plimack**

The rationale for adjuvant therapy is to reduce the incidence of recurrence — ie, increase the cure rate. For patients who are at high risk, this is an important unmet need, as recurrent metastatic disease cannot yet be cured. The ASSURE trial included patients at both low and high risk and showed no difference in disease free survival or overall survival between sorafenib, sunitinib or placebo.

**Dr Petrylak**

Patients with renal cancers larger than 4 cm at time of nephrectomy have systemic failure recurrence rates that range from 20% to 50%. Randomized trials showed that older biologic agents such as alpha interferon have no impact on the natural history of the disease; interleukin-2 has never been evaluated in an adequately powered randomized trial in this group of patients. To assess the effect of newer agents targeted against vascular endothelial growth factor (VEGF) in the adjuvant setting, investigators performed a Phase III, randomized, double-blind, placebo-controlled trial in which 1,943 renal cancer patients received the oral anti-angiogenic tyrosine kinase inhibitors sunitinib or sorafenib versus placebo for 54 weeks following nephrectomy. Patients had pathologic-stage, high-grade T1b or greater disease with completely resected nonmetastatic renal-cell carcinoma and adequate organ function. Patients were stratified by recurrence risk, performance status, and histology. Of note, the protocol was modified to expand accrual secondary to a higher than expected treatment discontinuation rate. At a median follow-up of 5.8 years, median disease-free survival (the primary endpoint) was similar with sunitinib, sorafenib, or placebo (70.0, 73.4, and 79.6 months, respectively); overall survival was also similar among the 3 treatment groups. The rate of treatment discontinuation due to adverse events was similar with sunitinib or sorafenib (44% and 45%, respectively). Given the lack of progression-free or overall survival benefit, routine use of these drugs as adjuvant therapy is not considered standard of care.
The S-TRAC trial showed a delay in time to recurrence of 1.2 years but no difference in overall survival. It should be noted that the OS data from the S-TRAC trial are not considered mature, but as the curves so very tightly overlap it is felt to be unlikely that a difference will ultimately develop with longer follow-up.

Below are my talking points with patients on this subject:

- Your surgeon removed all the cancer he/she could see, but you may still have microscopic cancer cells in your body.
- If these take root and form cancer deposits in your body (recurrence), we don’t have the tools to cure you as of today. We do have treatments that can control the disease, and we are working to improve these through clinical trials.
- Many clinical trials have tried to test different treatments after surgery, hoping to increase the rate of cure.
- Your risk of recurrence of your RCC is XX% (from cancernomograms.com)
- One large study suggests we may be able to delay your recurrence by up to about a year on average by treating you with sunitinib for 1 year. In another large study sunitinib did not delay recurrence. Neither of the studies convincingly show that a year of sunitinib will increase your chance of cure.
- Discuss side effects of sunitinib and strategies for coping with them, including dose reduction and treatment discontinuation.

Dr Petrylak

This Phase III trial randomized 615 high risk post-nephrectomy clear cell renal cancer patients to adjuvant administration of sunitinib 50 mg per day for 4/6 weeks (dose reduction only to 37.5 mg/d allowed) or placebo. The primary endpoint, disease-free survival, was assessed by an independent review committee.

The primary endpoint of the trial was met with a significantly longer disease-free survival of 6.8 years with sunitinib compared to 5.6 years with placebo (HR 0.761, \( p = 0.03 \)). Adverse events of Grade 3 or higher were more frequent with sunitinib (62.1%) compared to placebo (21.1%).

There were no deaths due to treatment toxicity. Of concern with this study is the fact that there is no survival benefit, and the fact that the ASSURE trial, discussed above, does not have a survival benefit leads one to conclude that adjuvant sunitinib is not a standard of care.
Dr Drake

These 2 abstracts present both new and updated data concerning the activity of the anti-PD-L1 antibody atezolizumab in metastatic bladder cancer. The data presented by Dr Arjun Balar are particularly important because they provide, for the first time, data on the activity of anti-PD-L1 in the up-front (first-line) setting. Prior to this report, the vast majority of studies of PD-1/PD-L1 blocking antibodies were in the second line and beyond, and it was not clear whether these drugs would have greater activity in the second line (because of potential immunogenic effects of chemotherapy) or if second-line activity was in fact attenuated due to immunosuppressive effects of prior immunotherapy.

In fact, neither was true — surprisingly the activity of atezolizumab in the first-line setting was similar to that observed in the third line and beyond. Dr Balar reported on a 119-patient cohort from the IMvigor trial who were cisplatin ineligible, who had an overall response rate of 24%, similar to the 15% noted in the larger post-chemotherapy cohort. Interestingly, in the first-line setting PD-L1 expression on myeloid cells was not associated with increased rates of OR, PR or CR.

Dr Dreicer provided an update on the 310 patients in Cohort 2 of IMvigor; these patients had been treated with prior platinum-based chemotherapy, and earlier results were published in The Lancet Oncology.

These updated data confirmed the earlier response rate of 16% and showed a 12-month OS of approximately 40% overall. As per previous data, in the second line response to atezolizumab is associated with PD-L1 expression on immune cells in the tumor, with a RR of 28% for patients with an IC score of 2/3 versus 9% for IC 0. Taken together these 2 talks support the activity and tolerability of atezolizumab in bladder cancer; the drug was recently approved in the second-line setting but has very clear activity in the first-line setting as well.

Dr Quinn

IMVigor 210 is a Phase II trial with 2 components: Cohort 1 for cisplatin-ineligible (70% due to renal impairment, 20% PS 2) and Cohort 2 for platinum-treated advanced or recurrent urothelial cancer patients. The primary endpoint for both cohorts was ORR
with requirement to be better than 10%, which was based on the historical response rate to chemotherapy in the group of patients. Cohort 1 reported an ORR of 24% (CR 7%, PR 17%), Cohort 2 of 16% (CR 7%, PR 9%). Cohort 1 median OS 14.8 months, Cohort 2 median OS 11.9 months in high PD-L1 expressers (IC 2/3), 6.7 months in low expressers (IC 0/1). The 2 cohorts had common and contrasting results: Median DOR has not been reached in either study; PD-L1 was a relatively strong predictor of response in Cohort 2 but not in Cohort 1, perhaps reflecting an effect for prior chemotherapy for this biomarker. Common adverse events were fatigue, diarrhea and pruritus: Around 15% of patients had some sort of event that was considered immune related. Cohort 2 resulted in accelerated approval for atezolizumab.

Comments: The OS outcomes and DOR are impressive for PD-L1 high patients in Cohort 1 and across the Cohort 2 group. Patients with low expression in Cohort 2 have similar outcomes to those with single-agent cytotoxic therapy in this population — Phase III studies will address this: Atezolizumab vs chemotherapy Phase III is accrued. If patients with low IC PD-L1 expression have similar outcomes with chemotherapy, will the FDA make us use the marker for atezolizumab?

Dr Plimack
In the first line setting, we’ve now seen data with the PD-1/PD-L1 inhibitors in the front line setting: atezolizumab (Balar ASCO16) and pembrolizumab (Balar ESMO16). Both yielded the exact same response rate of 24%; we will need data to mature to see whether these are durable. In cross comparison to chemotherapy, the response rate is overall lower than that seen with gem carbo (36%) but the overall survival is longer with the checkpoint inhibitors. Whether this reflects overall survival drift due to availability of new agents or a true benefit would require a randomized trial. These are ongoing.

Dr Petrylak
Dreicer et al updated the IMvigor 210 trial, in which 310 patients with platinum treated metastatic urothelial carcinoma were treated with atezolizumab 1,200 mg IV q3wk until loss of clinical benefit. The overall objective response rate by RECIST was 16%, with 28% of patients who stained positive for PD-L1 in the immune cells (IC2/3) demonstrating objective responses. Overall, 7% of patients demonstrated a complete response compared to 15% of patients who were IC2/3. What was particularly interesting about this abstract was the fact that in IMvigor 210 patients were permitted to be treated past disease progression if the investigator determined that they were gaining clinical benefit from treatment.

Of the 134 patients who met this criterion, 28 (19%) demonstrated at least a 30% reduction in the target lesion. This has important implications for treatment duration and subsequent entry into clinical trials.

Balar et al evaluated the same dose and schedule of atezolizumab in 118 patients who had not had prior chemotherapy and were classified as cisplatin ineligible (inadequate creatinine clearance, peripheral neuropathy, hearing loss). When compared to cisplatin ineligible patients treated with carboplatin/gemcitabine in an EORTC study, a higher objective response rate (36% vs 24%) and median survival (14.8 vs 9.3 months) were observed.
Of note, most view carboplatin/gemcitabine as inferior to cisplatin/gemcitabine, and the median survival is comparable to that seen in studies evaluating gemcitabine/cisplatin in metastatic urothelial cancer patients. What was surprising about the study was that in contrast to the results reported by Driecer et al, there was no correlation between PD-L1 status and outcome.

**Efficacy and safety of nivolumab monotherapy in metastatic urothelial cancer (mUC): Results from the phase I/II CheckMate 032 study**


**Dr Drake**

These data provide an early look at the activity of the anti-PD-1 antibody nivolumab in previously treated metastatic urothelial cancer; 1 arm of a 3-armed Phase I/II study was presented. The other 2 arms, involving combinations of anti-CTLA-4 with nivolumab, will presumably be reported upon later. Of the 78 patients treated with nivolumab monotherapy, the confirmed ORR was 24%, similar to that of the anti-PD-L1 antibody atezolizumab, which is FDA approved in this indication. Interestingly, and in contrast to the published and reported data on atezolizumab, there was no association of response rate with PD-L1 status.

Overall these data confirm the activity of PD-1/PD-L1 blockade in metastatic urothelial carcinoma but muddy the waters in terms of PD-L1 IHC as a biomarker. The more interesting data from this trial will come from the combination arms, where a higher RR and AE rate are expected based on prior experience in other tumor types.

**Dr Quinn**

CheckMate 032 dose-escalation and Phase I/II study of nivolumab in UC previously treated with platinum-based chemotherapy.

78 patients, median PFS 2.78 months, median OS 9.72 months, ORR 24.4% (CR 6.4%, PR 17.9%).

Responses durable, similar safety profile to nivolumab in other cancers. Phase II CheckMate 275 now accrued to support accelerated approval.

Sneak peek CheckMate 275

**BACKGROUND**

In metastatic urothelial carcinoma, responses to second-line treatments are uncommon. Nivolumab monotherapy demonstrated promising efficacy and acceptable safety in this setting in a Phase I/II expansion cohort. We evaluated nivolumab efficacy and safety in patients with metastatic or surgically unresectable urothelial carcinoma whose disease progressed despite platinum-based chemotherapy.
METHODS
In this Phase II single-arm study (CheckMate 275), patients received nivolumab 3 mg/kg intravenously every 2 weeks until disease progression or unacceptable toxicity. The primary endpoint was overall objective response rate confirmed by blinded independent review committee (RECIST v1.1). Other endpoints included overall survival, efficacy by tumor PD-L1 expression (≥5%, ≥1%), safety, quality of life and biomarkers.

RESULTS
In total, 270 patients received nivolumab and 265 were evaluated for efficacy. Median follow-up for overall survival was 7.0 months (range, 0.1 to 13.4). Confirmed objective response rate was 19.6% (95% CI, 15.0 to 24.9), with responses independent of tumor PD-L1 expression. Median duration of response was not reached (95% CI, 7.43 to not estimable).

Median overall survival was 8.74 months (95% CI, 6.05 to not estimable). Grade 3-4 treatment-related adverse events occurred in 17.8% of patients, most commonly fatigue and diarrhea (1.9% each). Patient quality of life remained unchanged. Interferon-γ gene expression and urothelial carcinoma molecular subtype were associated with nivolumab response.

CONCLUSIONS
Nivolumab monotherapy provided meaningful clinical benefit, regardless of PD-L1 expression, and an acceptable safety profile in previously treated patients with metastatic or surgically unresectable urothelial carcinoma.

Dr Plimack
Overall, each of the second line single agent checkpoint inhibitor trials shows a similar profile. Each is notable for a low rate of severe toxicity, and a consistent 15%–20% response rate with most responses being durable. Of note, the pattern of progression after response to these agents appears to be the appearance of a new lesion rather than growth of existing lesions as has been the pattern with chemotherapy.

Dr Petrylak
Nivolumab, an anti PD-1 checkpoint inhibitor, was evaluated in patients who had received prior platinum based chemotherapy for metastatic urothelial cancer. Seventy-eight patients received nivolumab 3 mg/kg q2wk. Seventy-eight percent of the study’s 78 patients had visceral metastases, including 26% with liver metastases at baseline. More than half (53.8%) had received 2 or 3 prior chemotherapy regimens, and 12.8% had undergone more than 3 prior treatment regimens. The confirmed objective response rate (ORR) was 24.4% (95% CI, 15.3-35.4). Complete responses were seen in 6.4% of patients and partial responses in 17.9%. Stable disease was reported for 28.2% of patients and progressive disease in 38.5%. A median survival of 9.72 months (95% CI, 7.26-16.16 months) was observed. Median progression-free survival was 2.78 months (95% CI, 1.45-5.85 months). PD-L1 positivity was defined by the same criteria as in the Motzer renal cancer trial, and no correlation with response was seen. ORR was 26.2% (95% CI, 13.9-42.0) among patients with less than 1% of tumors expressing PD-L1, and 24.0% (95% CI, 9.4-45.1) among patients with 1% or more of tumors expressing PD-L1. These results appear to be comparable to the results seen with anti-PD-L1 agents.
Dr Drake
This paper and the accompanying editorial report on the activity of the anti-PD-L1 antibody durvalumab in metastatic urothelial bladder cancer. 61 patients making up the urothelial cohort of a larger Phase I/II multi-center trial are presented. The results support the accumulating data that PD-1/PD-L1 blockade is active in bladder cancer — the ORR was 31% in the 42 patients who were evaluable for response, with a long duration of response ranging from 4.1 to 49.3+ weeks. Similar to atezolizumab, there were no Grade 4/5 AEs and only a small number (4.9%) of Grade 3 AEs. It’s worth mentioning that the initial 20 patients in this cohort were pre-selected for PD-L1 expression, leading to some enrichment of that population. What’s most interesting about this study is the novel, composite approach to PD-L1 evaluation the investigators applied, integrating both immune cell (IC) and tumor cell (TC) expression. For purposes of correlation, patients with ≥25% staining in EITHER TC or IC were designated as “positive,” whereas “negative” patients had <25% staining in BOTH the IC and TC compartments. This composite definition led to an apparent increase in negative predictive value: Patients with <25% staining of both the TC and IC compartments had a 0% ORR, although only 14 patients met those criteria in this small cohort. Integrating these data with the data on atezolizumab and nivolumab convincingly shows that PD-1/PD-L1 blockade is active in bladder cancer.

However, the predictive value of PD-L1 staining remains unclear, with the atezolizumab data showing weak but clear association in the post-chemo but not in the pre-chemo setting. For nivolumab, no correlation was noted (similar to what was seen in the pivotal trial in RCC), while the data with durvalumab suggest that a modified definition of “negative” might be of some use. It goes without saying that prospective evaluation of PD-L1 expression as a predictive biomarker of response in larger patient cohorts will be required to clarify its role in the clinic.

Dr Quinn
Phase I/II study of durvalumab in advanced UC.

42 patients, ORR 31% but 46% for PD-L1 expression ≥25% in either or both tumor cells and immune cells.

Selected biomarker population of patients with PD-L1-positive tumors for further development of durvalumab in UC: DANUBE (Ph III durvalumab +/- tremelimunab vs SOC chemotherapy first line), BISCAY and STUDY 10.
**Dr. Plimack**

The phase I basket studies of durvalumab (Massard JCO 16), atezolizumab (Petrylak ASCO 15), and the first line pembrolizumab study (Balar ESMO 16) all were used to develop the IHC assay, methodology of interpretation and cutpoint for PD-L1 positivity. In terms of using PD-L1 to select patients, an important point is that any biomarker will perform at its best in the sample set in which it was developed. How these perform on subsequent sets will determine the true utility of these biomarkers. Notably, the atezol biomarker does not perform as well in validation. We will wait to see if this is also true for pembrolizumab and durvalumab. In my opinion, a biomarker needs to be validated with a >80% positive and negative predictive value in order to be used to select treatment or trial entry.

**Dr. Petrylak**

As part of a larger Phase I trial, Massard et al evaluated durvalumab 10 mg/kg q2wk in 42 patients with metastatic urothelial carcinoma. The authors correlated objective response to treatment with staining of PD-L1 in both the immune cells and the tumor cells (positivity was defined as greater than 25% of the tumor cell staining positive and any immune cell staining positive). Of the 28 patients staining positive for PD-L1, 46% demonstrated an objective response by RECIST to durvalumab, whereas none of the 14 patients who stained negative for this marker responded. The DCR 12, defined as confirmed complete or partial response or stable disease for more than 12 weeks as defined by RECIST, was 53% and 29% in the PD-L1 positive patients and negative patients, respectively.

These results are in contrast to those with atezolizumab, where PD-L1 staining in the immune cells correlated best with response in IMvigor 210. Within the IMvigor study the ORR was 26% in patients positive for PD-L1 in immune cells (IC2/3) versus approximately 10% in the IC0/1 patients. Tumor cell IC was not found to correlate with response. In an editorial by Drake et al, the authors point out that different antibodies were used in the IMvigor 210 study (rabbit monoclonal SP1 42) than in the durvalumab trial (SP2 63). There is a discordance of approximately 25% between these antibodies, and no cross-companion studies have been performed.

The authors of this editorial are concerned about the negative predictive value of the PD-L1 assay in patients treated with durvalumab. Initially, 20 patients were treated regardless of their PD-L1 status, but subsequently patients were required to have ≥5% PD-L1 expression on tumor cells. The next 41 patients treated on study required PD-L1 positivity. Thus, the low numbers of PD-L1 negative patients make it difficult to interpret the negative predictive value of this test. The authors also point out that tissue heterogeneity may also explain why there is poor correlation between PD-L1 status and response.
Up-Front Treatment

Bortezomib, lenalidomide and dexamethasone vs lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT): Results of the randomized Phase III trial SWOG S0777


Dr Fonseca

Durie and colleagues have now reported a Phase III trial that shows the superiority of 3 versus 2 drugs. Patients (both eligible and ineligible for SCT) had better overall responses with the triplet (81.5% vs 71.5%) but also had better progression free survival (PFS) (43 vs 30 months) and overall survival (75 vs 64 months)(all significant). However, this came with a significant increase in peripheral neuropathy. Treating clinicians must maximize strategies to diminish neuropathy, particularly in first line therapy, given the long expected survival of myeloma patients now. While some investigators have studied and have used KRD as up-front therapy, VRd remains the standard of care for most patients.

Its widespread implementation started because of the promising results of a Phase II study that are now confirmed by a larger Phase III study. What remains unclear is the optimal duration of induction therapy in a patient who will transition to SCT. Should we stop at 4 cycles? Should we continue until best response? Currently bone marrows are not recommended in the pre-SCT evaluation, but perhaps they will be as dynamic monitoring for response becomes commonplace.

Dr Gertz

This comparative trial looked at the triplet bortezomib-lenalidomide-dexamethasone compared to lenalidomide-dexamethasone. Bortezomib was given days 1, 4, 8, 11. The triplet combination showed that response depth was greater; progression-free survival and overall survival were superior. In a multivariable analysis, predictors of superior outcome were international stage, hemoglobin level, and assignment to the triplet arm of the trial. Surprisingly, there was no increase in hematologic toxicity with the triplet combination, and the risk of Grade ≥3 neuropathy was 23% vs 3% in the 2 arms. One non-hematologic toxicity that was significantly greater in the triplet arm was diarrhea 8% vs 2%.

This is a practice-changing report, suggesting that the triplet of bortezomib-lenalidomide-dexamethasone should always be used preferentially to a doublet. Consideration of lenalidomide and dexamethasone should be reserved for the fragile elderly; and even in those instances, bortezomib-lenalidomide-dexamethasone “lite” could be
Multiple Myeloma

considered as an alternative. In another abstract presented at ASCO 2016, the triplet VTD was superior to VCD, suggesting that the optimal treatment for newly diagnosed multiple myeloma combines a proteasome inhibitor, an immunomodulatory agent, and a steroid.

Dr Orlowski

Bortezomib with lenalidomide and dexamethasone (RVD) has become one of the most popular induction regimens based largely on promising data from an early Phase I/II trial (Richardson et al. *Blood* 2010;116:679), but validation in a Phase III setting has been lacking. The SWOG-S0777 study randomized 525 myeloma patients who were transplant ineligible or were willing to defer transplantation to receive RVD or RD for 24 weeks, followed by continuous RD maintenance for both arms. Better overall (81.5% vs 71.5%) and complete response rates (15.7% vs 8.4%) were seen with the 3-drug regimen compared to RD. Also, progression-free and overall survival were improved with RVD by a median of 13 and 11 months, respectively, both of which were highly statistically significant.

Grade 3 neuropathy and gastrointestinal events were increased with RVD, but this trial used intravenous, twice-weekly bortezomib, and both would probably have been less frequent with subcutaneous dosing. Second primary malignancies were seen with equal frequency in both of the arms. These data establish RVD as a standard of care for induction therapy in both transplant-eligible and ineligible patients with symptomatic myeloma.

Dr Rajkumar

Until now we did not have data from randomized trials comparing 2 modern regimens in which an overall survival benefit was seen with a particular regimen. The SWOG-S0777 study is the first one to provide such data. This trial compared lenalidomide with dexamethasone (Rd) with bortezomib, lenalidomide and dexamethasone (VRd) in patients with previously untreated multiple myeloma. Treatment consisted of six 28-day cycles of Rd and eight 21-day cycles of VRd followed by Rd maintenance for all patients until progression, unacceptable toxicity or withdrawal of consent. Median PFS was 43 months (VRd) versus 30 months (Rd). The OS was also superior with VRd vs Rd: 75 (VRd) versus 64 months (Rd).

Based on this study, VRd is considered the standard of care for initial therapy of myeloma, both for transplant eligible and ineligible patients. Rd can still be considered for frail patients who may not be able to tolerate VRd. The other regimen used in the US, CyBorD, was tested in a separate trial in France; response rates were lower compared with VTD.
Dr Fonseca

In this interesting study by Cavo and colleagues 2 randomizations tested whether the addition of novel agents could eliminate the need for SCT (VMP vs SCT) and whether consolidation provided benefit beyond that of SCT alone. Preliminary results were presented with large numbers of patients (n = 1,192, not surprising for European trials!) where the superiority of transplant is still demonstrated over conventional agents alone. The results are again superior in regard to PFS (NR vs 44 months), deep response rates (VGPR or better, 85.5% vs 73.8%) and across all subgroups studied. No overall survival data are reported yet. A sub-analysis for high risk included patients with gains of 1q, and thus the effects of truly high-risk subpopulations may be masked. This criterion made the high-risk population rise to almost 40% when in most other studies patients at high risk comprise approximately 25%. Hopefully, future studies should be done with more restrictive criteria to define high risk. The study is also of interest since it will question whether a second SCT provides value in disease control. It seems that when we try to eliminate SCT it comes back with a vengeance and suggests sometimes 2 SCTs may be better!

Dr Gertz

This abstract explored the role of stem cell transplantation either single or in tandem compared to continuous novel-agent chemotherapy. All patients received induction with bortezomib-cyclophosphamide-dexamethasone followed by either bortezomib-melphalan-prednisone or 1 or 2 courses of high-dose melphalan. All patients then were randomized to consolidation with bortezomib-lenalidomide-dexamethasone vs no consolidation. High-dose melphalan produced improved progression-free survival with a hazard ratio of 0.73. In addition, it produced a superior VGPR rate. Variables affecting PFS included standard-risk cytogenetics, and benefit of transplant was independent of international stage. Moreover, tandem transplants were superior to single transplants with a \( p \)-value of 0.03 and a hazard ratio of 0.69. This abstract suggests that novel agent-based therapy does not obviate the benefit of stem cell transplant. Therefore, this is not a question of transplant or novel agents but obtaining the benefit from both. Based on these data, not referring patients (in this study \( \geq 65 \) years) for transplant would not meet the standard of care for newly diagnosed multiple myeloma.

Dr Orlowski

High-dose melphalan is often used as a consolidation therapy after induction treatment, but novel agent-based regimens with melphalan also have substantial activity
in this setting. Patients on the EMN02/HO95 MM trial received bortezomib, cyclophosphamide and dexamethasone (CyBorD) induction followed by stem cell mobilization, and then were randomized to consolidation with either bortezomib, melphalan, and prednisone (VMP) or high-dose melphalan for 1 or 2 courses. A higher very good partial response or better rate was seen in the transplant arm (85.5% vs 73.8%). Progression-free survival was superior for the transplant arm at 3 years (66.1% vs 57.5%), which was true for patients with standard- or high-risk cytogenetics, and tandem transplant appeared superior to single autologous transplant.

However, with the exception of fatigue and neuropathy, which were increased with VMP, hematologic, gastrointestinal, and infectious episodes were substantially more common in the transplant arms. The data do indicate that high-dose melphalan is a more efficacious consolidation after induction than standard-dose melphalan regimens. However, the use of a suboptimal induction in the form of CyBorD and the excess toxicity of transplant leave open the possibility that a more efficacious initial regimen, especially if better tolerated, could reduce the benefits of high-dose therapy.

Dr Rajkumar

Most trials that addressed the role of up-front transplant (ASCT) for myeloma were done prior to bortezomib and lenalidomide. In this randomized trial, patients received CyBorD (bortezomib/cyclophosphamide/dexamethasone) and then were randomized to 4 cycles of bortezomib/melphalan/prednisone (VMP) versus high-dose melphalan (HDM) and single or double ASCT. After transplant or VMP, patients were randomized to consolidation therapy with VRd versus no consolidation. All patients then received lenalidomide maintenance until progression or toxicity in both treatment arms. PFS was significantly prolonged in patients randomized to ASCT (HR = 0.73; 95% CI = 0.59-0.90; \( p = 0.003 \)), No overall survival differences were seen.

Although the trial purports to show that ASCT is superior to conventional therapy, there are many limitations. VMP is not a good comparator versus ASCT in transplant eligible patients. VRD would have been a better option. More importantly, the fact that PFS is prolonged is not necessarily indicative of a true clinical benefit. OS is similar, and further follow-up is needed. However, this trial, along with another one done by the IFM group, supports the notion that ASCT still has a role in initial therapy for myeloma.


Attal M et al.
Proc ASH 2015;Abstract 391.

Dr Fonseca

This and other studies continue to show the superiority of outcomes for the treatment of myeloma when SCT is employed as part of up-front therapy. The advent of novel therapies raised the question of the “value add” for transplant. Amongst these
the use of VRD gained great popularity as up-front therapy and achieved high levels of complete response. This international trial has completed the French portion of accrual (IFM), and additional results will be available when the American portion is completed (DFCI). Despite the promise of novel therapies, SCT is an important step, increasing the proportion of patients with deep and durable responses. The question is highly relevant since the Spanish group has shown that up to 30% of patients who achieve a CR with SCT may remain free from progression at 20 years (cured). While additional clinical trials are warranted, SCT remains part of the standard of care. Interestingly, it is estimated that about 30,000 new cases of MM occur each year in the US. If one half of them are eligible for SCT we should be performing about 15,000, and yet only about 5,000 patients undergo transplants per year. There is clearly a need for increased awareness.

**Dr Gertz**

The trial was a joint IFM, Dana-Farber trial, looking at novel agents vs novel agents plus transplant. Patients in the non-transplant arm received 8 cycles of lenalidomide-bortezomib-dexamethasone. In the transplant arm, patients received 3 cycles, then a stem cell transplant, and then 2 cycles of lenalidomide-bortezomib-dexamethasone followed by maintenance therapy with lenalidomide for 1 year. The patients who received stem cell transplant had significantly improved progression-free survival (43 vs 34 months). The hazard ratio for PFS (no transplant vs transplant) was 0.80. At 4 years, the PFS was 47% vs 35%, and the complete response rate for transplanted patients was 58% vs 46%. This is a practice-changing report as it indicates that transplant remains the standard of care for patients under the age of 65. This plus the prior abstract establishes the standard of care combining novel agents and stem cell transplant for optimization of results, keeping in mind that both trials included maintenance lenalidomide.

**Dr Orlowski**

The superior efficacy of our current novel agent-based induction regimens has led some to doubt the value of up-front stem cell transplant, and the IFM/DFCI 2009 trial was designed to evaluate this question. Patients received 3 cycles of induction with lenalidomide, bortezomib, and dexamethasone (RVD), stem cell mobilization, and either early transplant followed by RVD consolidation and R maintenance for 1 year or RVD consolidation and R maintenance for 1 year with transplant at first relapse. Very good partial remission or better (88% vs 78%) and complete response rates (59% vs 49%) were higher in the early transplant arm. Progression-free survival, which was the primary endpoint, was also superior with early stem cell transplantation (43 vs 34 months).

However, 4-year survival was equivalent (81% vs 83%) for the 2 arms, and early transplant was associated with a higher risk of death due to toxicity, as well as of second primary malignancies. These data demonstrate that early autologous stem cell transplantation for young, symptomatic myeloma patients does produce a greater response depth and durability but leave open the possibility that a first transplant performed as part of second line therapy can provide a similar overall survival.
Dr Fonseca

It has become increasingly clear that to effectively control myeloma in the long-term, deep responses are needed. The advent of treatment regimens that can produce a high rate of complete responses has brought to the forefront the possibility of incorporating even more sensitive methods for detection of minimal residual disease. Among these, the assessment of MRD via next generation sequencing was tested in this randomized Phase III trial of VRD versus VRD plus stem cell transplant. Achieving MRD negativity is a major factor predicting better progression free survival.

Interestingly, the main advantage of SCT over conventional treatment alone was that SCT as part of initial treatment increased the proportion of patients achieving MRD, but in a comparison of patients who achieved MRD negativity by each treatment, the outcomes were the same. Multiple methods exist for the detection of MRD and are being tested by large cooperative studies. They each have their advantages and limitations, but what is clear is that MRD testing is here to stay in the evaluation and management of myeloma.

Dr Gertz

Response depth has always predicted the duration of relapse-free survival in multiple myeloma. Patients who achieve a partial response do better than those who have stable disease. Very good partial responses and complete responses, respectively, do
better than the responses that have less depth. Stringent complete response appears to have the best outcome with polyclonal marrow plasma cells, no monoclonal protein by serum or urine immunofixation, and a normal free light chain ratio.

Minimal residual disease is the newest parameter for response depth and was applied to a prospective cohort of patients treated with novel agent-based chemotherapy with or without transplant. Minimal residual disease can be measured both by next-generation sequencing and by flow cytometry. Next-generation sequencing has been shown to be more sensitive, but the technique fails in 8% of patients. Both techniques are predictive of superior outcome. Minimal residual disease, when negative, indicates a 6-log reduction in tumor burden. Patients who are positive for minimal residual disease can be divided into a 4- to 6-log reduction and less than a 4-log reduction. In the reported trial, patients who had minimal residual disease negativity had an 83% 3-year progression-free survival. However, 17% still relapsed.

Biology had an important impact on outcome; patients with del(17p) very rarely achieved MRD negativity. This is not a practice-changing report, and measurement of MRD should not be incorporated into routine practice. MRD negativity is useful as a trial endpoint, particularly for rapid approval of new drugs and combinations by regulatory agencies. However, MRD negativity cannot, as yet, be used as an indication to stop therapy as has been done in patients with CML and BCR-ABL molecular response. Failure to achieve MRD negativity cannot be used as an indication for intensifying treatment or changing treatment to non-cross-resistant regimens. Measurement of MRD is a tool for clinical trials but cannot, as yet, be used to direct or select therapy and cannot be used as an indication of the need to discontinue therapy.

**Dr Orlowski**

Minimal residual disease (MRD) testing is now most commonly performed by multi-parameter flow cytometry, and MRD negativity is typically associated with longer time-to-event durations, but evaluations using next-generation sequencing (NGS) may be more sensitive. As part of the IFM/DFCI 2009 trial, MRD testing by both flow cytometry and NGS was performed after completion of consolidation with RVD, and then again after 12 months of lenalidomide. NGS to detect clonal immunoglobulin gene rearrangements proved to be feasible in 92% of myeloma patients. Three-year progression-free survival (PFS) in patients who were MRD-negative by NGS prior to maintenance at a sensitivity of \(<10^{-6}\) was 83%, compared with 53% at \(>10^{-6}\).

Among 163 patients who were MRD-negative by flow, 51% were positive by NGS testing, while 93% of flow-positive patients were also positive by NGS. MRD negativity by NGS generally predicted a better PFS than did MRD negativity by flow cytometry. Among high-risk patients, those with t(4;14) seemed to achieve MRD negativity more frequently than those with deletion 17p. These findings demonstrate the high success rate of MRD testing of marrow samples by NGS techniques, and they document that MRD negativity by NGS is more sensitive and associated with better PFS than that by flow.
**Dr Rajkumar**

With new MM therapies we are increasingly achieving deeper responses. Complete response (CR) was previously considered by many experts as a goal of therapy, at least in the front-line setting. But we recognize that many patients in CR still have minimal residual disease (MRD) detected by more sensitive techniques. MRD-negative state is now achievable with modern therapy for myeloma. In this study of VRD followed by lenalidomide maintenance with or without SCT, MRD was assessed by next-generation sequencing (NGS) and multicolor flow. Of 700 patients in the trial, a total of 246 patients were studied with NGS before maintenance and 178 after maintenance. Patients were classified in 3 categories: negative (<10\(^{-6}\)), low-positive (between 10\(^{-4}\) and 10\(^{-6}\)), and positive (>10\(^{-4}\)).

Using a cutoff at 10\(^{-6}\), patients below 10\(^{-6}\) had significantly longer 3-year PFS at 83% vs 53% pre-maintenance and 90% vs 59% post-maintenance. MRD had predictive value in CR patients. Half of the t(4;14) patients achieved MRD negativity versus only 1/16 patients with del(17p). This study demonstrates the prognostic value of MRD testing by NGS in myeloma. The flow method used in this study is not as sensitive as the next-generation flow (NGF) that has been developed by the Spanish group. Both methods now are incorporated into the new IMWG criteria for response assessment in myeloma.

We now need studies looking at whether change of therapy based on MRD result is of value in myeloma.

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**Improved efficacy after incorporating autologous stem cell transplant (ASCT) into KRD treatment with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (DEX) in newly diagnosed multiple myeloma**

Jakubowiak A et al.
*Proc EHA 2016;Abstract S101.*

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**Dr Fonseca**

In what probably represents one of the best outcomes for any clinical trial for up-front myeloma, the Multiple Myeloma Research Consortium study questioned whether the depth of response to KRD could be further improved by the addition of SCT. The results, even when the number of cases is rather small, are impressive. If the results of long-term follow-up published by the Spanish group hold true in this population, then we are witnessing the first glimpses of a sizable proportion of myeloma patients being cured. In particular, at the end of 8 cycles the rate of sCR was better with SCT (72% vs 30%), and this improved with even longer follow-up (88% vs 51% at completion of cycle 18). Notably, the 2-year PFS was 99% for KRD and SCT vs 92% for KRD without SCT. These survival numbers speak to the very high anti-myeloma activity of this combination. One can only start to imagine what a future will be like when triplets like this are combined with monoclonal anti-CD38 antibodies like daratumumab. It seems we are a drug, or a combination, away from the cure of a sizable fraction of patients — the arrival of an R-CHOP equivalent for this disease.
Dr Gertz

This abstract was built on the previous experience using carfilzomib-lenalidomide-dexamethasone in newly diagnosed multiple myeloma where a previous 55% stringent complete response rate and a 3-year progression-free survival of 79% were reported. In this Phase II trial, stem cell transplant was used to consolidate KRd induction, and then KRd was given post-transplant as consolidation through 18 cycles. In this regimen, carfilzomib was given at 36 mg/m² days 1, 2, 8, 9, 15, 16; lenalidomide was 25 mg days 1 through 21; and dexamethasone 40 mg weekly. Seventy-six patients were studied. In patients who received stem cell transplant by cycle 18, the stringent complete response rate was 88% compared with 51% in the prior Phase II study after 18 cycles. Moreover, KRd plus stem cell transplant produced an MRD negativity rate of 94%, indicating that stem cell transplant was better than a novel agent-based triplet therapy, and combining stem cell transplant with novel agents resulted in the best outcomes.

Dr Orlowski

Carfilzomib with lenalidomide and dexamethasone (KRD) is approved for relapsed myeloma after 1-3 prior therapies, and it also has shown high rates of complete response (CR) and minimal residual disease (MRD) negativity in a prior front-line study without stem cell transplant. In the current trial, high-dose melphalan was added after 4 cycles of KRD, and KRD was then resumed for 4 consolidation and 10 maintenance cycles. Stringent CR was achieved in 72% of 50 patients after cycle 8, compared to 30% in a historical control group treated with KRD without stem cell transplant. MRD negativity was seen in 94% of 31 patients tested by multi-parameter flow after cycle 8 and in 95% of 19 patients tested after cycle 18.

A finding of MRD negativity by next-generation sequencing (NGS) was associated with a 100% progression-free survival at 4 years in the historical KRD group, compared with only 78% if this was detected by flow. The data support the conclusions that high-dose melphalan followed by autologous stem cell transplantation augments the benefits of KRD-based therapy and that NGS-based measurements of MRD negativity are more sensitive than those by flow.

Dr Rajkumar

This abstract reports on results of 2 trials with KRd with and without ASCT for newly diagnosed MM. The KRd + ASCT study enrolled 76 patients; the KRd w/o ASCT study had 53 patients. At the end of cycle 8, stringent CR was 72% for KRd + ASCT versus 30% for KRd w/o ASCT. The 2-year PFS was 99% for KRd + ASCT versus 92% for KRd w/o ASCT. With KRd + ASCT, MRD by flow was negative in 94% of patients tested. The studies show that KRd is an active regimen in newly diagnosed MM. Whether it is superior to VRD remains to be seen. A trial comparing the two, the ECOG-E1A11 ENDURANCE trial, is ongoing. Meanwhile, caution should be exercised in interpreting these results.

Carfilzomib has been associated with cardiac side effects in a small proportion of patients. Further caution is needed given the lack of difference in efficacy with KMP versus VMP in the up-front CLARION trial. KRd may be considered for young high-
risk patients with newly diagnosed MM off study; for the rest of newly diagnosed MM patients, VRD is the standard of care.

**Phase 1/2 trial of ixazomib, cyclophosphamide, and dexamethasone for newly diagnosed multiple myeloma (NDMM)**

Lacy M et al. _Proc ASCO_ 2016;Abstract 8002.

**Dr Fonseca**

Lacy and colleagues presented their data on the oral version of CyBorD. While interest in this regimen has been waning due to the results of the IFM 2013-04 clinical trial, the regimen remains highly effective for the treatment of myeloma and other plasma cell neoplasms. In the IFM 2013-04 trial there were only 2 days of overlap with bortezomib and cyclophosphamide, and thus it is not fully representative of the possible synergy of these 2 medications. Ixazomib is considered an effective oral proteasome inhibitor and thus tested in the front line setting. Unfortunately the results do not achieve the level of response attained with other regimens for this population, such as VRD, KRD or even standard CyBorD. This does not diminish, however, the great interest that still exists in the use of ixazomib, particularly in combination with lenalidomide, in the relapsed setting.

**Dr Gertz**

Having established that triplet induction therapy for newly diagnosed multiple myeloma is superior to doublets, identifying an optimal triplet combination is important. The triplet combination of ixazomib 4 mg weekly, dexamethasone 40 mg weekly, and oral cyclophosphamide at a maximum tolerated dose of 400 mg/m2 represents an all-oral combination that requires a physician visit only once every 28 days. This triplet resulted in an overall response rate of 77% and a ≥VGPR in 35% and should not impact stem cell mobilization based on previously published data with cyclophosphamide-bortezomib-dexamethasone.

Using this all-oral triplet, the 1-year progression-free survival was 91%, and responses were rapid, median 1.8 months. Ixazomib produced no Grade 3-4 neuropathy, and Grade 1 and 2 neurotoxicity was not cumulative. This is a potentially practice-changing report because an all-oral triplet is particularly suitable for active working adults, minimizing time in a physician’s office, and is also useful for rural populations where distance plays a factor. The oral proteasome inhibitor, ixazomib, was well tolerated and appears to lack the neurotoxicity of bortezomib.

**Dr Orlowski**

Ixazomib is an orally available proteasome inhibitor recently approved in the United States in combination with lenalidomide and dexamethasone for patients with relapsed and/or refractory myeloma after at least 1 prior line of therapy. Its convenient dosing has prompted multiple studies in other combinations and settings, including the
current Phase I/II trial with cyclophosphamide and dexamethasone (ICD) for previously untreated symptomatic myeloma. The regimen proved to be tolerable, with only rare Grade 4 events restricted to hematologic toxicities, and no episode of Grade 3 or higher neuropathy. An overall response rate of 77% was reported, including 38% of patients with very good partial remission (VGPR) or better at the dose recommended for Phase II testing.

Progression-free survival was 91% at 12 months in this cohort, median time to response was a rapid 1.8 months, and median response duration was 18.4 months. A recent randomized study including bortezomib with cyclophosphamide and dexamethasone (CyBorD) as one arm (Moreau et al. Blood 2016;127:2569) found a 56.2% VGPR or better rate after 4 cycles, but this came at the cost of Grade 5 toxicities. Thus, ICD could provide a safer alternative for induction therapy, especially for patients who are unable to receive parenteral chemotherapy.

**Dr Rajkumar**

VRd is the preferred regimen for initial therapy in myeloma but is expensive and also needs parenteral administration at a physician’s office. We need highly effective oral regimens in MM, since a substantial proportion of patients with the disease are frail, elderly patients who may not be able to travel 1 or 2 times a week to a doctor’s office. The new oral proteasome inhibitor ixazomib provides such an option. In this Phase II trial, 51 patients were treated with ixazomib, cyclophosphamide, dexamethasone (ICD). Partial response or better was seen in 78%, including a VGPR rate of 38%. ICD is less expensive compared with the lenalidomide combinations. ICD is an excellent regimen to test in the future for treatment of myeloma. It is akin to oral CyBorD, with less risk of neuropathy and greater risk of GI side effects.

It is also less expensive than VRD. Once-weekly administration of all 3 drugs makes it very convenient for patients. Future trials should test ICD with another oral regimen that has been tested in this patient population, namely ixazomib, lenalidomide, dexamethasone (IRD). In current practice I would consider ICD (or IRD) for elderly patients who are unable to travel to get the parenteral dosing needed for VRd. These regimens allow us to deliver a triplet therapy to patients who would otherwise be treated with Rd alone.

**Phase I/II trial of the efficacy and safety of combination therapy with lenalidomide/bortezomib/dexamethasone (RVD) and panobinostat in transplant-eligible patients with newly diagnosed multiple myeloma**


**Dr Fonseca**

Panobinostat is the prototype of what drug development should be. The discovery of HDACs as potential therapeutic tools for MM was truly a bench to bedside effort
that stemmed from the laboratory investigations that showed the participation of acetylation and alternative pathways to the proteasome as mediators of resistance to bortezomib. Therefore, combinatorial strategies with bortezomib were explored in Phase I and II trials but ultimately were tested in a large Phase II trial (PANORAMA). This large trial showed what the laboratory had predicted, that the addition of panobinostat improved outcomes for MM patients receiving bortezomib, and yet the drug has not been used extensively in the clinic.

The major limitation has been diarrhea, which is now believed to be primarily a function of the dose and schedule studies. However, the scientific basis remains, and investigators like Shah have tested alternative dosing, even in the setting of new-diagnosis myeloma. While these studies are early on, the toxicity is better understood and other studies are under way with panobinostat in combination with carfilzomib and with IMIDs.

**Dr Gertz**

In this trial using the national standard for induction in newly diagnosed multiple myeloma, lenalidomide-bortezomib-dexamethasone, panobinostat was added in a Phase I dose escalation followed by a Phase II extension. Triplet therapy is established as the optimal induction for newly diagnosed disease; enhancing this triplet with a histone deacetylase inhibitor such as panobinostat is rational. A previous trial of panobinostat with bortezomib in relapsed/refractory disease demonstrated superior outcome for a pre-specified subset of patients, but tolerance using IV bortezomib was an issue.

In this trial, bortezomib was given subcutaneously days 1, 4, 8, 11; dexamethasone was given 20 mg the day of and the day after bortezomib; and panobinostat was given 10 mg orally days 1, 3, 5, 8, 10, 12 of each cycle. There were 48 evaluable patients. The ≥VGPR rate was 67%, comprising 21% VGPR and 46% nCR, CR, or sCR. This triplet combination with subcutaneous bortezomib was much better tolerated, with Grade 3-4 diarrhea seen in only 4% and Grade ≥3 neuropathy in 4%. This combination, although intriguing, is not yet practice changing because it will require a randomized Phase II trial of VRD vs panobinostat and VRD. The 4-drug combination produced an MRD negativity rate of 54%.

**Dr Orlowski**

Panobinostat is a histone deacetylase inhibitor that has been approved in combination with bortezomib and dexamethasone for relapsed and/or refractory myeloma patients who have had 2 or more lines of therapy including bortezomib and an immunomodulatory agent. To examine if it may have promise as part of induction therapy, panobinostat was added to lenalidomide, bortezomib, and dexamethasone (RVD) in this Phase I/II study. Beyond Grade 3-4 cytopenias, including anemia (seen in 10%), neutropenia (14%), and thrombocytopenia (36%), only fatigue (12%) was seen in at least 10% of patients. A dose of panobinostat at 10 mg given thrice weekly in weeks 1 and 2 with RVD was determined to be the recommended Phase II dose.

All patients who underwent stem cell mobilization were able to collect a high-quality product with no impact on subsequent engraftment. Within the first 4 cycles of therapy,
94% of 48 patients achieved at least a partial remission, with 46% having a near-complete response or better. Among 26 patients who had minimal residual disease (MRD) testing by multi-parameter flow cytometry prior to transplant, 54% were MRD-negative. This combination has the ability to induce rapid and deep responses in transplant-eligible myeloma patients, and it merits further study in a randomized setting.

Dr Rajkumar

This is a Phase II trial with panobinostat, a deacetylase inhibitor, in combination with lenalidomide, bortezomib and dexamethasone (Pano-VRD) in patients with newly diagnosed MM. 48 patients were studied. Partial response (PR) or better was seen in 94%. 54% of patients in the trial underwent ASCT. Compared with the relapsed-setting PANORAMA trial, gastrointestinal toxicity/diarrhea were less frequently seen. Overall this seems to be an active regimen for newly diagnosed disease. But it needs to be compared with triplet regimens in Phase III trials before this can be recommended for practice. There is also the issue of added cost, which will be substantial without clear proof of clinical benefit. The feasibility of this regimen does mean that this can be used in the salvage setting for patients with relapsed/refractory disease.

Smoldering Myeloma

Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): Long-term follow-up of a randomised, controlled, phase 3 trial


Dr Fonseca

What will it take? Hard to know, but in 2016 the vast majority of myeloma experts still recommend no treatment for smoldering MM (SMM), without distinction of risk. Should we wait for evidence of end organ damage and then treat? The new criteria from the IMWG state that we should not. They identified patients with an 80% risk of progression at 2 years with treatment now being recommended. And yet we (this author included) still recommend no treatment for SMM. Are we treating too late? The study by Mateos and colleagues shows that early introduction of lenalidomide delays progression to myeloma and also improves survival.

This effect was accomplished with an induction phase of lenalidomide combined with dexamethasone followed by lenalidomide maintenance. While not side effect free (and certainly not free!) the medication prevented progression and death with one of the most “patient friendly” regimens. Concerns about initial exposure to lenalidomide creating resistance are valid and need to be defined further with the longer follow-up of additional and larger studies. But if the results hold… will we change practice? If I were diagnosed with high risk SMM, would I want to start Rd?
Dr Gertz
This abstract represents an update of maintenance therapy for high-risk smoldering multiple myeloma. It is important to recognize that this does not apply to all smoldering myeloma but only high-risk, which as defined in this study included patients with 95% plasma cells expressing an aberrant immunophenotype, a technique that is not widely available outside Spain, and required immunoparesis and either ≥10% plasma cells in the bone marrow or an IgG >3 or an IgA >2 g/dL. This unblinded study demonstrated that TTP and OS favored the group treated with lenalidomide and dexamethasone. However, there are major drawbacks to this trial.

The definition of progression in controls required the development of symptoms, either a 2-gm drop in hemoglobin, hypercalcemia, renal failure, or the development of bone lesions, in order to begin therapy. This is not standard of care currently. Patients who had a significant increase in their M spike, such as an increase in the IgG from 3.5 to 4.5 gm, were not considered to have progression and continued to be monitored for CRAB symptomatology.

Patients in this trial did not undergo high-resolution imaging, such as PET/CT or whole-body MRI. Patients who would have gone immediately to treatment based on current IMWG criteria could have been enrolled and randomized to observation even though they would fulfill current criteria for active myeloma by + PET or + MRI. Thirdly, there was no uniform treatment for observation patients who progressed to active myeloma. In the article appendix, 13 different regimens were given to the 53 observation patients that progressed. Nineteen of them received either MPV or VD, and only 5 of the 53 received lenalidomide and dexamethasone. The lack of access to Rd and lack of uniform therapy at progression makes it very difficult to interpret the adequacy of therapy at the time an observation patient progressed.

My conclusion is that although the preliminary data are exciting for the treatment of high-risk smoldering myeloma patients pre-emptively, this trial has drawbacks. Current ongoing trials make this potentially practice-changing, but at this time I cannot recommend the routine use of lenalidomide-dexamethasone for high-risk smoldering myeloma (definition in the United States differs from Spain) until confirmatory studies have been completed and additional data are available.

Dr Orlowski
Patients with smoldering myeloma are currently followed with watchful waiting, but high-risk subpopulations progress to symptomatic disease with a high frequency in the first 2-5 years after diagnosis. The QuiRedex study therefore evaluated the benefits of lenalidomide and dexamethasone (RD) induction and then R maintenance versus observation, and the current report provides longer-term follow-up on this trial. Median time to progression to active disease remained superior for RD compared to observation (not reached vs 23 months). The median overall survival had not been reached in either group, but only 10 (18%) RD-treated patients died versus 22 (36%) of those who underwent observation.
Adverse events seen with RD treatment were consistent with its known safety profile, and while 6 RD-treated patients (10%) developed second primary malignancies compared to only 1 (2%) in the observation group, several of the 6 had evidence of antecedent conditions. On the surface, the data support early treatment with RD for those with high-risk smoldering myeloma. However, the use of only plain radiographic surveys to look for bony disease, the addition of dexamethasone for biochemical progression on R maintenance, and the recent redefinition of what constitutes symptomatic myeloma limit the applicability of these data to current practice.

**Dr Rajkumar**

This is a long term follow up of a study that was previously published in the *NEJM* in 2013. SMM patients have a risk of progression to MM of 10% per year. High risk SMM patients have a risk of progression of 25% per year. This high risk group was randomized in this trial to lenalidomide plus dexamethasone (Rd) versus observation. 125 patients were enrolled. Rd continued to show improved time to progression compared with observation (median not reached vs 23 months). OS was also improved (HR 0.43 [95% CI 0.21-0.92], \( p = 0.024 \)). The frequency of second primary malignancies was higher with Rd than observation (6 [10%] of 62 patients vs 1 [2%] of 63 patients). This trial shows that early therapy can prolong survival in newly diagnosed myeloma.

However, there are many caveats, including age difference between the groups, the lack of standardization by which risk classification was done, and the small sample size. Still, this is an important study that was critical for the development of the new IMWG diagnostic criteria for myeloma. At present observation is still standard of care for high risk SMM. But in selected patients with multiple high risk factors, therapy can be considered.
Multiple Myeloma

Relapsed Disease and New Therapies

Phase III randomized controlled study of daratumumab, bortezomib, and dexamethasone (DVd) versus bortezomib and dexamethasone (Vd) in patients (pts) with relapsed or refractory multiple myeloma (RRMM): CASTOR study

Daratumumab, bortezomib, and dexamethasone for multiple myeloma

An open-label, randomised phase 3 study of daratumumab, lenalidomide, and dexamethasone (DRD) versus lenalidomide and dexamethasone (RD) in relapsed or refractory multiple myeloma (RRMM): POLLUX

Daratumumab, lenalidomide, and dexamethasone for multiple myeloma

Palumbo A et al.
1 Proc ASCO 2016;Abstract LBA4.
Dimopoulos MA et al.
3 Proc EHA 2016;Abstract LB2238.

Dr Raje

Daratumumab is a human IgG1k monoclonal antibody that targets CD38, a transmembrane glycoprotein highly expressed in myeloma cells. It has been evaluated in a Phase I/II study where it demonstrated striking effectiveness as a single agent in heavily pretreated patients. This study included patients refractory to IMiDs and proteasome inhibitors, demonstrating an ORR in this group of 36%. These observations were corroborated by the SIRIUS study in a similar refractory MM population, where the median number of prior therapies was 5, and many of these patients were refractory to the latest agents, including carfilzomib (48% refractory) and pomalidomide (63% refractory).

These findings established daratumumab as the first monoclonal antibody with single-agent activity, particularly in a challenging patient population with refractory disease. Based on these findings, the FDA approved daratumumab in November 2015 in patients who had 3 or more prior lines of treatment.

Two Phase III trials evaluating combinations with daratumumab in earlier stages of relapse were just presented and may potentially change practice. The CASTOR study (MMY3004) randomized patients with relapsed disease after one or more prior lines of treatment to daratumumab with bortezomib SC and dexamethasone vs bortezomib and dexamethasone.
The ORR and PFS were significantly higher in the daratumumab arm: 82.9% vs 63.2% (p < 0.001) and not estimable vs 7.2 months; HR 0.39 (p < 0.001). The POLLUX study (MMY3003) randomized patients with one or more prior lines of therapy to daratumumab with lenalidomide and dexamethasone vs lenalidomide and dexamethasone. Patients with prior lenalidomide exposure who were not refractory were permitted to enroll but comprised a small proportion of the trial population, 18%. Similar to the CASTOR study, the daratumumab arm had significantly higher ORR and PFS, 93% vs 76% (p < 0.0001) and not estimable vs 18.4 months with a HR of 0.37 (p < 0.0001).

Both of these trials showed unprecedented improvement in outcomes with the addition of daratumumab and set the stage for using a daratumumab combination earlier in the course of the disease.

**Dr Anderson**

The CD38 antigen is expressed on normal and abnormal plasma cells as well as on activated B and T cells, natural killer cells, leukocytes, hematopoietic progenitor cells, and endothelial cells. Preclinical studies of the anti-CD38 monoclonal antibody daratumumab revealed that it triggers complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) as well as inhibiting CD38 activity. In addition, crosslinking of CD38 on the MM cell surface triggers apoptotic signaling. Moreover, daratumumab triggered synergistic MM cytotoxicity in combination with either lenalidomide or bortezomib in preclinical xenograft models of human MM. Excitingly, Phase I/II clinical trials defined the schedule of administration (weekly x 8, biweekly x 8, then monthly) and dose (16 mg/kg) of daratumumab that achieved 30% overall response (OR), including complete response (CR) and very good partial response (VGPR), in multiply relapsed MM. Although CD38 is shed from the MM cell surface and its levels correlate with progression of disease, this dose and schedule effectively targets tumor cells, even in far-advanced disease. Therefore, single-agent daratumumab received accelerated approval from the US Food and Drug Administration.

In the CASTOR trial reported by Palumbo et al, 498 patients with relapsed or relapsed and refractory MM were randomized to receive bortezomib 1.3 mg/m² and dexamethasone (20 mg) alone or together with daratumumab (16 mg/kg). At interim analysis with median follow-up of only 7.4 months, there were 67 events, an estimated disease-progression rate of 60.7% at 12 months, and a progression-free survival (PFS) median not reached in the triplet group compared with 122 events, an estimated PFS of 26.9% at 12 months, and a median PFS of 7.2 months in the doublet group.

This finding represents a 61% reduction in the risk of disease progression or death, and the independent data and safety monitoring committee recommended that this trial be unblinded and that daratumumab be given to treat disease progression in the control group. The PFS prolongation was evident irrespective of prior bortezomib treatment, in MM refractory to the last line of previous therapy, in patients aged < and ≥ 65 years, in all International Staging System stages of MM, and regardless of the number of lines of previous therapy or prior autologous stem cell transplantation. Moreover, OR rate was 82.9% in the daratumumab group vs 63.2% in the control group.
(p < 0.0001), with ≥VGPR in 59.2% vs 29.1% (p < 0.0001) and CR in 19.2% vs 9.0% (p = 0.0012).

Due to the short follow-up, median PFS during the next line of therapy and median overall survival (OS) were not reached in either treatment group. Tolerability was good, with adverse events observed with daratumumab triplet treatment similar to those attendant to bortezomib/dexamethasone, including thrombocytopenia, peripheral sensory neuropathy, and diarrhea. The major difference observed with daratumumab was infusion-related reactions, which occurred with the first infusion and were readily treated with corticosteroids. Daratumumab can bind to the typing red cells and interfere with the type and crossmatch for transfusion, but novel modifications now avoid this interference. Treatment discontinuation rates were similar in both groups: 7.4% in daratumumab vs 9.3% in control groups.

At the 2016 European Hematology Association meeting, Dimopoulos et al reported the POLLUX trial that randomized 569 patients with relapsed or refractory MM to lenalidomide (25 mg days 1 to 21), dexamethasone 40 mg weekly, with or without daratumumab (16 mg/kg). Time to progression was not reached in the daratumumab group vs 18.4 months in the control group. At median 13.4 months follow-up, the daratumumab-treated cohort had a 63% reduction in risk of disease progression or death. OR and ≥CR rates were 93% vs 76% and 43% vs 19% in the daratumumab vs control groups, respectively, including MRD negativity. Side effects were as expected for this drug combination.

These results with the addition of daratumumab to bortezomib/dexamethasone or to lenalidomide/dexamethasone represent a significant prolongation of PFS, associated with the highest rates and extent of response yet achieved with any therapy for relapsed MM. Moreover, responses were observed even in refractory and high-risk del(17p) MM, a subgroup in which early relapses are common and durable responses rarely observed. This analysis was done very early, and further follow-up is needed to assess the durability of responses and PFS as well as the adverse events that may manifest only with prolonged treatment, such as low blood cell counts due to progenitor cell depletion or opportunistic infections in the setting of depletion of activated immune effector cells expressing CD38.

Unexpectedly, it has recently been reported that those regulatory T cells that highly express CD38 are depleted by daratumumab, leading to enhanced clonal anti-MM responses. Clinical trials will identify biomarkers of response and determine whether therapy can be discontinued at the time of maximal response, especially in those patients achieving CR with minimal residual disease (MRD) negativity. Therefore, it may be possible with daratumumab combination therapy not only to deplete MM to the level of MRD negativity, but also to restore host anti-MM immunity.

The CASTOR and POLLUX studies have therefore changed the treatment paradigm for relapsed/refractory MM, establishing that daratumumab can augment either lenalidomide or bortezomib therapy alone, setting the stage for daratumumab, lenalidomide, and bortezomib combination therapy with daratumumab. This 4-drug combination in newly diagnosed MM is expected to further increase the MRD-negative CR rate and markedly improve patient outcome.
Elotuzumab is a humanized recombinant monoclonal IgG1 antibody that targets signaling lymphocyte activation molecule (SLAMF7), a cell surface glycoprotein that is highly expressed on both normal and MM plasma cells and is also found to a lesser extent on lymphocytes such as natural killer (NK) cells. Elotuzumab is proposed to have several modes of action: flagging myeloma cells for recognition by NK cells and enhancement of NK cell activity against MM cells by binding to SLAMF7 found on NK cells.

As a single agent elotuzumab does not show significant clinical activity but is effective when given in combination. ELOQUENT-2 is a Phase III study that compared the combination of elotuzumab with lenalidomide and dexamethasone to lenalidomide and dexamethasone in patients with relapsed disease. Of note, the trial limited enrollment of patients with prior lenalidomide treatment to 10%, and these patients had to previously demonstrate at least a partial response to lenalidomide. This trial enrolled 646 patients with a median of 2 prior lines of therapy. The elotuzumab-containing arm had superior PFS (19.4 vs 14.9 months in the control group, hazard ratio 0.7, \( p < 0.001 \)), and the ORR was also higher (79% vs 66%, \( p < 0.001 \)).

Adverse effects were similar between both arms, aside from infusion reactions with elotuzumab (10% Grade 1-2). In November 2015, the FDA approved elotuzumab in combination with lenalidomide and dexamethasone in patients who have received 1 to 3 prior lines of treatment. Therefore, this should be considered an option of treatment for patients who are being considered for lenalidomide based therapy.

Elotuzumab binds to SLAMF-7, an antigen universally expressed on MM cells, and mediates antibody dependent cellular cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) as well as binding to SLAMF-7 and CD16 on NK cells, thereby activating them. Phase I single-agent studies in relapsed MM achieved stable disease, but not responses, in patients with relapsed MM. Importantly, preclinical studies showed that lenalidomide markedly enhanced ADCC and MM cytotoxicity, setting the stage for combination studies.

Richardson et al report on a Phase Ib-II dose escalation study of lenalidomide 25 mg days 1 to 21 and dexamethasone 40 mg weekly with either 10 mg/kg or 20 mg/kg elotuzumab. Rates of OR, VGPR, and PR were 92% vs 76%, 42% vs 47%, 28% vs 27% in the 10 mg/kg vs 20 mg/kg cohorts, respectively. Treatment was well tolerated, with Grade 3 to 4 lymphopenia and neutropenia in 21% and 19% patients, respectively.
This study importantly established that an agent that achieved only stable disease as a single agent can achieve responses in combination therapy. It further established that more is not necessarily better, since the 10 mg/kg dose achieved saturation of the SLAMF-7 antigen on MM and NK cells as well as having at least comparable efficacy and fewer side effects. Most importantly, it set the stage for the ELOQUENT trial in patients with relapsed MM in patients with 1 to 3 prior therapies comparing lenalidomide/dexamethasone/elotuzumab vs lenalidomide/dexamethasone.

This trial achieved median PFS of 19.4 vs 14.9 months in the elotuzumab vs control groups, with 1-year and 2-year PFS of 68% vs 57% and 41% vs 27%, respectively, providing the basis for its FDA approval in patients with 1 to 3 prior therapies. However, the true place of elotuzumab/lenalidomide/dexamethasone in the management of MM remains to be determined, since most patients in North America receive lenalidomide/dexamethasone, often with bortezomib, as initial therapy.

Therefore, relapsed MM is often lenalidomide refractory, and we do not yet know whether the addition of elotuzumab will restore sensitivity or be active in this setting. Nonetheless, due to its activity and tolerability, elotuzumab is now used primarily in treatment of early and more indolent relapsed disease. Future directions of research include evaluation of this regimen as initial therapy as well as combination therapies with pomalidomide or with checkpoint inhibitors to enhance immune effector cells and response in relapsed disease.

**Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma**


**Dr Raje**

Ixazomib is a new, oral boronic acid PI. TOURMALINE-MM1 compared ixazomib combined with lenalidomide and dexamethasone (IRd) vs lenalidomide and dexamethasone (Rd) in a Phase III, double blind, randomized study of 722 patients with relapsed disease and 1-3 prior lines of treatment. The majority (69%) had received bortezomib and only 12% had received lenalidomide. The median PFS was significantly longer in the IRd arm, 20.6 vs 14.7 months, with a HR of 0.74 ($p = 0.01$), and the ORR was higher with IRd, 78% vs 72% ($p = 0.04$). The toxicity profile was generally similar in both arms, including peripheral neuropathy, though Grade 3-4 rash occurred in 5% of patients vs 2% in the control arm.

Based on these encouraging findings, the FDA approved ixazomib in November 2015 as part of a combination with lenalidomide and dexamethasone in patients with relapsed disease who have received at least 1 prior therapy. This was an important advance as an all-oral triplet for relapsed disease. As treatment duration becomes longer (especially given the tolerability and efficacy), convenience for patients will become increasingly important, and the availability of an oral PI may be important specifically in the context of maintenance approaches.
**Dr Anderson**

Ixazomib is a second-generation boronic acid-based proteasome inhibitor that is oral and has a half-life of 3 to 4 days. Two Phase I/II clinical trials tested once-a-week and twice-a-week schedules in patients with relapsed MM; both studies achieved single-agent response rates of 20%, and the once-a-week schedule was chosen for further study.

Moreau et al reported on 722 patients with relapsed, refractory, or relapsed refractory MM treated with lenalidomide 25 mg days 1 to 21 orally, dexamethasone 40 mg weekly (d1, 8, 15, 22), with or without ixazomib 4 mg (d1, 8, 15). The ixazomib prolonged PFS (20.6 vs 14.7 mo), which was evident in all patient subgroups, including those with high-risk genetics. The time to response was 1.1 months vs 1.9 months, OR rate was 78% vs 72%, ≥VGPR was 48% vs 39%, and median duration of response was 20.5 vs 15.0 months, in ixazomib vs control groups. Serious adverse events were similar in both cohorts, including neuropathy. The most common adverse events in the ixazomib group were thrombocytopenia, gastrointestinal, and rash, and were manageable.

This is the first all-oral regimen combining immunomodulatory drugs, proteasome inhibitors, and dexamethasone, which is both active and well tolerated. The patients treated in this study had to have MM that was naïve or sensitive to lenalidomide; however, in North America lenalidomide is commonly used as part of initial therapy and relapsed disease is therefore lenalidomide resistant. Future studies are needed to determine whether the addition of ixazomib to lenalidomide/dexamethasone can restore sensitivity in this setting. Already ixazomib/lenalidomide/dexamethasone has been evaluated as an all-oral regimen in newly diagnosed MM, where it achieved nearly universal responses. Extent of response increased with time on treatment. Moreover, patients in this trial were eligible to receive single-agent ixazomib maintenance therapy, which was well tolerated and upgraded the extent of response. The utility of ixazomib is currently being further evaluated in combination with pomalidomide for relapsed MM, as well as for post-transplant maintenance therapy.

**CHAMPION-1: A phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma**

Berenson JR et al. 
Proc ASH 2015;Abstract 373.

**Dr Raje**

Carfilzomib is a second generation proteasome inhibitor that received accelerated approved in July 2012 for patients with relapsed disease based on a Phase II study of carfilzomib as a single agent showing an ORR of 23.7%. In the initial studies, unlike with bortezomib, treatment-emergent peripheral neuropathy was uncommon, with Grade 3-4 neuropathy occurring in 1.1% of patients. However, toxicities unique to carfilzomib included cardiac failure in 7% of patients. Dyspnea was reported in 34% of patients, including approximately 5% experiencing Grade 3 dyspnea. The other inconvenience of carfilzomib is its schedule as it has to be given twice a week, 3 weeks in a row.
In the CHAMPION-1 study, the authors have used a more convenient weekly schedule without compromising dose. A weekly dose of 70 mg/m² was feasible and was well tolerated with it being efficacious as well. This will allow easy administration of this otherwise very active drug.

**Dr Anderson**

Carfilzomib is an epoxyketone irreversible inhibitor primarily of the chymotryptic-like activity of the proteasome. It received accelerated FDA approval at a dose of (20/27 mg/m² on days 1, 8, 15) due to a response rate of 20% in patients with MM refractory to bortezomib and exposed to an immunomodulatory drug. Subsequently, it received full FDA approval in relapsed MM due to a prolongation of PFS of 6 months when carfilzomib was added to lenalidomide/dexamethasone compared to lenalidomide/dexamethasone alone.

In these studies, carfilzomib was initially used at 20/27 mg/m² and 36 mg/m² on days 1, 2, 8, 9, 15, 16. Subsequently carfilzomib 56 mg/m² with dexamethasone 40 mg was compared to bortezomib (1.3 mg/m² on days 1, 8, 15) and dexamethasone 40 mg and found to markedly increase PFS, without attendant neuropathy. Berenson and colleagues report on a Phase I/II trial testing dose escalation of carfilzomib at a once-a-week schedule (d1, 8, 15) with dexamethasone 40 mg (d1, 8, 15, 22) in patients with relapsed MM after 1 to 3 prior therapies. The MTD was 70 mg/m² weekly. OR rate was 77% and median PFS was 12.6 months, with Grade ≥3 events of fatigue and hypertension but no significant neuropathy.

This study therefore shows efficacy and tolerability of once weekly carfilzomib and dexamethasone. The rapidity and depth of response is increased relative to bortezomib and ixazomib. Carfilzomib has now been combined with lenalidomide/dexamethasone to treat newly diagnosed MM and achieved high extent and frequency of CR, including MRD negativity. In the relapsed setting, carfilzomib has been combined with pomalidomide/dexamethasone and achieved 70%-80% responses lasting nearly 2 years. A caveat is the small but real incidence of cardiac and pulmonary adverse events, suggesting that it should be used judiciously in patients with underlying heart or lung disease.

**Safety of treatment (Tx) with pomalidomide (POM) and low-dose dexamethasone (LoDEX) in patients (Pts) with relapsed or refractory multiple myeloma (RRMM) and renal impairment (RI), including those on dialysis**

Ramasamy K et al. *Proc ASH* 2015;Abstract 374.

**Dr Raje**

Pomalidomide is a third generation IMiD that importantly is effective in disease refractory to lenalidomide or bortezomib. Renal insufficiency (RI) and failure is a common toxicity noted in patients with MM. Data from both pivotal trial MM-002 and MM-003 included patients with only moderate RI. This ongoing study includes patients with
Multiple Myeloma

Given that daratumumab has shown remarkable efficacy in quadruple refractory MM patients as a single agent and given the promising data with the CASTOR and POLLUX studies, combining daratumumab with pomalidomide was the next logical step. Data

Dr Raje

Dr Anderson

Pomalidomide is an FDA approved treatment for patients with relapsed and refractory MM, based upon Phase II clinical trials of pomalidomide 4 mg days 1 to 21 with dexamethasone 40 mg d1, 8, 15, and 22 showing 30%-40% responses lasting 8 months in patients with MM resistant to lenalidomide and/or bortezomib. A Phase III trial in which pomalidomide/dexamethasone prolonged PFS compared to high-dose dexamethasone at 40 mg d1-4, 9-12, and 17-20 (4 mo vs 2.0 mo, respectively) confirmed its efficacy. Pomalidomide is active in high-risk del(17p) MM and can be used safely in the setting of renal compromise. It is commonly now combined with either bortezomib or carfilzomib to treat relapsed disease, where the response rates are 70%-80% lasting up to 2 years.

Ramasamy and colleagues carried out a study of pomalidomide 4 mg days 1 to 21 with dexamethasone 40 mg d1, 8, 15, and 22 in patients with relapsed MM who had moderate (GFR ≥30 and <45 mL/min), severe (<30 mL/min), and dialysis-requiring renal compromise. In an interim analysis of 47 patients of a planned 80 patient accrual, the most common adverse events were neutropenia, anemia, and thrombocytopenia in all 3 cohorts and required dose modification in 5 patients. The rates of neutropenia, thrombocytopenia, and infections were similar to reports of pomalidomide/dexamethasone treatment of relapsed MM in patients without renal compromise. Pomalidomide is therefore a useful agent in patients with multiply relapsed high-risk MM, even in the setting of renal compromise, and is now also often combined with proteasome inhibitor bortezomib or carfilzomib in this setting.

Open-label, multicenter, Phase 1b study of daratumumab in combination with pomalidomide and dexamethasone in patients with at least 2 lines of prior therapy and relapsed or relapsed and refractory multiple myeloma

Chari A et al. Proc ASH 2015;Abstract 508.

Dr Raje

Given that daratumumab has shown remarkable efficacy in quadruple refractory MM patients as a single agent and given the promising data with the CASTOR and POLLUX studies, combining daratumumab with pomalidomide was the next logical step. Data
presented in this abstract confirms the tolerability and efficacy of this combination in patients after at least 2 prior lines of treatment. In 75 patients, the ORR was 71%, with 4 stringent complete responses (sCR), 3 complete responses (CR), 25 very good partial responses (VGPR), 21 partial responses (PR), 2 minimal responses, 17 stable disease, and 3 progressive disease (PD). Many responses deepened over time. The addition of DARA to POM-D was well tolerated and did not result in additional toxicities with the exception of DARA-related infusion reactions. Deep and durable responses were observed quickly, along with a high response rate.

Dr Anderson
Daratumumab is a single-agent monoclonal antibody targeting CD38 and is FDA approved based upon 31% responses with 19.9 months median OS in multiply relapsed MM. The combination of bortezomib or of lenalidomide/dexamethasone with daratumumab can markedly enhance response and prolong PFS, with a 60% decrease in progression of disease or death. At present, lenalidomide/dexamethasone is commonly used with or without bortezomib to treat newly diagnosed MM, and relapsed MM is therefore commonly refractory to lenalidomide. The second-generation immunomodulatory drug pomalidomide with dexamethasone is therefore now used to treat relapsed MM, often in combination with the proteasome inhibitor carfilzomib.

Chari and colleagues report on the use of daratumumab 16 mg/kg with pomalidomide 4 mg daily for days 1 to 21 and dexamethasone 40 mg weekly in patients with ≥2 lines of therapy including lenalidomide and bortezomib but who are pomalidomide naïve. Two thirds of patients were IMiD and PI refractory. Of 98 patients enrolled, Grade ≥3 adverse events occurred in 91% patients, most commonly neutropenia. In 75 patients, OR is 71% with 42% ≥VGPR and 28% PR. At a median follow-up of 4.2 months, the 6-month PFS is 66%.

These studies provide the framework for a randomized trial of pomalidomide/dexamethasone with or without daratumumab in relapsed disease. As was noted when daratumumab was added to lenalidomide/dexamethasone or to bortezomib, it is expected that triplet therapy will increase extent, depth, and durability of response. Moreover, activity of this regimen in IMiD and PI resistant disease reflects clinical practice in North America, where lenalidomide, bortezomib, and dexamethasone are now commonly used as initial therapy and relapsed disease is resistant to these agents.
Dr Raje

Here the authors used pembrolizumab in a Phase I dose-escalation study evaluating safety and efficacy of pembro in combination with lenalidomide (len) and low-dose dexamethasone (dex) in patients with RR MM. Three DLTs from the pembro 2 mg/kg, len 25 mg cohort were observed in 17 patients in the dose determination/confirmation phase: Grade 3 and 4 neutropenia, Grade 3 pneumonia, and Grade 3 tumor lysis syndrome with Grade 4 hyperuricemia. Based on the dose-confirmation phase, pembro 200 mg + len 25 mg and dex 40 mg was the MTD/MAD.

With a median follow-up of 9.7 months, patients evaluated for efficacy in dose determination/confirmation responded to treatment, including 4 VGPRs (2 len refractory) and 9 PRs (3 len refractory), with median duration of response 9.7 months (range, 0+ to 16.7+). Three patients (18%) had stable disease. 94% had a reduction in M protein or free light chains. Importantly, a lot of these patients were len refractory and pembro was able to restore sensitivity. These data show promising activity of checkpoint blockade in MM.

Dr Anderson

PD-L1 is expressed on MM cells as well as accessory myeloid-derived suppressor cells (MDSCs) and plasmacytoid dendritic cells (pDCs), which promote tumor growth and suppress the immune system. PD-1 is expressed on immune effector T, NK, and NK-T cells. Checkpoint blockade may therefore not only relieve checkpoint inhibition of effector cells by tumor, but also abrogate effects of these accessory cells as well. Our preclinical studies have shown that the combination of IMiDs with checkpoint inhibitors triggers autologous T-cell cytotoxicity and MM cell apoptosis.

Dr Mateos and colleagues carried out a Phase I clinical trial of lenalidomide/dexamethasone with pembrolizumab in relapsed/refractory MM (≥2 therapies including a PI and IMiD). The final MTD was 25 mg lenalidomide days 1 to 21, with 40 mg dexamethasone d1, 8, 15, 22 and pembrolizumab 200 mg q2wk. Adverse events were as expected for lenalidomide/dexamethasone/pembrolizumab, with Grade ≥3 neutropenia in 65% patients. Immune-mediated adverse events occurred in 2% to 4% patients. In the 40 patients evaluable for efficacy, OR was 50%, including 38% in lenalidomide-refractory MM. At a median follow-up of 9 months, median duration of response is 11.3 months.

This study provides the framework for the ongoing Phase III trials of lenalidomide or pomalidomide and dexamethasone, with or without pembrolizumab. It confirms the potential of combination immune therapies to achieve high response rates and durable responses, even in high-risk, multiply relapsed disease.

Pembrolizumab in combination with lenalidomide and low-dose dexamethasone for relapsed/refractory multiple myeloma (RRMM): Final efficacy and safety analysis

Mateos MV et al.
Proc ASCO 2016;Abstract 8010.
Dr Raje

Similar to data from the solid tumor world, PD-1 blockade is finally showing efficacy in MM. Expression of PD-L1 on myeloma cells and the abundance of PD-1 on various bone marrow microenvironment components contribute to tumor-mediated immune suppression. The addition of pembrolizumab, a PD-1-blocking antibody, to pomalidomide in RR MM patients was carried out to augment clinical responses. In this ongoing single arm, Phase II study, 27 patients with RR MM received 28-day cycles of pembrolizumab (200 mg IV) every 2 weeks plus pomalidomide (4 mg daily x 21 days) and dexamethasone 40 mg weekly. Treatment was in general well tolerated, with a few patients developing immune mediated toxicities that were easy to manage.

Objective responses were observed in 16 of 27 evaluable patients (60%), including stringent complete response (n = 1) and very good partial response (n = 4). Pembrolizumab in combination with pomalidomide and dexamethasone has promising therapeutic activity and an acceptable safety profile in heavily treated RR MM patients and provides yet another option of treatment for RR MM.

Dr Anderson

Badros and colleagues report on a Phase II study of pembrolizumab 200 mg IV q2wk, pomalidomide 4 mg daily days 1 to 21, and dexamethasone 40 mg weekly in relapsed/refractory MM. As noted above, immune checkpoint blockade can not only relieve suppression of immune effector cells but also abrogate the effects of accessory myeloid-derived suppressor cells and plasmacytoid dendritic cells, including the promotion of tumor cell growth, survival, and drug resistance and suppression of the immune system. All patients had received proteasome inhibitors and immunomodulatory drugs, and 70% were refractory to both. All patients had abnormal cytogenetics.

Autoimmune thyroiditis, transaminitis, and pneumonitis were immune-related side effects. OR rate was 60%, including 55% in both proteasome inhibitor- and immunomodulatory drug-refractory MM and 50% in high-risk disease. This study again indicates the potential of combination immune therapies. Such combination immune therapies have the greatest potential of all available therapies to achieve high extent and rate of durable responses in multiply relapsed and refractory, high-risk disease.

This Phase II study has established the preclinical framework for an ongoing randomized Phase III trial of pomalidomide/dexamethasone with or without pembrolizumab led by Shah et al in this patient population. This and future studies will not only determine optimal treatment dose and schedule, but they will define biomarkers and mechanisms of response.
Dr Raje

The humanized monoclonal antibody pembrolizumab blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, leading to antitumor immune response. In the Phase I KEYNOTE-023 trial, pembrolizumab + lenalidomide and low-dose dexamethasone had an acceptable safety profile and promising preliminary efficacy in patients with RR MM, supporting further evaluation. The randomized, open-label, multicenter Phase III KEYNOTE-183 study is to compare the efficacy of pomalidomide and low-dose dexamethasone with or without pembrolizumab for RR MM. Randomization is 1:1 to pomalidomide 4 mg on days 1-21 with low-dose dexamethasone 40 mg on days 1, 8, 15 and 22 of repeated 28-day cycles, with or without pembrolizumab 200 mg every 3 weeks. Stratification will be based on number of prior lines of treatment (2 vs ≥3) and disease status (refractory vs sensitive to lenalidomide). Treatment will continue until progressive disease or unacceptable toxicity. Response will be assessed every 28 days by Clinical Adjudication Committee blinded central review and investigator review using IMWG criteria.

Adverse events will be assessed throughout treatment and for 30 days thereafter (serious AEs, 90 days), graded per NCI CTCAE v4.0. Primary endpoint: progression-free survival; secondary endpoints to include overall survival, overall response rate and safety and tolerability. Enrollment is ongoing, target ~300 patients.

T cells expressing an anti–B-cell maturation antigen chimeric antigen receptor cause remissions of multiple myeloma

Dr Raje

This was a first-in-human clinical trial of chimeric antigen receptor (CAR) T cells targeting BCMA. Twelve patients received CAR-BCMA T cells on this dose-escalation trial. Among the 6 patients treated on the lowest 2 dose levels, limited anti-myeloma activity and mild toxicity occurred. On the third dose level, 1 patient obtained a very good partial remission. Two patients were treated on the fourth dose level of 9 x 10^6 CAR+ T cells/kg body weight. These patients were heavily pretreated and demonstrated a response to this cellular therapy approach. Both patients treated on the fourth dose level had toxicity consistent with cytokine-release syndrome, including...
fever, hypotension, and dyspnea. Both patients also had prolonged cytopenias. These are the first data on BCMA-directed CAR T cells and demonstrate promise with such an approach.

Dr Anderson

CD19 chimeric antigen receptor (CAR) T cells have shown remarkable activity, particularly in children with multiply relapsed acute lymphocytic leukemia. In adults, CD19 CAR T-cell therapy has been studied and a remarkable response observed in a single patient with MM, but CD19 is not expressed on MM cells and so is not the optimal target. Rather, B-cell maturation antigen (BCMA) is expressed selectively only on normal plasma cells and MM cells. Signaling triggered by APRIL, which has higher affinity for BCMA than BAFF, via binding to BCMA mediates MM cell growth, survival and drug resistance.

Ali and colleagues treated 12 patients with relapsed MM with a dose escalation of BCMA-directed CAR T cells. Although no responses were observed in 5 of the 6 patients treated at the 2 lowest dose levels, 1 patient at the third dose level achieved a VGPR. At the fourth dose level, 1 patient achieved a transient sCR and the second patient a VGPR. Both patients had cytokine release syndrome with fever, hypotension, and dyspnea, as well as prolonged cytopenias.

This study establishes proof-of-principle for CAR T-cell therapy in MM. Ongoing research will decrease acute toxicity on the one hand, and determine how to promote CAR T-cell survival postinfusion by avoiding T-cell exhaustion. Anti-IL-6R antibody can treat the acute cytokine release syndrome, and ongoing efforts are utilizing immune approaches, ie, lenalidomide and checkpoint inhibitors, to promote cell survival. Importantly, relapses post CAR T-cell therapy have been attributed to antigen shedding, internalization, or mutation. Ongoing efforts are therefore examining CAR T cells targeting more than one antigen or, alternatively, bispecific antibodies targeting BCMA and CD3 to recruit activated T cells selectively to BCMA-bearing MM cells.
Breast Cancer

HER2-Positive and Triple-Negative Breast Cancer

A phase III trial of adjuvant capecitabine in breast cancer patients with HER2-negative pathologic residual invasive disease after neoadjuvant chemotherapy (CREATE-X, JBCRG-04)

Toi M et al.
San Antonio Breast Cancer Symposium 2015;Abstract S1-07.

Dr Blackwell

The CREATE-X study enrolled 910 patients who had residual disease having received neoadjuvant chemotherapy and definitive surgery to either no additional therapy or treatment with capecitabine. Over half of the ER+ premenopausal breast cancer patients did not receive endocrine therapy. The treatment arm received up to 8 cycles of standard dose capecitabine, and only 38% completed all 8 cycles. At 5 years, the disease-free survival rate (the primary endpoint) was 74.1% with capecitabine compared to 67.7% in the control arm, a statistically significant 30% reduction in risk (one-sided \( p = 0.00524 \)). Five-year overall survival rates were 89.2% and 83.9%, respectively, a statistically significant 40% reduction in risk (one-sided \( p < 0.01 \)). The benefit appears to be larger in the triple-negative patients.

This study is different from either early-stage breast cancer study as it used capecitabine as a single agent whereas previous studies had only used the drug in combination with other chemotherapy. If longer follow-up validates the initial findings, the CREATE-X study will create a new standard for the treatment of breast cancer that does not have a pCR to neoadjuvant chemotherapy.

Dr Sledge

Following neoadjuvant therapy, patients with significant residual disease in either the breast or regional lymph nodes are at high risk for systemic recurrence. CREATE-X evaluated the role of post-neoadjuvant chemotherapy with capecitabine in a Phase III trial performed in Japan and Korea. Capecitabine was administered at a dose of 2,500 mg/m\(^2\)/day for 14 of 21 days over 8 cycles in HER2-negative patients with residual disease. The surprising result of CREATE-X (surprising because of repeated failures of capecitabine in adjuvant trials and because \( \sim 60\% \) of trial patients had received adjuvant fluorouracil) was a significant improvement in both disease-free survival (the primary endpoint) and overall survival. 5-year DFS was 74.1% in the capecitabine arm versus 67.7% in the no-capecitabine arm (\( p = 0.00524 \)).

OS was improved by over 5% at 5 years. The benefits were seen in both ER-positive and ER-negative patients. One would dearly love to see a confirmatory trial, given the manifest failure of capecitabine in the adjuvant setting. If correct, these results imply that the post-neoadjuvant setting differs in some fundamental way from the adjuvant setting.
a finding whose implications might go well beyond capecitabine. For the moment, however, CREATE-X represents a tantalizing finding for a high-risk population.

Dr Swain

It is clear that patients with residual tumor after neoadjuvant therapy have a higher risk of relapse. Therefore, it is the ideal setting in which to test the addition of a non–cross-resistant therapy. Patients with Stage I to III breast cancer with HER2 negative residual invasive cancer or node positive after anthracycline- and/or taxane-containing neoadjuvant therapy were randomized to standard treatment (RT, hormone therapy as appropriate) with or without 8 cycles of capecitabine (X). The primary endpoint was disease-free survival (DFS). The 5-year DFS rate was 74.1% for the arm with X and 67.7% for no X, which was statistically significant with a trend for increased 5-year OS with X (89.2% vs 83.9%). The majority of the benefit was in the hormone receptor negative group.

Toxicities were greater in the group receiving X, including hand-foot syndrome, diarrhea, and neutropenia. The addition of X in patients with residual or node positive disease after neoadjuvant therapy is a reasonable option, especially in patients with hormone receptor negative disease. However, because of a high risk of relapse in TNBC with residual disease, these patients still should be considered for other clinical trials, including those with immunotherapeutic agents.

Dr Blackwell

PHEREXA examined the addition of pertuzumab at standard doses to the backbone of capecitabine and trastuzumab in 452 HER2+ MBC patients having progressed on first line trastuzumab-based therapy (pertuzumab-naïve). Median progression-free survival was 9.0 months without pertuzumab compared to 11.1 months with pertuzumab (hazard ratio = 0.82; p = .07). All Grade ≥3 events were similar for the pertuzumab arm (51.8%) versus the no pertuzumab arm (59.6%), but pertuzumab-treated patients had more Grade ≥3 diarrhea (16% vs 10%) and left-ventricular systolic dysfunction (7% vs 3%).

Although the study demonstrated a 2 month absolute improvement in PFS, it did not reach statistical significance and will probably not lead to utilization of pertuzumab in the second line setting in combination with capecitabine and trastuzumab. Likewise, the study design does not contribute to our knowledge regarding the use of pertuzumab past the first line setting, nor does it answer the question, Could patients who progress on pertuzumab-based therapy benefit from continuing it and switching the chemotherapy backbone (the way trastuzumab is currently utilized)?
Dr Sledge

The stunning results of the CLEOPATRA trial established the combination of a taxane with trastuzumab and pertuzumab as front-line therapy for metastatic HER2-positive breast cancer, based on impressive overall survival results. But what is the role of pertuzumab in patients progressing on front-line HER2-targeted therapy? PHEREXA, a Phase III trial randomizing patients who had received prior taxane and HER2-targeted therapy to either capecitabine and trastuzumab or capecitabine plus trastuzumab plus pertuzumab, attempted to answer this question. The results were disappointing, with a median PFS of 9 months for X + T versus 11.1 months for X + T + P, a non-significant difference.

Curiously enough, the 3-drug combination out-performed X + T for overall survival (36.1 vs 28.1 months, respectively, HR = 0.68, p-value unknown as “statistical significance for overall survival cannot be claimed due to the hierarchical testing”). Where does this leave us? In patients receiving pertuzumab as front-line therapy, this trial is not particularly relevant, but in patients who did not receive front-line pertuzumab (most of the world outside the US) the role of pertuzumab is uncertain.

Dr Swain

Patients who receive trastuzumab in the metastatic setting eventually experience disease progression and need further therapy. Previous studies have shown that the addition of capecitabine to trastuzumab increases the time to progression in this group of patients. Also, treatment with trastuzumab and pertuzumab in patients previously treated with trastuzumab shows activity. Those studies provided the rationale for this study. The PHEREXA study was designed to answer the question whether patients who had already received trastuzumab had increased activity with trastuzumab and capecitabine (Arm A) versus trastuzumab, capecitabine at a lower dose, and pertuzumab (Arm B).

The median PFS for Arm A was 9 months and Arm B 11.1 months by an independent review facility, which was not significantly different (p = 0.07). However, the investigator PFS difference was significant with a 2.8-month difference. The OS showed a longer survival for Arm B of 36.1 compared to 28.1 months for Arm A, an 8-month difference, but this could not be claimed as significant due to the hierarchical testing. Almost all patients received anti-HER2 therapy after the study drugs in subsequent lines of treatment. The question really is what treatment is best for those patients who received pertuzumab and trastuzumab in the first line setting, since that combination is currently the standard of care. This is usually T-DM1.

The PHEREXA study does show activity with Arm B, so that combination could be used in patients who had not received pertuzumab in the first line setting if a taxane were not the chemotherapy of choice due to neuropathy.
Breast Cancer

Neratinib after trastuzumab-based adjuvant therapy in patients with HER2-positive breast cancer (ExteNET): A multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Chan A et al. 

**Dr Blackwell**

ExteNET enrolled 2,840 women with early-stage HER2-positive breast cancer who had all completed a year of adjuvant trastuzumab and were without evidence of disease. With a 2 year data cutoff, only 70 invasive disease-free survival events had occurred in patients in the neratinib group (n = 1,420) versus 109 events in those in the placebo group (n = 1,420); stratified hazard ratio 0.67, 95% CI 0.50-0.91. Seventeen percent of patients discontinued neratinib due to diarrhea. These results differ from other trials that have looked at extended (past 1 year) durations of HER2-based therapy. Even more interesting is that the subgroup of breast cancer that benefited the most was the ER+ subgroup.

Whether neratinib will become a standard of care for early-stage breast cancer will depend on longer term follow-up (which appears to continue to show a benefit for neratinib but will probably require a survival advantage), better toxicity management, further subgroup predictive analysis, and regulatory approval. Ongoing clinical trials will examine the role of neratinib in the neoadjuvant setting and in HER2 mutated solid tumors.

**Dr Sledge**

The failure of lapatinib to alter outcome in the adjuvant HER2 setting in the ALTTO trial diminished enthusiasm for the use of small-molecule receptor tyrosine kinase inhibitors in breast cancer. Similarly, clinical trials have shown no benefit for the use of HER2-targeted therapy for more than 1 year. Chan et al studied the RTKi neratinib as maintenance HER2-targeted therapy after adjuvant trastuzumab in a Phase III trial. Patients could initiate neratinib up to 2 years following completion of trastuzumab, and they received a year’s worth of treatment.

With a median 2 years of follow-up, 70 invasive events occurred in patients in the neratinib group versus 109 events in the placebo group (stratified hazard ratio 0.67, 95% CI 0.50-0.91; p = 0.0091), and the 2-year invasive disease-free survival rate was 93.9% (95% CI 92.4-95.2) in the neratinib group versus 91.6% (90.0-93.0) in the placebo group. Neratinib was associated with a significant incidence of diarrhea (40% Grade 3). These results are interesting rather than practice changing, with inadequate follow-up and no differences in overall survival. They do suggest that RTKis may one day have an adjuvant role in HER2-positive disease.

**Dr Swain**

ExteNET is a multicenter, randomized, double-blind, placebo-controlled, Phase III trial for patients with Stage I to III HER2-positive breast cancer who completed neoadjuvant
Breast Cancer

GeparSepto was a Phase III trial that examined whether weekly nab-paclitaxel produces a higher pathological complete response rate compared to solvent-based paclitaxel in the neoadjuvant setting when added to an anthracycline. 1,206 women received treatment. The pCR was higher in the nab-paclitaxel group (233 patients [38%, 95% CI 35-42]) than in the solvent-based paclitaxel group (174 patients [29%, 25-33]; OR 1.53, 95% CI 1.20-1.95; unadjusted \(p = 0.00065\)). There was a higher incidence of anemia and neuropathy in the nab-paclitaxel group. Nab-paclitaxel holds great promise as an active chemotherapeutic agent in breast cancer. This study demonstrated that it can be safely used in the neoadjuvant setting and results in a higher pCR rate. In fact, the improvement in pCR with nab-paclitaxel over solvent-based paclitaxel is similar to the benefit of adding platinum in this setting with less toxicity. Other studies will look at its role in combination with platinum agents in both the neoadjuvant and metastatic settings. This study should allow for at least consideration of using this novel taxane in the neoadjuvant treatment of early-stage BC, especially in high-risk patients that would have a contraindication for a taxane-platinum doublet.

Dr Blackwell

GeparSepto was a Phase III trial that examined whether weekly nab-paclitaxel produces a higher pathological complete response rate compared to solvent-based paclitaxel in the neoadjuvant setting when added to an anthracycline. 1,206 women received treatment. The pCR was higher in the nab-paclitaxel group (233 patients [38%, 95% CI 35-42]) than in the solvent-based paclitaxel group (174 patients [29%, 25-33]; OR 1.53, 95% CI 1.20-1.95; unadjusted \(p = 0.00065\)). There was a higher incidence of anemia and neuropathy in the nab-paclitaxel group. Nab-paclitaxel holds great promise as an active chemotherapeutic agent in breast cancer. This study demonstrated that it can be safely used in the neoadjuvant setting and results in a higher pCR rate. In fact, the improvement in pCR with nab-paclitaxel over solvent-based paclitaxel is similar to the benefit of adding platinum in this setting with less toxicity. Other studies will look at its role in combination with platinum agents in both the neoadjuvant and metastatic settings. This study should allow for at least consideration of using this novel taxane in the neoadjuvant treatment of early-stage BC, especially in high-risk patients that would have a contraindication for a taxane-platinum doublet.

Dr Sledge

The role of different formulations of paclitaxel has been a subject of controversy. Untch et al compared nab-paclitaxel with standard paclitaxel in a large Phase III neoadjuvant trial (GeparSepto), with pathologic complete response as a primary endpoint. Patients received either nab-paclitaxel or paclitaxel 80 mg/m² on days 1, 8, and 15 for four 3-week cycles, each followed by epirubicin plus cyclophosphamide for 4 cycles; HER2-positive patients received concomitant trastuzumab and pertuzumab.
Pathologic complete response was more common in patients receiving nab-paclitaxel (38% vs 29%, \(p = 0.00065\)). Serious (Grade 3/4) peripheral neuropathy was more common in nab-paclitaxel patients.

Though the authors conclude that “these results might lead to an exchange of the preferred taxane, solvent-based paclitaxel, for nab-paclitaxel,” this is open to question. No data suggest that the modest difference seen in pCR rates is associated with improved overall survival, and the significant difference in peripheral neuropathy is a real issue. An exception might be ER-negative patients, where the difference in pCR rates (56% vs 37%) was impressive, with a positive interaction test by hormone receptor status \((p = 0.029)\). These results stand in contrast to an earlier CALGB trial that failed to show any preferential benefit for nab-paclitaxel.

**Dr Swain**

The GeparSepto trial is a Phase III randomized neoadjuvant non-inferiority trial in patients with primary breast cancer. Patients were treated for 12 weeks with either nab paclitaxel (nab-p) for four 3-week cycles or paclitaxel (p) for four 3-week cycles. This was followed by epirubicin and cyclophosphamide in both groups, and patients with HER2 positive tumors received concurrent trastuzumab and pertuzumab. The pathologic complete response (pCR) rate was significantly higher in the nab-p group at 38% versus 29% for p. The only pre-defined subgroup in which a benefit was seen was those patients with hormone receptor negative tumors, with pCR 56% with nab-p versus 37% for p.

There were no differences in hormone receptor positive or HER2 positive disease. Peripheral neuropathy was significantly higher for the nab-p group. It is unclear whether the differences in pCR, a surrogate endpoint, will result in a DFS or OS benefit for patients. Therefore, though it is reasonable to consider using nab-p as a backbone for immunotherapy trials since no steroids need to be given, replacing p with nab-p in everyday practice is not warranted until we see the outcome data. This is based on the increases in neurotoxicity seen with nab-p, which needs to be justified with better overall outcomes.

**ETNA (Evaluating Treatment with Neoadjuvant Abraxane)**

*randomized phase III study comparing neoadjuvant nab-paclitaxel (nab-P) versus paclitaxel (P) both followed by anthracycline regimens in women with HER2-negative high-risk breast cancer: A MICHELANGELO study*

Gianni L et al.
*Proc ASCO 2016;Abstract 502.*

**Dr Blackwell**

This study was a randomized neoadjuvant study of weekly nab-paclitaxel versus solvent-based paclitaxel followed by standard anthracycline-cyclophosphamide in 695 patients facing triple-negative or luminal B breast cancer. The primary endpoint was
looking for an absolute 10% difference in pCR between the arms. The study did not reach its primary endpoint; the absolute difference was only a 3.9% increase in pCR in the nab-paclitaxel arm. These results are different from those of the GeparSepto study, which did show a significant improvement in pCR with the incorporation of nab-paclitaxel. It is not clear why no benefit was seen with nab-paclitaxel, and the study characteristics were very similar to the GeparSepto study.

**Dr Sledge**

The ETNA (Evaluating Treatment with Neoadjuvant Abraxane) trial is a companion piece to the Untch trial. In this open-label, multi-center Phase III trial, patients with HER2-negative high-risk breast cancer were randomized to either neoadjuvant paclitaxel (90 mg/m² weekly for 3 of every 4 weeks) or nab-paclitaxel (125 mg/m² weekly for 3 of every 4 weeks) for 4 cycles, followed by 4 cycles of anthracycline-based chemotherapy. In the intent to treat analysis of pathologic complete response, nab-paclitaxel failed to reach a statistically significant improvement over paclitaxel in either the overall study group ($p = 0.1858$) or the luminal B (odds ratio [OR] = 0.69) or triple-negative (OR = 0.85) subgroups.

These results stand in contrast to the GeparSepto trial and should add a note of caution regarding the routine use of nab-paclitaxel. Where does one use nab-paclitaxel in breast cancer? Its place remains uncertain, though its combination with checkpoint inhibitor therapy may represent the best long-term case for its use.

**Dr Swain**

The addition of taxanes in the neoadjuvant setting increases pathologic complete response (pCR) rates. Nab paclitaxel (nab-p) has been shown to have a higher pCR rate than paclitaxel (p) in the GeparSepto trial. The ETNA study was designed to test whether nab-p increases the pCR rate for patients with triple-negative or luminal B-type breast cancer. Patients received either nab-p or p (both weekly 3 of 4 weeks) followed by an anthracycline containing regimen, then surgery. The pCR rate was 18.6% with p and with nab-p 22.5%, which was not significantly different. In a subset analysis of TNBC versus luminal B type there was a very significant difference. There was more toxicity with peripheral neuropathy, excessive lacrimation, fatigue, vomiting, and neutropenia with the nab-p.

At the current time, unless steroid prophylaxis is an issue this study does not support the use of nab-p as standard of care in the neoadjuvant setting. Further evaluation of the TNBC cohort with DFS and OS data is warranted as it may be the one group in which nab-p is beneficial.
Dr Blackwell

This study, also known as I-SPY 2, was a Phase II adaptively randomized trial in the neoadjuvant setting examining the PARP inhibitor veliparib in combination with carboplatin. 72 patients with at least 2 cm of TNBC in the breast received the experimental agent, and 44 similar patients received the control chemotherapy. The pCR rates for the PARP inhibitor/carboplatin-treated patients was 51% versus 26% in the control group, predicting that in a Phase III study there was an 88% chance that the veliparib-carboplatin combination would outperform standard chemotherapy. There was more toxicity in the veliparib arm. This study offers proof that PARP inhibitors are going to play a role in the treatment of non-BRCA related TNBC. Studies continue in both the BRCA and non-BRCA spaces incorporating multiple PARP inhibitors. It will be interesting to see which one gathers an approval first, and they will become widely adapted for TNBC.

Dr Sledge

The I-SPY 2 program is a multi-institutional collaborative, based out of UCSF, that studies novel therapeutic agents through rolling Phase II randomized trials in the neoadjuvant setting. The program makes use of adaptive randomization, which allows the investigators to be parsimonious with that most important clinical resource, patient volunteers. Over the years I-SPY 2 has performed admirably in examining cutting-edge agents. This particular trial examined the combination of paclitaxel plus the PARP inhibitor veliparib plus the DNA-damaging agent carboplatin in HER2-negative patients, followed by doxorubicin and cyclophosphamide, and compared this to paclitaxel followed by doxorubicin and cyclophosphamide.

In the subset of HER2-negative patients who were also ER- and PR-negative (ie, triple-negative breast cancer), pathologic complete response rates were 51% versus a 26% pCR rate in the control arm. While one should not make too much of randomized Phase II trials, even those as elegant as I-SPY 2, this work suggests that a PARP inhibitor/DNA-damaging agent combination is promising in TNBC. An imbalance in BRCA mutation status (17% vs 7%) may have contributed to the investigational arm’s success, but this still represents an intriguing result. Veliparib and other PARP inhibitors are under active study in Phase III trials of metastatic TNBC, particularly BRCA-mutated breast cancer.

Dr Swain

The I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response through Imaging and Molecular Analysis 2) is a randomized, neoadjuvant Phase II “platform” trial in Stage II or III breast cancer with a unique trial design. In this trial adaptive randomization is used with a primary endpoint of pathologic complete response (pCR). The current results discuss the use of veliparib, a poly(ADP-ribose) polymerase (PARP) inhibitor.
polymerase (PARP) inhibitor, and carboplatin. They found that the combination of veliparib-carboplatin with paclitaxel had an 88% predicted probability of success in a future Phase III trial for patients with TNBC. The estimated rates of pCR in TNBC patients were 51% for patients receiving the combination of veliparib and carboplatin and paclitaxel versus 26% in the paclitaxel-alone control.

There was no difference in the HER2 negative and ER positive subgroups. This study was designed to more rapidly determine efficacious therapies by use of a surrogate endpoint to be taken to the Phase III setting to improve survival and ultimately enable them to be available for patients.

Pembrolizumab in patients with advanced triple-negative breast cancer: Phase Ib KEYNOTE-012 study


Dr Blackwell

KEYNOTE-012 was a nonrandomized Phase Ib trial of single-agent pembrolizumab (anti-PD-1 antibody) given at standard doses to a variety of solid tumors. Dr Nanda reports the results of 27 evaluable MBC patients whose tumors overexpressed PD-L1 and were triple-negative. The overall response rate was 18.5%; the median time to response was 17.9 weeks (range, 7.3 to 32.4 weeks); and the median duration of response was not yet reached (range, median of 5 doses, 15.0 to ≥47.3 weeks). Toxicity was mild and included arthralgia and fatigue. These results are promising, especially for a single-agent antibody and in a heavily pre-treated population of TNBC. Although not ready for prime time, the response results are similar to other successful single agents in MBC, comparable to single agent trastuzumab and with a similar toxicity profile. The real activity of pembrolizumab will be determined in future and ongoing KEYNOTE studies, including one comparing single-agent pembrolizumab to standard forms of chemotherapy in second- and third-line metastatic TNBC.

Dr Sledge

Immune checkpoint inhibitor therapy has revolutionized the treatment of many human cancers. Triple-negative breast cancer represents both an important unmet medical need and a biologically rational breast cancer subset to test the role of PD-1 targeted therapy. The KEYNOTE-012 study was a multi-center randomized Phase Ib trial that included a triple-negative breast cancer cohort treated with pembrolizumab given intravenously at 10 mg/kg every 2 weeks. All patients were PD-L1 positive (≥1%) by immunohistochemistry. 32 patients were treated, and 27 were evaluable for response, with an overall response rate of 18.5% and a median duration of response that was not yet reached (range, 15.0 to ≥47.3 weeks).

Toxicities were similar to those seen with checkpoint inhibitor therapy in other diseases, with 5 patients experiencing Grade ≥3 toxicity with 1 treatment-related death. These results are interesting, not so much in themselves but by comparison with
other diseases where checkpoint inhibition is regularly used. The existence of patients with prolonged remissions is encouraging, and indeed has led to the development of single-agent Phase II trials of pembrolizumab in TNBC.

Dr Swain
KEYNOTE-012 was a multicenter, nonrandomized Phase Ib trial of single-agent pembrolizumab with advanced PD-L1–positive (expression in stroma or ≥1% of tumor cells by immunohistochemistry) TNBC, gastric cancer, urothelial cancer, and head and neck cancer. There is a rationale for studying immunotherapy in TNBC, including gene expression profiling and tumor infiltrating lymphocytes seen in patients with TNBC, which are associated with better outcomes. PD-1 is an immune inhibitory receptor on T cells with ligands PD-L1 and 2. Pembrolizumab is a monoclonal antibody against PD-1.

Thirty-two women were enrolled, and 27 patients who had all received previous chemotherapy for advanced and early stage disease were evaluable for antitumor activity. The overall response rate was 18.5%, with a median time to response of 17.9 weeks. The most common toxicities were arthralgia (18.8%), fatigue (18.8%), myalgia (18.8%), and nausea (15.6%). Five Grade 3 toxicities occurred and were anemia, aseptic meningitis, lymphopenia, headache, and pyrexia. Other toxicities that could have been related include a Grade 3 colitis, Grade 3 hepatitis, and Grade 2 hypothyroidism. These results do suggest activity with an immune checkpoint inhibitor and support further studies, which are ongoing.

Phase Ib trial of atezolizumab in combination with nab-paclitaxel in patients with metastatic triple-negative breast cancer (mTNBC)\(^1\)

IMpassion130: A Phase III randomized trial of atezolizumab with nab-paclitaxel for first-line treatment of patients with metastatic triple-negative breast cancer (mTNBC)\(^2\)

\(^1\) Adams S et al. Proc ASCO 2016;Abstract 1009.
\(^2\) Emens LA et al. Proc ASCO 2016;Abstract TPS1104.

Dr Blackwell
These 2 studies examine the role of atezolizumab, a humanized mAb against PD-L1, in combination with nab-paclitaxel in the treatment of metastatic triple-negative breast cancer. The first study was a Phase Ib study evaluating atezolizumab + nab-paclitaxel in 32 patients with mTNBC treated with ≤2 prior lines of therapy. The ORR was 46% in the first line setting, 22% in the second line setting and 40% in the third line setting. This study demonstrated that this combination is safe and has some activity in TNBC. The second study (IMpassion130) is an ongoing Phase III trial evaluating this regimen in previously untreated mTNBC patients (NCT02425891) and comparing it to nab-paclitaxel alone. Interestingly, there is no atezolizumab-alone arm.
Questions will remain even after the results of IMpassion130 and include: What is the need for chemotherapy in combination with immune checkpoint inhibitors in breast cancer, and which patient will derive the most benefit? There appears to be a specific subgroup of patients that derive tremendous benefit and other patients that derive no benefit from these agents. In addition, further research will need to include whether immune checkpoint agents should be utilized early in the treatment of metastatic breast cancer or whether they retain activity in later lines of therapy. Other ongoing studies in the neoadjuvant setting with this agent will help define promising predictive biomarkers and the need for either PD-L1 or PD-1 testing as a requirement for benefit.

**Dr Sledge**

Pembrolizumab targets PD-1, the receptor on the T cell; in contrast, atezolizumab targets PD-L1, the ligand for PD-1 found on tumor cells, preventing its binding to the receptor. This study looked at the combination of atezolizumab with nab-paclitaxel, the latter being used because it does not require concomitant steroids that might interfere with immune function. Patients in this trial had triple-negative disease and could have received up to 3 lines of prior therapy. While safety was the primary endpoint of this Phase Ib trial, the overall response rate of approximately 40% was promising, and the taxane did not affect activated CD8+ T cells in a negative way. The results are sufficiently promising to warrant further exploration of this combination, and such a trial (IMpassion130) has already been launched.

While this may be somewhat of a leap (the numbers in the Phase Ib trial being a relatively thin reed to bear the weight of a Phase III trial), Phase III benefits from the genuine interest in checkpoint inhibitor therapy, eager to advance immune-oncology for triple-negative breast cancer.

**Dr Swain**

PD-L1 is a receptor that inhibits the immune system and is expressed on tumors and cells infiltrating the stroma, such as T cells. Since TNBC has high levels of tumor infiltrating immune cells and increased PD-L1 expression, this group is an ideal group in which to test the checkpoint inhibitors of the immune system. Atezolizumab is a monoclonal antibody that binds to PD-L1 to inhibit binding of PD-L1 to PD-1. The study by Adams tested the combination of atezolizumab and nab-paclitaxel in 32 patients with metastatic TNBC who had 2 or fewer prior treatments. The objective responses were 46% in first line, 22% in second line, and 40% in third line. Responses were seen in both PD-L1 positive and negative groups. 88% had received prior taxanes.

Given this high signal for efficacy, a Phase III study is in progress to test atezolizumab and paclitaxel in the first line setting in the IMpassion130 study in 900 patients with TNBC. Tumors will be evaluated for PD-1 and PD-L1 but are not required to be positive for study entry. Co-primary endpoints are PFS and OS.
Management of ER-Positive Advanced Disease

70-gene signature as an aid to treatment decisions in early-stage breast cancer

Cardoso F et al.

**Dr O’Regan**

The 70-gene signature (MammaPrint®) has been demonstrated to be prognostic for patients with early stage breast cancer with up to 3 involved lymph nodes. MINDACT is a prospective validation of the 70-gene signature in which patients with up to 3 positive nodes were treated based on the clinico-pathologic and genomic features of their cancer. Patients with tumors with concordant clinico-pathologic and genomic features did not receive chemotherapy if both were low and received chemotherapy if both were high; for patients with discordant risk, either the genomic or the clinical risk was used to determine use of chemotherapy. All patients with ER-positive cancers received endocrine therapy.

1,550 (23%) patients were deemed to have high risk cancers using clinico-pathologic features but low risk according the genomic analysis. At 5 years the rate of distant metastasis free survival was 95% among those who did not receive chemotherapy, higher than the 92% expected. Interestingly, there was no significant difference in 5-year DMFS in patients with discordant cancers regardless of whether they received chemotherapy or not. Like other genomic assays, MammaPrint can identify patients with early stage breast cancer who have a favorable prognosis regardless of whether they receive chemotherapy or not.

**Dr Winer**

The 70-gene signature has been demonstrated to be prognostic in the setting of early-stage breast cancer with 3 or fewer positive lymph nodes. The MINDACT study is a complex study that attempted to test a number of questions including the prospective validation of the 70-gene signature in patients with 3 or fewer involved nodes. Over 6,600 patients were enrolled and divided into 4 groups depending on their clinical and genomic (defined by 70-gene assay) risk. Those considered high risk by both clinical and genomic parameters were assigned to receive chemotherapy. Patients who were low risk by both parameters were assigned to receive hormonal therapy alone if they had HR+ disease and no therapy if HR-.

If patients had a high genomic score and low clinical risk or high clinical risk and low genomic score, they were included in the randomization to chemotherapy or not. All patients with ER-positive disease received endocrine therapy. Twenty-three percent of patients were identified as being at high risk for recurrence according to clinicopathologic features but low risk according to genomic analysis. The rate of distant metastasis-free survival (DMFS) at 5 years was 95% among those who did not receive chemotherapy,
higher than the 92% expected. No significant difference was observed in 5-year DMFS in patients with discordant levels whether they received chemotherapy or not.

The 70-gene signature, like other genomic assays, can identify patients with early-stage breast cancer who have a favorable prognosis regardless of administration of chemotherapy. At this time, in spite of this study, our group at Dana-Farber continues to use the 21-gene assay. In my view, we have more data correlating the 21-gene assay with outcomes following chemotherapy. The ongoing I-SPY neoadjuvant trials use the 70-gene signature, and emerging findings may strengthen the case for using this assay in clinical practice.

Dr Gradishar

European investigators recently reported the results of the Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy (EORTC 10041, BIG 3-04 MINDACT) study. This randomized, Phase III trial enrolled 6,693 women with early stage breast cancer, of whom 79% were node-negative, 20.9% had 1-3 positive axillary nodes, 88.4% were ER-positive and/or PR-positive, and 9.5% were HER2-positive. Clinical risk of recurrence was assessed using a modified version of Adjuvant! Online, and genomic molecular risk was assessed using the 70-gene signature test (MammaPrint®).

Women determined to be at both low clinical and low molecular risk of recurrence did not receive chemotherapy, whereas those patients with both a high clinical and a high molecular risk of recurrence did receive chemotherapy. In patients with discordant clinical and molecular results, either the clinical risk or the molecular risk was used to determine the use of chemotherapy. The primary endpoint of the study was to assess, among patients with a high clinical risk and low molecular risk who did not receive chemotherapy, whether the lower boundary of the 95% confidence interval for the rate of 5-year survival without distant metastasis would be ≥92% (non-inferiority).

With a median follow-up of 5 years, the 1,550 patients who fell into this discordant group (high clinical risk/low molecular risk) had a 94.7% rate of survival (95% CI 92.5% to 96.2%) without distant metastases.

Among these patients, 48% were axillary node-negative, 58% of tumors measured ≥2 cm and 90% had the luminal HER2-negative subtype. In this group, the patients who received chemotherapy had a survival rate that was 1.5% higher than those who did not receive chemotherapy, although this endpoint analysis was statistically underpowered.
Breast cancer-specific survival in patients with node-positive hormone receptor positive invasive breast cancer and Oncotype DX Recurrence Score results in the SEER database

Roberts MC et al. Proc ASCO 2016;Abstract 6575.

Dr O’Regan
Based on an analysis from the SWOG 8814 trial, the Oncotype DX® Recurrence Score® (RS) has been used in patients with node-positive disease, and the use of this assay for patients with ER-positive breast cancers and up to 3 positive nodes is endorsed by the NCCN. Using the SEER database from 2004 through 2012, patients with ER-positive breast cancer with positive nodes in whom the Oncotype DX RS was utilized were identified. An increase in the use of Oncotype DX was noted over the 8-year period. Patients with positive nodes for whom Oncotype DX was ordered were older, of higher SES, had cancers that were larger and more likely to be grade 2. Median RS increased somewhat with increasing positive nodes, but was within high low risk and low intermediate risk in all nodal groups. Chemotherapy use increased with increases in RS. Breast cancer specific survival at 5 years was extremely favorable in patients with low numbers of involved lymph nodes and low or intermediate scores, worsening with greater number of involved nodes and high RS. Oncotype DX appears valid for patients with up to 3 positive nodes, and results of the RxPONDER trial will confirm its use in these patients.

Dr Winer
Roberts and colleagues identified almost 8000 patients in the SEER database who underwent testing with the Recurrence Score and for whom it was possible to ascertain breast cancer-specific mortality at 5 years. All patients were diagnosed between 2004 and 2012, and the use of the Recurrence Score among women with positive lymph nodes increased during that time. Among women with Recurrence Scores of 18 or less with involvement of a single lymph node, the 5-year breast cancer-specific survival was over 99%. In contrast, among women with 3 positive lymph nodes the breast cancer-specific mortality was 5.3%, and this increased to 15% for women with 4 or more positive nodes and Recurrence Scores of 18 or less. Treatment was administered at the discretion of the prescribing physician.

Although it is impossible to conclude that chemotherapy is unnecessary in women with 3 or fewer nodes and a Recurrence Score of 18 or less (because many of the women in the study undoubtedly received chemotherapy), it is noteworthy that the event rate is so low. Clearly, these women have an excellent prognosis and it is actually unlikely that chemotherapy played a significant role in the outcome given what we know about the benefits of chemotherapy in women with low Recurrence Scores. While not definitive, this study provides further evidence that Recurrence Score testing is able to identify women with a very low risk of recurrence and, in all likelihood, that these women derive very little benefit from chemotherapy.
Dr Gradishar

The Oncotype DX® 21 gene Recurrence Score® (RS) has been used clinically for over a decade. The initial use was largely restricted to patients with ER-positive, axillary node-negative disease, where it was validated to be both prognostic and predictive of the benefit from chemotherapy. Ongoing trials are focusing on its utility in the node-positive population, but reported experiences have suggested that it may have similar utility, and in recent years there has been greater use of the RS in node-positive patients with lower nodal burden (1-3). Roberts and colleagues used the SEER database (2004-2012) to assess the 5-year breast cancer specific survival (BCSS) among patients with lymph node positive disease and determine the uptake of Oncotype DX in this population.

They found that the 5-year BCSS was very good for those patients with low RS and minimal nodal burden. For example, for those with only micrometastases, 5-year BCSS was 99.4%, while for those with 4+ nodes it was 85.7%. A similar spectrum of recurrence risk was identified in the RS 18-30 and RS ≥31 groups, with those with lower nodal burden having lower risk of recurrence compared to those with higher nodal burden. This report is limited because of underreporting of chemotherapy use in SEER as well as no reporting of HER2 status until 2010. With respect to prognosis, the data suggest an ability to stratify risk of recurrence using the RS even in those with node-positive disease.

Validation of a prognostic model integrating Breast Cancer Index (BCI) with tumor size and grade for prediction of distant recurrence in hormone receptor-positive (HR+) breast cancer with 1-3 positive nodes

Zhang Y et al. Proc ASCO 2016;Abstract 541.

Dr O’Regan

Breast Cancer Index (BCI) comprises the molecular grade index (MGI) with the HoxB13/IL17BR (H/I) ratio. BCI has been demonstrated to be prognostic for both early (up to 5 years) and late (5 to 10 years) recurrences in patients with ER-positive, node-negative breast cancers, and, using the H/I ratio, predictive of extended adjuvant endocrine therapy with letrozole based on an analysis of the MA17 trial. A new prognostic model incorporating BCI with tumor size and grade, BCIN, was evaluated using 402 patients with ER-positive breast cancers with N1 disease who had received up to 5 years of adjuvant endocrine therapy, with a median follow-up of 12 years. The addition of tumor size and grade improved the prognostic ability of BCI for patients with N1 disease. In multivariate analysis, only BCIN was prognostic for 15-year and post-5-year distant disease free survival (DDFS). BCIN was able to identify approximately 20% of patients with N1 disease deemed low risk who had 1.3% risk of distant recurrence through 15 years, regardless of HER2 status. BCIN can identify patients with cancers that are at such a low risk of recurrence, extended adjuvant endocrine treatment may not offer any substantial benefit.


**Dr Gradishar**

Patients with node-positive, ER+ breast cancer have a risk of recurrence 2x that of those with ER+, node-negative disease over a 10 year period. Node-positive patients usually receive a recommendation for adjuvant chemotherapy and endocrine therapy for as long as 10 years. Being able to identify those patients with node-positive disease who have a very low risk of late recurrence could help define a population that would not require extended adjuvant endocrine therapy. The Breast Cancer Index (BCI) is a gene expression–based assay that provides both prognostic and predictive information in patients with early stage, ER+ breast cancer. The prognostic component was validated in lymph node–negative patients and provides risk of overall (10 y), early (0-5 y) and late (≥5 y) distant recurrence.

The predictive component was shown to predict likelihood of benefit from endocrine therapy for ≥5 years. Zhang and colleagues developed a prognostic tool integrating the BCI with tumor size and tumor grade in patients with ER+ disease and 1-3 positive lymph nodes. Included in the analyses, with 12 years follow-up, were over 400 ER+ patients, the majority of whom received adjuvant chemotherapy. All patients received 5 years of endocrine therapy. In their model, referred to as BCIN+, a significant fraction of women with N1 disease were found to have an exceedingly low risk of distant recurrence (1.3%) over 15 years of follow-up.

These data suggest that we may be able to discriminate which patients benefit from longer duration endocrine therapy and those that do not require it. The incorporation of molecular tools may refine decision-making for women with ER+ disease. Prospective data are lacking, but the retrospective data are compelling.

**A randomized trial (MA.17R) of extending adjuvant letrozole for 5 years after completing an initial 5 years of aromatase inhibitor therapy alone or preceded by tamoxifen in postmenopausal women with early-stage breast cancer**

Extending aromatase-inhibitor adjuvant therapy to 10 years

Goss PE et al.  
¹ Proc ASCO 2016;Abstract LBA1.  

**Dr O’Regan**

The MA.17R trial was designed to evaluate extended aromatase inhibitor therapy beyond 5 years. Patients who had received 4.5 to 6 years of an aromatase inhibitor, preceded by tamoxifen or not, were randomized to letrozole or placebo for another 5 years. Given the low event rate, the trial was amended from an event-based to a time-based analysis. Five-year disease free survival (DFS) was significantly improved from 91% in the placebo arm to 95% in the letrozole arm. Notably, much of the DFS benefit was due to an almost 60% reduction in contralateral breast cancers. The trial definition of DFS did not include deaths from other causes, and when these were included there was no significant difference between the 2 arms.
To date there is no difference in survival. In this selected group of patients who had already tolerated 5 years of aromatase inhibitor therapy, overall toxicities and quality of life were similar between the 2 arms. However, although almost 50% of patients were taking bisphosphonates, there was a significant increase in fractures and in new onset osteoporosis with letrozole. Extending aromatase inhibition beyond 5 years is an option in an as yet undetermined subset of patients, and results of NSABP-B-42, addressing a similar question, are awaited.

Dr Winer

Goss and colleagues conducted a randomized trial of 5 years vs 10 years of aromatase inhibitor therapy for hormone receptor positive breast cancer. Participants could have either received 5 years of aromatase inhibitor alone or tamoxifen followed by 5 years of an aromatase inhibitor prior to randomization. Nineteen hundred and eighteen women participated in the trial. Women who received the additional 5 years of an aromatase inhibitor had a statistically significant superior disease-free survival, with an absolute improvement of 3.2% in DFS. In spite of this difference, there was only a difference of 11 distant events and no difference in overall survival. Most of the events that were prevented (1.8%) were contralateral primaries.

In summary, the study demonstrated that extending letrozole to 10 years was safe but that the benefit seen with prolongation of therapy was predominantly a result of prevention of second primaries. For most women with node negative disease or a small number of involved lymph nodes, the benefits of continuing letrozole do not necessarily outweigh the side effects and nuisance of being on a medication unless they are particularly concerned about a contralateral primary. On the other hand, continuing therapy for a patient at particularly high risk of distant recurrence, presumably because of Stage III disease, is entirely reasonable.

Dr Gradishar

Data presented by Paul Goss at the ASCO 2016 plenary session and recently published in *The New England Journal of Medicine* suggest that extended durations of the aromatase inhibitor letrozole for as long as 10 years may provide further reduction in the risk of disease recurrence in postmenopausal patients with ER-positive, early stage breast cancer. He presented data from the NCI-Canada MA.17R trial, a study that was an outgrowth of the earlier MA.17 trial, which demonstrated that after 4-6 years of adjuvant tamoxifen, letrozole for 5 years significantly improved DFS compared to placebo. Those patients who were originally randomized to letrozole, at the completion of 5 years of letrozole were re-randomized to receive an additional 5 years of therapy with letrozole or placebo.

A total of 1,918 postmenopausal patients were randomized and followed for a median of 6.3 years. Out of the 165 DFS events, 42 and 53 were distant recurrences in the letrozole and placebo groups, respectively. Interestingly, contralateral breast cancer occurred in 13 and 31 of the patients receiving letrozole and placebo, respectively. Overall survival was identical between the 2 groups. The MA.17 trial showed that extended letrozole therapy resulted in further reduction in the odds of a breast cancer
event, with the 5-year DFS being 95% for the letrozole arm and 91% for the placebo arm, but only about 1% of the difference is accounted for by distant recurrences. These results also raise the issue of whether extended therapy should be recommended for all patients.

Although the quality of life data suggest equivalence between the 2 arms, there may have been self-selection in those patients already able to complete the first 5 years of letrozole with few side effects and willing to be re-randomized for further treatment. The NSABP-B-42 study is even more rigorously addressing the issue of extended duration of AI therapy by randomizing 4,000 patients who received 5 years of an AI (or tamoxifen sequenced with an AI for 5 years) to an additional 5 years of an AI or placebo. Additionally, there may be cases where this strategy is most relevant (higher grade, tumor size and nodal involvement, etc).

Deborah Schrag discussed these data from the standpoint of value according to both ASCO and ESMO frameworks and suggested that long durations of therapy may not add value for an entire health system since some patients will need treatment for fractures and osteoporosis that may occur. As is frequently the case, these data suggest that recommendations must be individualized.

**Predictors of recurrence during years 5-14 in 46,138 women with ER+ breast cancer allocated 5 years only of endocrine therapy (ET)**

Pan H et al.
Proc ASCO 2016;Abstract 505.

**Dr O’Regan**

ER-positive cancers are known to be at a significant risk of late recurrences, supporting the concept of extended adjuvant endocrine therapy. Predictors for recurrence and survival were assessed in more than 46,000 women with ER-positive breast cancer who had received 5 years of endocrine therapy. Overall for ER-positive breast cancers there was a continuous recurrence risk through 20 years. Risk of recurrence and mortality years 5 through 14 following diagnosis were related to a greater number of involved nodes, larger tumor size, higher grade and higher Ki67. However, even patients with low grade, Stage I cancers had a significant risk of recurrence beyond 5 years. These data support consideration of extended adjuvant endocrine therapy in the majority of patients with early stage ER-positive disease.

**Dr Gradishar**

Pan et al evaluated the Early Breast Cancer Trialists’ Collaborative Group (“Oxford Overview”) data set in an effort to identify clinical-pathological factors that may predict for late recurrences in years 5-14 of follow-up in those women who received only adjuvant endocrine therapy for 5 years. The data set included >46,000 women with early stage, ER+ breast cancer. They found that the risk of recurrence steadily increased for up to 20 years. The factors predicting for late distant recurrence included...
Breast Cancer

Dr O’Regan

PALOMA-2, the confirmation study of PALOMA-1, evaluated the addition of the CDK inhibitor palbociclib to letrozole as first-line treatment for patients with HR-positive metastatic breast cancer. The addition of palbociclib to letrozole significantly improved investigator-assessed progression-free survival (PFS) by 10 months from 15 months to 25 months. A similar improvement in PFS was noted in a centrally assessed analysis. All pre-defined patient subgroups benefited from the addition of letrozole to palbociclib, and there were no new safety concerns reported. PALOMA-2 provides level 1 evidence for the use of palbociclib and letrozole as first-line treatment for patients with metastatic HR-positive breast cancer.

To date no definitive biomarker for palbociclib has been identified, and it remains possible that a subset of patients could be treated with endocrine therapy alone in the first-line setting, given the improved outcome for patients treated with fulvestrant and palbociclib in the pre-treated setting from PALOMA-3.

Dr Winer

Finn and colleagues conducted a randomized trial in the first-line metastatic setting comparing letrozole plus placebo vs letrozole plus palbociclib in 666 patients. Women who received palbociclib had a median progression-free survival of 24.8 months vs 14.5 months for those who received placebo. Not only is this difference highly statistically significant, but it is also clinically significant, particularly in light of the favorable side-effect profile of palbociclib. Remarkably, the results were very similar to those seen in the PALOMA-1 study (Phase II randomized trial with identical agents) and are consistent with the results from PALOMA-3 (second-line trial of fulvestrant +/- palbociclib).

Taken together, these studies have established a clear role for palbociclib in the treatment of HR+ metastatic breast cancer, and most clinicians are now using palbociclib in the first-line setting. That said, in the absence of a survival benefit, there are some clinicians who prefer to hold off on palbociclib treatment until the second-line setting. These results have also led to the development of a 4,600 person adjuvant trial that

axillary node positivity (RR 2.08), tumor size (RR 1.73), high grade for T1N0 (RR 2.02) and high Ki67. The characteristics associated with the lowest risk of any recurrence were those of T1N0/low grade tumors (distant recurrence 5% and any recurrence 12%).

These data highlight the persistent risk of recurrence in ER+ disease up to 20 years, but there may be individuals at greatest risk making them the better candidates for prolonged endocrine therapy.

**PALOMA-2: Primary results from a phase III trial of palbociclib (P) with letrozole (L) compared with letrozole alone in postmenopausal women with ER+/HER2- advanced breast cancer (ABC)**

Finn RS et al.  
*Proc ASCO 2016;Abstract 507.*
Breast Cancer

seeks to determine if palbociclib can improve disease-free survival in patients with Stage II/III HR+ disease.

Dr Gradishar

The PALOMA-2 trial compared letrozole plus palbociclib to letrozole plus placebo in postmenopausal women with ER+/HER2- advanced breast cancer. Palbociclib is an oral CDK4/6 inhibitor that prevents cancer cell progression through the cell cycle by affecting the interaction between CDK4/6 and retinoblastoma (Rb). By preventing hyperphosphorylation of Rb, the inhibitor sustains Rb activity and prevents cell cycle progression. There are also preclinical data showing the synergy between palbociclib and endocrine agents. Patients were eligible for the trial if they had received no prior treatment for advanced disease and were not deemed resistant to aromatase inhibitors (administered in the adjuvant setting).

The results demonstrated that letrozole plus palbociclib was associated with a 10-month improvement of PFS (24.8 months vs 14.5 months), though there is no improvement in overall survival at this time. The benefit was observed across all subsets of patients in the trial. The most common adverse events were neutropenia and leukopenia, but neutropenic fever was uncommon. These data show a significant improvement in outcome with the combination of letrozole and palbociclib, but the question arises as to whether all women require this combination. We all have exceptional responders to monotherapy with endocrine agents, but it is challenging to know who they are.

Since the PALOMA-3 trial demonstrated increased efficacy (PFS) with the combination of fulvestrant and palbociclib in those that had progressed after receiving an aromatase inhibitor, the option of starting with monotherapy is viable in some patients.

Dr O’Regan

Mutations in the estrogen receptor (ESR1) are rarely seen in primary cancers but have been noted in more than 20% of aromatase inhibitor-resistant, metastatic ER-positive breast cancers. The SOFEA trial noted a differential benefit for fulvestrant over exemestane in patients with ESR1 mutant cancers, but not in ESR1 wild-type cancers. Patients enrolled in PALOMA-3 were noted to have a 27% incidence of ESR1 mutations in circulating DNA. Interestingly, ESR1 mutations were seen only in patients treated with prior aromatase inhibitor but not in those treated with tamoxifen. Patients in PALOMA-3 randomized to receive fulvestrant and palbociclib had a significantly improved PFS regardless of whether they had ESR1 mutations or not, compared to those treated with fulvestrant alone.
Abemaciclib is a selective, potent inhibitor of CDK4/6 with demonstrated activity, both as a single agent and with endocrine therapy, in patients with HR-positive metastatic breast cancer. In contrast to other CDK inhibitors, abemaciclib can be given continuously on a twice daily basis. MONARCH1 is a phase 2 trial evaluating the use of single agent abemaciclib in patients with pre-treated HR-positive metastatic breast cancer. Enrolled patients had received a median of 5 prior lines of therapy, including a median of 3 in the metastatic setting, and had not received prior therapy with a CDK inhibitor. The overall response rate was 20% with a clinical benefit rate at 6 months of 42%. Median PFS and overall survival were 6 months and 18 months, respectively, with a median duration of response of 9 months.

In contrast to palbociclib, the most common side effect of abemaciclib is diarrhea, which was grade 3 in 20% of patients. Single agent abemaciclib may provide a new option for patients with heavily pre-treated HR-positive metastatic breast cancer, further prolonging the time to chemotherapy.

Dr O’Regan

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In contrast to palbociclib, the most common side effect of abemaciclib is diarrhea, which was grade 3 in 20% of patients. Single agent abemaciclib may provide a new option for patients with heavily pre-treated HR-positive metastatic breast cancer, further prolonging the time to chemotherapy.

Dr Winer

The MONARCH 1 study is a trial of abemaciclib administered as a single agent to women with hormone receptor positive metastatic breast cancer who had progressed on prior hormonal therapy and had received 1-2 chemotherapy regimens for their metastatic disease. A total of 132 patients enrolled and approximately half had received 2 prior chemotherapy regimens for metastatic disease. The overall response rate was 19.7% and the clinical benefit rate (CR + PR + SD for 6 months) was 42.4%. The median duration of response was 8.6 months and over 28% maintained a response for a year or more. The most common toxicities were diarrhea and fatigue. Grade 3 diarrhea was seen in 20% and Grade 3 fatigue in 13%.

Apart from these toxicities, the treatment was reasonably well tolerated. The study demonstrates the single agent activity of abemaciclib, and the results of combination trials are pending. It is unclear at this time if abemaciclib will be active when patients have progressed on other CDK4/6 inhibitors or whether it will be more or less effective in combination. A wide variety of trials are in process.
Dr Gradishar

Maura Dickler presented data on the MONARCH 1 trial that evaluated the monotherapy activity of the CDK4/6 inhibitor abemaciclib in postmenopausal patients with ER+/HER2-metastatic disease who had progressed on or after endocrine therapy and chemotherapy. A total of 132 patients were recruited, who had received a median of 3 prior lines of therapy for metastatic disease including 2 that were chemotherapy. Abemaciclib was administered orally every 12 hours (200 mg) on a continuous schedule. An objective response rate of 19.7% and a clinical benefit rate of 42.4% were observed with a PFS of 6 months. These results compare favorably to what chemotherapy drugs such as eribulin and capecitabine would achieve in a similar clinical scenario.

At this time point there are not sufficient data available to draw comparisons to the approved CDK 4/6 inhibitor, palbociclib. There do appear to be some differences in toxicities between the 2, with hematologic toxicity being observed predictably with palbociclib and low-grade diarrhea being observed more frequently with abemaciclib. The key abemaciclib registration trials, MONARCH 2 and 3, along with the third drug in this class, ribociclib (MONALEESA trials), will generate much data for consideration over the next few years. The development plan for abemaciclib is very similar to those for palbociclib and ribociclib, with a series of pivotal randomized trials comparing endocrine monotherapy with the combination of the same endocrine agent with abemaciclib. Abemaciclib was granted breakthrough status by the FDA in 2015.

Interim results from neoMONARCH: A neoadjuvant phase II study of abemaciclib in postmenopausal women with HR+/HER2-breast cancer


Dr O’Regan

Abemaciclib is an oral, potent inhibitor of CDK 4/6 with demonstrated clinical activity as a single agent or with endocrine therapy. Abemaciclib is given continuously twice daily with diarrhea being the most common adverse event.

The neoMONARCH trial randomized patients with hormone receptor-positive, untreated early stage breast cancer to receive abemaciclib plus anastrozole, anastrozole alone or abemaciclib alone for 2 weeks, after which all patients received the combination of abemaciclib and anastrozole for 14 weeks followed by surgery. Loperamide was administered prophylactically to prevent abemaciclib-related diarrhea.

At a 9-month interim analysis, reduction in Ki67 geometric mean percent change from baseline to 2 weeks was significantly greater in the abemaciclib plus anastrozole combination arm and the abemaciclib alone arm compared to the anastrozole alone arm. Diarrhea was less frequent and severe with loperamide prophylaxis. These data demonstrate the anti-proliferative effects of abemaciclib alone and with anastrozole, compared with anastrozole alone, in hormone receptor-positive breast cancer.
Breast Cancer

Dr O’Regan

Ribociclib is an orally bioavailable selective CDK4/6 inhibitor. Early phase evaluation demonstrated a once-daily dose of 800 mg 3 out of 4 weeks as optimal dosing schedule. The MONALEESA-2 study randomized almost 700 postmenopausal patients with hormone receptor-positive advanced breast cancer to letrozole plus ribociclib or letrozole plus placebo. Primary endpoint was progression-free survival (PFS), with secondary endpoints of overall survival, response, clinical benefit and safety. Approximately 60% of patients had visceral disease. A third of patients had de novo disease and the remainder had a disease-free interval of more than 12 months prior to study entry.

This interim analysis demonstrated a significant improvement in PFS for patients randomized to receive ribociclib, with median PFS not being reached compared to 14.7 months in the placebo arm. Almost all pre-defined subgroups had a significant improvement with the addition of ribociclib to letrozole. Response rate was significantly improved in the ribociclib arm. The most common adverse event was neutropenia with 50% and 10% of patients experiencing Grade 3 and 4 neutropenia, respectively, though only 1.5% of patients experienced febrile neutropenia. Overall 7.5% of patients discontinued ribociclib and letrozole due to adverse events.

These results support the use of ribociclib with letrozole as first-line therapy for patients with hormone receptor-positive breast cancer. Differences between individual CDK inhibitors may become apparent with real-world use.

Dr O’Regan

CDK inhibition has been demonstrated to significantly and meaningfully improve outcome when added to first-line aromatase inhibitor therapy in the first-line setting.
of HR-positive metastatic breast cancer. Ribociclib (LEE011) is a selective inhibitor of CDK4/6, given once daily for 21 days of a 28-day cycle, that has demonstrated activity when added to letrozole in patients with HR-positive metastatic breast cancer. MONALEESA-3 is a randomized phase 3 trial evaluating the addition of ribociclib to fulvestrant in patients with HR-positive metastatic breast cancer who have received up to 1 line of prior endocrine therapy in the metastatic setting.

Ribociclib is additionally being evaluated with fulvestrant in patients with previously treated HR-positive metastatic breast cancer in MONALEESA-2, which will be presented at ESMO 2016, and with tamoxifen or a non-steroidal aromatase inhibitor together with ovarian suppression in premenopausal patients with HR-positive metastatic breast cancer in MONALEESA-7. Positive results of these trials could provide a new CDK inhibitor for patients with HR-positive breast cancer. It is still unclear whether CDK inhibition should be continued through progression, and ongoing trials are addressing this question.

**Dr Winer**

The authors report on a trial in progress comparing ribociclib vs placebo in patients with hormone receptor positive metastatic disease who are receiving fulvestrant and have received 1 or fewer regimens in the metastatic setting. The trial is of similar design to the PALOMA-3 study (conducted with palbociclib, one of the other CDK4/6 inhibitors). Results will be available in the next 1-2 years.

**Dr Gradishar**

The MONALEESA-3 trial is a Phase III randomized clinical trial (double-blind, placebo-controlled) comparing fulvestrant plus placebo to fulvestrant plus ribociclib. Patients are eligible if postmenopausal with ER+ disease that has never been treated ( naïve) or that relapsed during adjuvant endocrine therapy or after 12 months of adjuvant endocrine therapy and one line of endocrine therapy for metastatic disease. The accrual goal is 660 patients, with a primary endpoint of progression-free survival, and secondary endpoints include overall survival and quality of life measures. At present no clinical data have been reported from this trial. Of interest, the MONALEESA-2 trial, comparing letrozole to letrozole and ribociclib, was recently reported at ESMO and in *The New England Journal of Medicine*.

The results are comparable to the PALOMA-2 trial, which showed a significant improvement in progression-free survival (increase of 10 months) favoring the doublet of letrozole and palbociclib in patients receiving first line therapy for metastatic breast cancer. In the MONALEESA-2 trial, after 18 months, the progression-free survival rate was 63.0% (95% CI, 54.6 to 70.3) in the ribociclib group and 42.2% (95% CI, 34.8 to 49.5) in the placebo group. The median duration of progression-free survival was not reached in the ribociclib group and was 14.7 months in the placebo group. The toxicity profiles of palbociclib and ribociclib appear to be similar, with neutropenia common to both.

The ultimate issues should ribociclib be approved are whether there is a discernible difference between the 2 drugs and whether one can be used after disease progression on the other.
**Chronic Lymphocytic Leukemia**

**Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia**

Roberts AW et al.  

**Dr Smith**

A fundamental mechanism of CLL survival and chemoresistance is Bcl-2 upregulation. Targeting Bcl-2 has been difficult, with agents failing to account for the complexity and redundancy of Bcl-2 family members. Venetoclax, an oral second generation BH3 mimetic, effectively inhibits Bcl-2 and has a diminished impact on Bcl-XL, removing the mechanism-associated thrombocytopenia seen with its predecessor. This large Phase I dose-finding study with an expansion cohort shows impressive activity of venetoclax monotherapy: Among 56 highly resistant patients in the dose-escalation phase plus 60 patients in the expansion cohort, the overall response rate was 79% with 20% CRs. Notably, there was activity at all dose levels and no MTD was found.

However, 3 cases (1 death) of TLS prompted a revision to admit patients with bulky disease (>10 cm) or >5 cm with 25K circulating white cells. Overall, the incidence of TLS was 18%. The CRs, and the MRD negativity achieved in 5% of patients, are unusual for the current generation of oral targeted agents. None of the patients in this study had prior ibrutinib therapy, but other reports indicate venetoclax efficacy following oral kinase inhibitor failure in CLL. This is an exciting agent with a rational target, and combination studies are under way.

**Dr Sharman**

Impressive gains have been made in the therapeutic landscape for chronic lymphocytic leukemia. Novel inhibitors of B-cell receptor signaling, including ibrutinib and idelalisib, have transformed treatment algorithms, and most patients are poised to benefit from the development of these drugs. Ibrutinib now has a broad front-line indication so that it is available to virtually all patients, and idelalisib has very good activity in the relapsed/refractory setting although it is limited to some degree by side effects. Furthermore, the second-generation anti-CD20 antibody obinutuzumab has a front-line treatment indication in combination with chlorambucil and is likely to expand its footprint to additional CLL treatment indications. Despite these impressive gains, perhaps the most clinically active drug has only just recently been approved. Venetoclax is a novel Bcl-2 inhibitor with a remarkable degree of clinical activity. Whereas B-cell receptor signaling inhibitors generally affect the CLL cells over a lengthy period of time, venetoclax results in rapid cellular death such that tumor lysis remains the primary concern for use of this drug even in heavily pretreated high-risk CLL.

In this Phase I study with expansion cohorts, a response rate of about 80% was seen with 20% complete remissions and 5% of patients negative for minimal residual disease.
on flow cytometry with a nearly 70% 15-month progression-free survival. Tumor lysis was seen early in this protocol and so the dose escalation strategy was altered, and clinical tumor lysis was not seen in any of the expansion-cohort patients. GI side effects, including diarrhea and nausea, were some of the more bothersome chronic side effects of the medication. Neutropenia was also fairly common.

Several interesting observations include slightly lower response rate in the 17p deletion population and perhaps a slightly lower progression-free survival in the same group. Clinical complete response patients experienced a longer duration of response. This drug now has FDA approval for those patients with 17p deletion. Based upon pivotal studies that are either fully accrued or pending, broad FDA approval for multiple different treatment settings is likely in the next 1 to 3 years.

**Dr Williams**

The selective Bcl-2 inhibitor venetoclax has marked clinical activity in relapsed chronic lymphocytic leukemia (CLL), including del(17p) patients, but with risk of severe tumor lysis syndrome (TLS). In this Phase I dose-escalation trial for relapsed or refractory CLL/SLL, a stepped-up dosing regimen with intensive laboratory monitoring and IV hydration were employed, including inpatient monitoring for ≥24 hours during initial dosing at the 20-mg and 50-mg levels. Target doses ranged from 150 to 1,200 mg/d, with 400 mg/d utilized in an expansion cohort. Treatment was continued until disease progression or unacceptable toxicity.

Of the 116 enrolled patients, 79% responded, including 20% complete remissions; 5% became MRD negative by peripheral blood flow cytometry. The expansion cohort of 60 patients who received 400 mg/d had a 15-month progression-free survival of 69%. The median PFS for patients in the dose-escalation cohort was 25 months. Treatment was discontinued due to disease progression in 41 (35%; 18 with Richter’s transformation), and in 9 due to adverse events. Toxicities included Grade 3-4 neutropenia (41%) and anemia or thrombocytopenia (12% each); 3 patients had clinically significant TLS, 1 fatal and 1 requiring dialysis.

Venetoclax has a unique mechanism of action and provided clinical benefit in most patients. Importantly, responses were similar for the poor-risk subgroups with del(17p) or IGHV unmutated status, and it is FDA-approved for use in CLL patients with del(17p) who have had at least 1 prior therapy.

Venetoclax should be utilized for those failing ibrutinib, or for those with ibrutinib contraindications such as significant bleeding risk, ongoing anticoagulation therapy, or atrial fibrillation. Stepwise dose escalation and intensive TLS prophylaxis and monitoring via initial hospital admission are necessary. Monitoring for neutropenia is needed, at times with growth factor support. Ongoing trials combining venetoclax with other targeted agents and immuno-chemotherapy are in progress.

**Dr LaCasce**

The anti-apoptotic protein Bcl-2 is critically important in the pathogenesis of chronic lymphocytic leukemia. This study is a Phase I trial of venetoclax, an oral Bcl-2 antag-
onist, in patients with relapsed/refractory CLL. 56 heavily pretreated patients, 89% of whom had poor prognostic indicators, were treated in the dose escalation phase starting at doses of 150 mg to 1,200 mg per day. 3 patients developed clinical tumor lysis syndrome (TLS), which was fatal in one. In an expansion cohort, 60 additional patients were enrolled for a slow up-titration of the drug, starting at 20 mg, to a target dose of 400 mg, with no resulting cases of TLS. Venetoclax was otherwise well tolerated, with mild diarrhea, nausea and reversible neutropenia being the most common adverse events.

Therapy was remarkably effective with 79% of patients responding, including patients with 17p deletions, unmutated IGHV and resistance to fludarabine. The complete remission rate was 30%, with 5% achieving MRD negative status. Progression free survival at 15 months was 69%. Overall, this is an important study in CLL. Prior to the availability of venetoclax, patients, particularly those with 17p deletion, whose disease progressed on ibrutinib and idelalisib had very limited therapeutic options. In addition, the toxicity profiles of both ibrutinib and idelalisib are significant, including atrial fibrillation and bleeding with the former and immune mediated effects and infection with the latter.

Multiple ongoing studies are evaluating venetoclax in combination with anti-CD20 antibodies, chemotherapy and other novel agents.

Safety and efficacy of a combination of venetoclax (GDC-0199/ABT-199) and obinutuzumab in patients with relapsed/refractory or previously untreated chronic lymphocytic leukemia — Results from a Phase 1b study (GP28331)

Flinn IW et al. Proc ASH 2015;Abstract 494.

Dr Smith

While rituximab has improved overall survival when combined with chemotherapy in CLL, monotherapy trials showed an inferior response rate compared to other B-cell malignancies such as FL. Obinutuzumab is a Type II glycoengineered anti-CD20 that is more potent than rituximab in CLL when combined with chemotherapy (ie, the CLL11 trial). The current Phase Ib trial of venetoclax plus obinutuzumab tested 2 dose levels and schedules for 6 cycles followed by venetoclax monotherapy. The majority of patients (n = 26) had R/R disease. The 2 agents were safely combined with a dose of 400 mg/d of venetoclax, with an ORR of 100% and a 24% CR rate.

The most common AE, frequently leading to discontinuation, was cytopenias. These are exciting, albeit preliminary, data. Longer follow-up will be helpful to understand the duration of response, and both an expansion phase and Phase III trials are under way.

Dr Sharman

Venetoclax is a novel Bcl-2 inhibitor with dramatic single-agent activity in patients with chronic lymphocytic leukemia. Tumor lysis syndrome was seen early in the develop-
Hodgkin and Non-Hodgkin Lymphoma

ment of this molecule with 2 patients experiencing fatal TLS. Evaluation across multiple venetoclax studies identified risk factors for TLS, including lymph node size greater than 5 cm or lymphocyte count in excess of 25,000, to categorize patients into low, medium, high-risk populations. A 5-week ramp up of dosing was subsequently developed, and clinical tumor lysis is now rarely seen in protocol patients and laboratory tumor lysis is considerably less frequent. Nonetheless, these risk factors are commonly present such that a high fraction of patients are considered at medium or high risk for tumor lysis at the time of treatment initiation, and they have an arduous monitoring schedule that often requires hospitalization as well as aggressive hydration and TLS risk modification.

These clinical barriers are significant, and consequently there is interest in evaluating strategies to “debulk” patients before initiating venetoclax in order to diminish the risk of TLS. This study was initiated before the risk of TLS was fully understood. Obinutuzumab represents an obvious treatment partner for venetoclax as it offers a chemotherapy-free combination. This drug combination is currently the subject of ongoing randomized front-line Phase III trials in Germany. If this study is positive, as can be broadly expected, it could lead towards front-line label indication for venetoclax.

Dr Williams

In this early-phase study of venetoclax plus the type 2 anti-CD20 monoclonal antibody obinutuzumab, 2 dosing schedules were employed, starting with one or the other agent as initial treatment before adding the second. Most patients were at medium or high risk for tumor lysis syndrome (TLS). Six of the 32 enrolled patients were treatment naïve.

The ORR was 100%, with 24% achieving CR or CR with incomplete marrow recovery. CR rates increased over time, and 26/32 patients remained on study at the time of analysis. Toxicities included infections, infusion reactions to obinutuzumab, diarrhea, neutropenia and nausea; laboratory but not clinical TLS was observed in 4/32 patients.

These early results support continued investigation of the combined use of these agents and the ability to modulate TLS risk with dosing and prophylactic measures. An expansion cohort was planned using venetoclax at 400 mg daily plus standard dose and schedule of obinutuzumab.

The potential for deep, MRD-negative responses without administration of traditional cytotoxic chemotherapy should encourage enrollment of patients in clinical trials investigating such approaches.

Dr LaCasce

Obinutuzumab, the Type II glycoengineered anti-CD20 antibody, is associated with improved outcomes in CLL compared to rituximab in combination with chlorambucil. The combination of venetoclax plus rituximab is highly active with an overall response rate of 84%. In this Phase I study patients with both treatment naïve (TN) and relapsed/refractory (R/R) CLL were treated with venetoclax at doses of 100 to 400 mg per day, with a gradual ramp up to mitigate the risk of TLS, in combination with obinutuzumab in 1 of 2 dosing schedules. One group initiated therapy with venetoclax and the other with obinutuzumab. All patients received 6 cycles of combination therapy.
Treatment naïve patients then received 6 months of single agent venetoclax, and those who had R/R disease continued on venetoclax until disease progression. At the time of presentation, 32 patients (26 R/R and 6 TN) were enrolled, with median time on study of 5.5 months. 96% of patients were at medium or high risk of TLS. The most common Grade 3 AEs were neutropenia (34%), infection (19%) and TLS (13%), and the only Grade 4 event was neutropenia in 13%. The overall response rate was 100%, with complete remission in 23.5% with incomplete bone marrow recovery. Of 76.5% of patients in PR after 3 cycles, 3 patients achieved a CR after cycle 6. A Phase III study of the combination is ongoing.

The combination of venetoclax and obinutuzumab is highly active with an excellent safety profile thus far and will likely become a standard regimen. The complete remission and MRD negative rates will be key to determining the feasibility of discontinuing therapy, particularly in patients who are treatment naïve.

**Acalabrutinib (ACP-196) in relapsed chronic lymphocytic leukemia**

Byrd JC et al.  

**Dr Smith**

Targeting the B-cell receptor (BCR) has been tremendously successful in CLL, with ibrutinib now approved for all risk groups in the front-line and relapsed settings. However, as a first generation agent, ibrutinib targets not only the BCR but also other kinases, which may be responsible for some of the toxicity such as increased bleeding risk. Acalabrutinib is a second generation BCR inhibitor more specific for BTK with fewer predicted off-target effects. This Phase I/II trial tested safety, efficacy, PK and PD of acalabrutinib in 61 relapsed CLL patients. The main findings were the RP2D of 100 mg BID and significant activity across several dose levels. With a median follow-up of 14.3 months, the response rate of 95% is impressive and persisted across all risk groups, although with no complete remissions. All patients (100%) with 17p deletion had a response. Importantly, acalabrutinib did not inhibit EGFR, TEC or ITK signaling. The main AEs included headache in 43% of patients, diarrhea (39%), weight gain (26%), fever/pyrexia (23%) and URT infections (23%) but not bleeding or bruising. Despite the relatively high frequency of these toxicities, Grade 3 or 4 AEs were rare. The preserved efficacy with diminished toxicity makes acalabrutinib an exciting agent for development.

**Dr Sharman**

Targeting BTK has proven to be a transformative therapeutic advance in the management of chronic lymphocytic leukemia. Ibrutinib was the first successful drug to do this, and quite a few drugs since that time have attempted to replicate the efficacy of ibrutinib. Unfortunately drugs such as CC-292 failed for excessive albumin binding, and another version of the drug, which was non-covalent, lacked adequate enzyme inhibition. A number of other BTK inhibitors are in clinical development. Acalabrutinib may be the next BTK inhibitor to succeed. Two pivotal Phase III studies are currently ongoing in
both the front-line and relapsed/refractory settings for patients with CLL. Acalabrutinib has a different pharmacologic profile with less off-target activity. It would appear that this may reduce the risk of bleeding and rash. Atrial fibrillation also appears to be less frequent with this drug compared to ibrutinib. However, a head-to-head Phase III study in relapsed/refractory high-risk CLL is ongoing and should help clarify the pharmacologic properties of these medications in greater detail than a single-arm Phase II study.

It has been observed that there is some low level residual B-cell receptor signaling prior to the next dose of ibrutinib, which is administered once daily. It has been hypothesized that this residual signaling may help contribute to disease resistance. Acalabrutinib is dosed twice daily, resulting in complete B-cell receptor signaling inhibition. Based upon preliminary results reported here, the clinical activity is impressive, and it is likely that this drug will gain FDA approval unless some unanticipated side effect emerges in subsequent studies.

**Dr Williams**

B-cell receptor pathway activation typifies most B-cell malignancies, including CLL. Targeting the Bruton tyrosine kinase (BTK) can provide marked therapeutic efficacy. Acalabrutinib (ACP-196) is an irreversible BTK inhibitor that appears to lack some of the “off-target” effects of the first-in-class agent, ibrutinib. This Phase I/II clinical trial of acalabrutinib was conducted in patients with relapsed or refractory CLL using an initial dose-escalation phase followed by an extension phase at 100 mg orally twice daily. 61 patients were enrolled, with a median age of 62 y (44-84 y) and a median of 3 prior treatment regimens. Rapid improvement in adenopathy was observed in 60/61 patients; as with ibrutinib, there was a transient increase in lymphocytosis that declined over time. With a median follow-up of 14.3 months, 95% of patients responded, including all 18 patients with del(17p). Headache was observed in 43% of patients, usually Grade 1-2 early in the treatment course with subsequent resolution, and diarrhea in 39%. One death from pneumonia occurred at 13 months. Only 13% of patients discontinued study treatment.

Acalabrutinib thus produced durable responses with comparatively less toxicity than reported in clinical trials of ibrutinib, including rash, major bleeding and atrial fibrillation. Patients with del(17p) responded equally as well as patients with lower-risk molecular subtypes, although one developed disease progression while on therapy.

A head-to-head comparison of acalabrutinib versus ibrutinib in relapsed and high-risk CLL is presently in progress, and referral for enrollment in this trial is encouraged.

**Dr LaCasce**

Acalabrutinib is an irreversible inhibitor of Bruton’s tyrosine kinase with improved specificity in comparison to ibrutinib. In this study, 61 patients with relapsed/refractory CLL were treated with acalabrutinib at doses from 100 to 400 mg daily in the Phase I portion of the study and 100 mg twice a day in Phase II. Patients had received a median of 3 prior therapies and 31% had deletion 17p. There were no dose limiting toxicities, and the most common adverse events were headache and diarrhea. No
cases of atrial fibrillation or severe bleeding were reported. With a median follow-up of 14.3 months the overall response rate was 95%, with 85% and 10% of patients achieving a partial response and PR with lymphocytosis, respectively.

Acalabrutinib is associated with impressive activity and a very favorable toxicity profile in comparison to ibrutinib with its association with bleeding and atrial and even perhaps ventricular arrhythmias. Longer follow-up is required to evaluate for the emergence of these events, which were not seen in the earlier reports of ibrutinib. An ongoing study is comparing acalabrutinib to ibrutinib in relapsed/refractory CLL.

Idelalisib is a first-in-class inhibitor of the delta isoform of PI3K. It is FDA approved as monotherapy for R/R iNHL, R/R CLL and in combination with rituximab based on significant efficacy. This placebo-controlled Phase III randomized trial tested a standard salvage regimen in CLL, bendamustine plus rituximab (BR), with and without idelalisib (idela) 150 mg BID in patients with R/R CLL; all patients had prerequisite prior purine analog or bendamustine AND prior anti-CD20 therapy, as well as progression within 36 months and fitness to receive chemotherapy. 416 patients were enrolled, and the study was halted early due to an independent review board finding substantial benefit to the arm with idelalisib. Of note, this was a very high-risk population with one third of patients having refractory disease, one third with p53 mut/17p del, and over 80% with unmutated IgVH. The study met its primary endpoint of improved PFS (23 months versus 11 months) in all risk groups and also improved overall survival. The PFS curves separate quite early, even before the BR component is complete. The main toxicities increased in the idela arm were known and predictable based on monotherapy trials and included Grade ≥3 increased AST/ALT elevation (15%-20% vs 3%) and diarrhea (7.2% vs 1.9%). The authors conclude that BR plus idela is an important option for patients with R/R CLL.

While this is a promising combination, it is important to note that a similar trial of BR with or without ibrutinib found similar results (HELIOS trial, ASCO 2015 LBA 7005) whereby PFS was improved. It is worth asking 2 questions: 1) what does the chemioimmunotherapy add to the oral kinase inhibitors in the relapsed setting and 2) which combination (BR plus idela or BR plus ibrutinib) is superior?
Dr Sharman

Idelalisib was approved around the same time as ibrutinib. Unfortunately, the medication had a higher degree of side effects observed in studies, including high rates of bothersome diarrhea, concerning LFT elevations, and some additional infectious complications. Those infectious complications subsequently were found to be unacceptably high in the front-line setting, resulting in additional patient death due to CMV and PJP. As a result, idelalisib has not enjoyed the same broad utilization as ibrutinib in relapsed and refractory chronic lymphocytic leukemia.

Three randomized Phase III studies were concurrently launched studying idelalisib in the relapsed and refractory setting. The study that randomly assigned to rituximab plus or minus idelalisib patients considered suitable for rituximab monotherapy led to the FDA approval of the medication and demonstrated both dramatic progression-free survival as well as clinically meaningful overall survival benefits. A second study, which randomly allocated patients to ofatumumab plus or minus idelalisib, also reported significant progression-free survival and a trend towards overall survival benefit.

This final Phase III study evaluated those patients suitable for bendamustine-based therapy in the relapsed setting. Patients received bendamustine and rituximab on standard schedules plus or minus idelalisib. Approximately one third of patients had deletion 17p and 80% had unmutated IgVH consistent with other studies in this population. The progression-free survival favored treatment with idelalisib with median PFS of 23 versus 11 months, and there was a statistically significant improvement in overall survival. There were greater rates of neutropenia and fever associated with idelalisib as well as the expected increase in diarrhea, although this was lower than in other studies.

It is noteworthy that the median PFS in this healthy and more fit population treated with idelalisib was 23 months whereas in the rituximab and idelalisib study it was approximately 19 months, calling into question the relative benefit of bendamustine. Furthermore, it should be noted that in those patients with deletion of 17p, the approximate 12-month PFS amongst those patients treated with idelalisib is surprisingly low. Cross-trial comparisons would indicate that the bendamustine may be harming these patients relative to idelalisib and rituximab alone.

Dr Williams

The B-cell receptor pathway signaling molecule PI3K delta is therapeutically targeted by idelalisib, an FDA-approved agent for relapsed CLL. This study tested its use in combination with standard-dose bendamustine-rituximab. At a planned interim analysis, both progression-free and overall survival were significantly improved and the study was unblinded. A benefit with idelalisib was observed for standard-risk patients as well as for the high-risk subgroups with del(17p) or TP53 mutations, those with unmutated IGHV and those refractory to fludarabine. Increased rates of neutropenia, transaminitis and diarrhea were observed in the idelalisib arm versus placebo.

Although combined idelalisib plus BR significantly improved responses, toxicities were of concern. Importantly, the recognition of increased infection-related fatalities in the
study arm subsequent to the initial report led to suspension of this and other CLL and NHL clinical trials combining idelalisib with cytotoxic chemotherapy. Such combinations should be avoided pending further analysis and updates.

**Dr LaCasce**

Idelalisib is a PI3K delta inhibitor approved in relapsed and refractory CLL and has activity in patients with 17p deletion. In this Phase III study, patients with R/R CLL were randomized to 6 cycles bendamustine (70 mg/m² days 1-2) plus rituximab (375 mg/m² cycle 1 and 500 mg/m² cycles 2-6), with idelalisib (150 mg/m²) or placebo until progression. The primary endpoint was progression-free survival and crossover was not permitted. 416 patients were enrolled, with a median number of 2 prior therapies. 33% harbored 17p deletion or p53 mutation. At a pre-specified interim analysis, the idelalisib was associated with improvement in both progression-free and overall survival and the study was unblinded.

The most common Grade 3 or higher adverse events were neutropenia (60%) and febrile neutropenia (20%) in the idelalisib arm and neutropenia (46%) and anemia (12%) in the placebo arm. The median PFS was 23 months in the idelalisib arm compared with 11 months in the placebo arm. For overall survival, although the median was not reached in either arm, the idelalisib was associated with superior outcome with a hazard ratio of 0.55. In the forest plot, only 17p deletion was not associated with improved PFS. Overall, the results of this study are encouraging. Given the short follow-up, however, it will be important to assess for ongoing toxicity in patients on idelalisib, particularly with respect to colitis, pneumonitis and infection (PJP and CMV reactivation).

Given the outstanding outcomes in patients treated with novel agents, with or without anti-CD20 antibodies, the additional benefit of standard chemotherapy agents such as bendamustine is unclear, particularly given the high rates of neutropenic fever and risk for stem cell damage. Unfortunately, many studies using idelalisib are on hold because of the recent toxicity reports.

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**Idelalisib given front-line for treatment of chronic lymphocytic leukemia causes frequent immune-mediated hepatotoxicity**


**Dr Smith**

Idelalisib is an oral inhibitor of the delta isoform of PI3K and is currently approved in combination with rituximab for relapsed CLL and as monotherapy for R/R iNHL. Based on significant efficacy in relapsed populations, this Phase II study evaluated idelalisib as a 2-month lead-in followed by idelalisib plus ofatumumab for an additional 6 cycles. Ofatumumab is a humanized anti-CD20 antibody currently approved for R/R CLL. This trial enrolled 24 of 50 intended patients and was modified due to frequent and significant hepatotoxicity. Even before the ofatumumab was introduced, the majority of
patients (79%) developed transaminase elevation, including 54% Grade ≥3 transaminitis. Analogous to other studies with increased colitis, biopsy of the liver in 2 patients showed a lymphocytic infiltrate with decreased circulating T-helper cells and supports an immune-mediated effect. The authors propose that toxicity was age related, since the median age of patients with early hepatotoxicity was 61 years versus 72 years ($p = 0.02$) for patients without any hepatotoxicity. There was also a trend of increased hepatotoxicity in patients with a mutated IGVH ($p = 0.039$). Patients with hepatotoxicity were treated with steroids, with a median time to resolution of 8 days; 1 patient also needed MMF. Twelve patients were rechallenged with idelalisib after resolution of transaminase elevation, which rapidly recurred in 6 of those patients after 1-4 days; however, rechallenge with idelalisib while on steroids may be protective against recurrence of transaminase elevation. Outside of this trial, several other front-line combination trials of idelalisib have been halted (fda.gov) based on increased deaths attributed to viral infections. This study is a cautionary note as new agents with potential immune-modifying effects are moved into the front-line setting.

Dr Sharman

Idelalisib inhibits the delta isoform of PI3 kinase. While this is an important target for B-cell receptor signaling, it also modulates T regulatory cells. This inhibition can result in immune hyperactivity and is thought to underlie the mechanism for both diarrhea and LFT abnormalities.

In patients with chronic lymphocytic leukemia that has been previously treated particularly with the immunosuppressive medication fludarabine, it appears that this inhibition of T regulatory cells is clinically significant. However, it still results in improved outcomes when given in combination with bendamustine and rituximab, ofatumumab, or rituximab monotherapy. In front-line CLL, however, the immune dysregulation results in unacceptably high levels of side effects. In this paper of patients treated in the front-line status approximately 80% of patients had LFT abnormalities with over half experiencing greater than or equal to Grade 3 transaminitis. Liver biopsies showed activated T-cell infiltrates within the liver.

This report emerged approximately concurrently with interim analysis of several front-line studies involving idelalisib in which higher rates of CMV and PCP were noted. Multiple different Phase III studies were abruptly closed, and front-line development of this molecule was discontinued. FDA guidance was issued confirming that idelalisib is not indicated for front-line use. While idelalisib is an active drug in CLL, this combination of toxicity signals represents a significant barrier for broad clinical utilization of the medication.

Dr Williams

The PI3Kδ inhibitor idelalisib is an oral B-cell receptor pathway inhibitor with activity in relapsed or refractory CLL. This Phase II trial, conducted in previously untreated CLL patients, administered single-agent idelalisib 150 mg twice daily x 2 months, followed by 6 months of combination idelalisib plus the anti-CD20 monoclonal antibody ofatumumab. Idelalisib maintenance was then continued until disease progression or toxicity.
The 24 enrolled patients had a median follow-up of 15 months, and this report focused on toxicity rather than response. Early onset transaminitis was observed in the majority of patients, and 13 (54%) cases were Grade 3-4. All patients had resolution upon holding the drug or initiating immunosuppression (one received mycophenolate mofetil). Over the course of the study, 67% of patients received steroids for transaminitis and 79% overall for autoimmune toxicities. Of note, younger patients and those with IGHV mutated disease were at increased risk for early hepatotoxicity.

Liver biopsies in 2 patients, elevated serum CCL-3 and CCL-4 inflammatory cytokine levels, and decreased circulating regulatory T-cell levels were consistent with immune-mediated hepatotoxicity.

Autoimmune complications of idelalisib and other PI3K inhibitors are well recognized, including transaminase elevations, inflammatory colitis and pneumonitis. The higher rates observed in previously untreated patients likely relate to the presence of a more intact immune system capable of mediating such toxicities, compared with the more heavily pre-treated and relapsed patients in the earlier registrational trials — by inference, the immunosuppression associated with advanced disease and prior therapy may have mitigated the frequency and severity of autoimmune complications.

Front-line use of idelalisib should be avoided, either alone or in combination immunochemotherapy regimens; increased infection-related fatalities have been observed with the latter, leading to the closing of several recent combination trials. Idelalisib use in patients with relapsed/refractory CLL should be accompanied by antimicrobial prophylaxis.

Dr LaCasce
The PI3K delta inhibitor idelalisib is approved in relapsed/refractory CLL. In this study, 24 patients with previously untreated CLL were treated with idelalisib monotherapy for 2 months followed by 6 months of combination therapy with ofatumumab. Nearly 80% of patients developed transaminitis, with 54% having at least Grade 3 elevations. Transaminitis developed early, at a median of 28 days, and occurred prior to the addition of ofatumumab. Two patients underwent liver biopsy and were seen to have lymphocytic infiltration suggestive of immune mediated toxicity. The pro-inflammatory cytokines CCL-3 and CC-4 were elevated, and regulatory T cells declined in patients who developed hepatitis. The mechanism is thought to be related to on-target inhibition of the p110δ isoform of PI3kinase. Interestingly, younger age and mutated immunoglobulin gene status were associated with increased risk. The transaminitis improved with holding idelalisib and/or treating with immunosuppression (steroids with mycophenolate required for one patient). Some patients tolerated resumption of idelalisib administered concurrently with steroids, which were slowly tapered. Overall, this drug should be used with caution in naïve patients or those with relatively intact immune systems and requires close monitoring for transaminitis, other auto-immune complications and infectious complications, including PJP and CMV reactivation. Unfortunately, a number of ongoing trials with idelalisib have been withdrawn or are on hold.
Hodgkin and Non-Hodgkin Lymphoma

Dr Smith

Although CLL expresses CD20, the surface expression is typically dim and rituximab monotherapy is relatively less active than in indolent lymphomas. Obinutuzumab, a glycoengineered Type II anti-CD20 monoclonal antibody, is significantly more potent and has superior efficacy in Phase III randomized trials. However, there are also more infusion-related reactions and myelosuppression. The current study is designed to test the safety and efficacy of obinutuzumab when combined with standard CLL regimens. This is a very large Phase IIIb trial evaluating obinutuzumab plus either FC, chlorambucil or bendamustine or as monotherapy in treatment-naïve and R/R CLL patients. This is not a randomized trial, but patients are divided based on CIRS criteria into either “fit” or “unfit” groups. Overall, 825 patients were enrolled (485 treatment naïve, 340 R/R) into G-FC (n = 159), G-chl (n = 97), G-B (n = 463), or G monotherapy (n = 106). Patients receiving G-FC were much younger than all other groups, with a median age of 57 years. Overall, there was myelosuppression across all groups, including 25% Grade 3-5 neutropenia in the G monotherapy arm, although only 3% of patients had febrile neutropenia in this group. Also, tumor lysis syndrome (TLS) occurred in 51 patients (6.2%), including 2 fatal cases in the G-B arm, which prompted a “Dear Doctor” letter outlining TLS risk factors, which include any lymph node ≥10 cm OR lymph node size 5-10 cm plus >25K ALC OR lymph node size between 5 and 10 cm plus CrCl <70 cc/min. The efficacy of the treatment arms was not reported. Overall, the success and clinical utility of these G combinations will depend on the balance between efficacy and toxicity and comparison to rituximab-based counterparts, and we await those results. In addition, the current report does not mention any information on cytogenetic risk features and does not clearly separate the treatment-naïve and R/R groups; these factors will also influence the ability to adopt obinutuzumab on a wide-scale level.

Dr Sharman

The German CLL11 study, which evaluated chlorambucil versus chlorambucil with either rituximab or obinutuzumab, demonstrated the superiority of chemotherapy/immunotherapy over simple chemotherapy and furthermore the apparent superiority of obinutuzumab compared to rituximab. This resulted in the FDA approval of obinutuzumab given in combination with chlorambucil for the front-line management of CLL. After establishing regulatory approval there was interest in understanding how obinutuzumab would work with other typical CLL regimens, and the “GREEN” study was subsequently performed, which allowed patients with CLL in need of therapy to select a backbone regimen with their provider and then utilize obinutuzumab rather than

Preliminary safety data from the phase 3b GREEN study of obinutuzumab (G) alone or combined with chemotherapy for previously untreated or relapsed/refractory chronic lymphocytic leukemia (CLL)

rituximab. This was primarily performed as a safety study and evaluated obinutuzumab monotherapy, obinutuzumab in combination with chlorambucil, obinutuzumab in combination with fludarabine and cyclophosphamide, and finally obinutuzumab in combination with bendamustine. This trial was available for both previously untreated as well as relapsed and refractory patients.

At the American Society of Hematology Annual Meeting in 2015 we saw efficacy results of the bendamustine and obinutuzumab arm of this study demonstrating very high rates of minimal residual disease negativity. However, there was perhaps a slightly higher toxicity signal than what has been expected from bendamustine and in addition with rituximab when given in the front-line setting. In the current GREEN study SAEs were reported in between 38% and 48% of patients, depending upon the regimen, and fatal adverse events were as high as 4.5% in the bendamustine and obinutuzumab arm. The most common Grade 3 or higher adverse event was neutropenia, with febrile neutropenia occurring in about 8%-10% of the chemotherapy combination arms. Growth factors were not mandated in the context of the study and may have lowered that frequency if more broadly utilized.

Tumor lysis syndrome with obinutuzumab alone was about 4% and slightly higher at 5% in the bendamustine arm. Most of the tumor lysis syndrome cases occurred in patients with either diminished creatinine clearance or CIRS score higher than 6. While most tumor lysis syndrome was merely Grade 3, there were 2 Grade 5 events in this large population, both in patients with risk factors.

Obinutuzumab monotherapy is commonly utilized, and combination therapy with chlorambucil is FDA approved. It is unlikely that combination therapy with fludarabine and cyclophosphamide is going to be broadly utilized on the basis of this study. The biggest question is the combination with bendamustine. It appears to be a highly active regimen but with a slightly higher toxicity profile. Given the prevalence of bendamustine utilization in the community, it may be a suitable backbone for chemoimmunotherapy with those patients with favorable molecular risk markers likely to derive the most sustained benefit from therapy, provided they have adequate performance status to receive treatment.

**Dr Williams**

The type 2 anti-CD20 monoclonal antibody obinutuzumab has shown increased clinical activity compared with rituximab in CLL. In this trial, untreated or R/R CLL patients received obinutuzumab (G) alone or, at the investigator’s discretion, in combination with fludarabine plus cyclophosphamide (for fit patients), chlorambucil (for unfit patients) or bendamustine (for any patient).

This preliminary safety analysis of 825 patients found Grade 3-4 neutropenia (25%) and thrombocytopenia (10%) with single-agent G, as well as Grade ≥3 infections and infusion reactions. Roughly twice the rate of cytopenias was observed with G plus chemotherapy, whereas infections and infusion reactions were very similar to single-agent G. 14% of patients discontinued G due to adverse events. 43 patients died, including 19 treated in the first line and 24 R/R patients; 32 deaths were due to AEs and 11 due to disease progression.
The response rates among the treatment arms in this trial will be of interest, although the patient selection bias intrinsic to the study will preclude comparing responses among the regimens. Whether the relatively similar AEs observed in this safety analysis relate to use of growth factors, antimicrobial prophylaxis or other interventions awaits the full report.

**Dr LaCasce**

The GREEN study is a Phase IIIb study comparing single agent obinutuzumab (G) for 6 cycles alone or in combination with chemotherapy (investigator’s choice of fludarabine/cyclophosphamide in fit patients only, chlorambucil in unfit patients or bendamustine for any) in patients with previously untreated or relapsed/refractory CLL. Patients who were refractory to prior G were required to receive combination therapy. During cycle 1 all patients received split-dose G over 2 days. In the preliminary results, 825 patients (485 previously untreated and 340 R/R) were analyzed with a median follow-up of 12.7 months. 106 patients received G alone. 159 patients received G in combination with FC, 97 with Clb and 463 with B, respectively.

The most common Grade 3 or higher adverse event was neutropenia at 45% (25% G alone, 59% G-FC, 42% G-Clb and 45% GB). Grade 3 or higher infections were seen in 15% of patients and were similar across all arms. Infusion reactions were highest in the G alone group at 23.6% and were 21%, 20% and 16% in the other arms, respectively. 14% of patients discontinued G due to toxicity. 4% of patients experienced a fatal SAE, similar across all groups. Overall, this study confirms prior experience with obinutuzumab in terms of severe adverse events, which are predominantly infusion reaction and risk of infection in approximately 25% of patients each.

The addition of chemotherapy, not unexpectedly, was associated with higher rates of neutropenia and thrombocytopenia without significantly higher rates of infection or death compared to G alone. Overall, obinutuzumab appears to have similar safety compared to rituximab, with high activity in CLL, and will likely become the standard antibody used in combination regimens in this disease.

**Follicular, Diffuse Large B-Cell and Mantle-Cell Lymphomas**

**Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): A randomised, controlled, open-label, multicentre, phase 3 trial**


**Dr Smith**

Despite novel therapies, indolent non-Hodgkin lymphoma (iNHL) remains incurable, so patients require multiple sequential treatment options. Rituximab-refractory is an accepted regulatory definition but includes a heterogeneous population. GADOLIN
compared obinutuzumab + bendamustine (OB) x 6 cycles followed by obinutuzumab monotherapy with 6 cycles of single-agent bendamustine at 120 mg/m² without any maintenance as the control arm. Bendamustine is active in this setting, although more commonly is now used as initial therapy. Also, though based on the package insert, this dose is not commonly used.

The independent review committee found prolonged progression-free survival (PFS), median not reached, compared with 15 months for bendamustine; investigator PFS estimates were 29 vs 14 months, respectively. Toxicities were similar in each arm. Note that at the end of induction, overall and complete response rates and PFS were not different, suggesting the observed PFS benefit largely reflects maintenance anti-CD20. Nonetheless, GADOLIN led to FDA approval of OB + maintenance obinutuzumab for treatment of patients with rituximab-refractory FL. While GADOLIN included all iNHL, 81% had FL, so it is not powered for other iNHL. The study has not answered more general questions, including whether obinutuzumab is “better” than rituximab, or if maintenance vs treatment at progression is the preferable strategy.

Dr Kahl
GADOLIN explored the role of obinutuzumab in rituximab refractory indolent lymphoma. Obinutuzumab is a novel glyco-engineered Type 2 anti-CD20 monoclonal antibody that may have properties that make it somewhat more efficacious than rituximab. Patients were randomized to receive single agent bendamustine at the FDA approved dose of 120 mg per square meter on days 1 and 2 of each cycle versus the experimental treatment, which was bendamustine plus obinutuzumab. Obinutuzumab was administered at a flat dose of 1,000 mg on days 1, 8, and 15 of cycle 1 and then on day 1 of 2-6. Obinutuzumab was then administered as a maintenance therapy of 1,000 mg every 2 months for up to 2 years in the obinutuzumab-containing arm.

The primary endpoint of this study was progression-free survival assessed by an independent review committee. The trial enrolled 396 patients. Toxicity was comparable between the 2 arms; there were slightly more infusion reactions in the obinutuzumab-containing arm. There were not substantial differences in cytopenias between the 2 arms. The progression-free survival was significantly longer with obinutuzumab plus bendamustine compared to bendamustine alone, with a hazard ratio of 0.55. At the time this paper was published there was no difference in the overall survival between the 2 arms, but an update of this data will be presented at the 2016 American Society of Hematology meetings, and it is possible that clinically significant differences in overall survival will emerge between the 2 arms.

If in fact the bendamustine-obinutuzumab arm does show improvement in overall survival compared to bendamustine alone, this would be a very significant finding. It would suggest that obinutuzumab is actually a superior anti-CD20 monoclonal antibody in follicular lymphoma and will likely lead to more frequent use of obinutuzumab in this population.
Dr Flinn

In the GADOLIN study, patients with rituximab-refractory low-grade lymphoma were randomized to receive bendamustine monotherapy versus bendamustine with obinutuzumab followed by obinutuzumab maintenance. The study showed that despite there being no difference in CR or OR with the induction, there was a substantial difference in the PFS favoring the obinutuzumab arm. This study, which ultimately led to the FDA approval of obinutuzumab in this setting, is fraught with several design issues and controversies. The 2 arms of the study are unbalanced in terms of the duration of the therapy. Obinutuzumab could be administered every 2 months for up to 2 years, whereas the control arm received nothing. The second issue is the definition of rituximab refractory.

These investigators used the standard definition of rituximab refractoriness (failure to respond or progression within 6 months of last dose of rituximab). However, it is unclear how many rituximab-refractory patients would not progress if you gave them a dose of rituximab every 2 months, raising the question of whether randomizing against no maintenance at all is the appropriate control. Finally, bendamustine is frequently given as a front-line therapy in the US and its use in the relapsed setting has dropped off. When it is given it is not used as a single agent at the doses used in the GADOLIN study.

If one looks at the entirety of data with obinutuzumab, it appears that it is a superior antibody to rituximab but with increased neutropenia and infusion toxicities. The magnitude and importance of this difference likely vary on the setting. Because of this I would tend to use obinutuzumab unless there were insurance or other barriers.

Dr Leonard

The novel anti-CD20 monoclonal antibody obinutuzumab has been established as an important agent in CLL. This study evaluated its use in combination with bendamustine in rituximab-refractory indolent NHL patients. During the period of concurrent therapy (B/O vs B alone) the efficacy results were similar. The obinutuzumab-containing arm included maintenance obinutuzumab every 2 months for 2 years, and over that period a progression-free survival benefit emerged. Treatment was well tolerated. This results in a positive study showing benefit with B/O versus bendamustine alone. Unfortunately it is unclear whether rituximab (in combination with bendamustine) would have shown a similar benefit, particularly since rituximab is commonly continued with chemotherapy even in the rituximab-refractory setting.

Therefore, the implications for changing practice in my view are unclear. At the end of the day, overall survival and quality of life are the key parameters that define benefit in indolent lymphoma. From my perspective, I rarely if ever use bendamustine alone in this setting, so the applicability of the control group of this study to my practice is limited. In most cases I will continue to use BR in this setting, though in cases where I am convinced that rituximab has little added value, substituting obinutuzumab is something I will consider.
Hodgkin and Non-Hodgkin Lymphoma

Dr Smith

BR is commonly used as initial therapy for FL, based on randomized comparisons to R-CHOP showing superiority in PFS (STiL) and non-inferiority in CR rate (BRIGHT). Bortezomib (V) is active against lymphoma and has been added to various regimens, including BR. E2408 compares initial therapy for patients with advanced stage FL meeting high tumor burden GELF criteria (92%) or FLIPI score 3-5 (55%) with 3 arms (1:2:2 randomization): BR x 6 cycles of induction followed by maintenance R (MR) as “standard,” addition of bortezomib to induction (BVR + MR), and BR with addition of lenalidomide to maintenance R. This initial report is only for the BR vs BVR induction question. As expected, overall response rate (ORR) was high (91%) in both arms.

For the primary endpoint of end-induction CR, however, BVR was superior (74% vs 58%, \( p = 0.016 \)). Toxicity was similar, except for more Grade 3-4 sensory neuropathy when V was given IV, not SQ. Longer follow-up is needed to determine if the higher CR rate translates into longer PFS or other clinical benefit, as well as for the lenalidomide maintenance question.

Dr Kahl

This was a front-line follicular lymphoma study designed and conducted by the Eastern Cooperative Oncology Group. The trial is attempting to build on a standard BR immunochemotherapy backbone. The goal of E2408 was to test whether the addition of bortezomib to the BR backbone can improve the complete response rate. A secondary goal was to see if lenalidomide administered in conjunction with rituximab can improve disease-free survival. The patient population under study was untreated follicular lymphoma with high tumor burden by GELF criteria or a FLIPI score of 3-5. Patients received bendamustine-rituximab with or without bortezomib for 6 cycles. Patients then received either rituximab as a single agent given every other month for a total of 2 years or rituximab combined with lenalidomide.

The lenalidomide was given at a dose of 20 mg daily for 21 out of each 28 days. This was continued for the first year of maintenance rituximab therapy. The presentation of this study at the 2016 ASCO meeting focused solely on the induction questions comparing response rates between bendamustine-rituximab and bendamustine-bortezomib-rituximab. 289 patients were enrolled. The median age was 60. Most patients had advanced-stage disease. About 90% of patients had high tumor burden by GELF criteria. The treatment was overall well tolerated. Partway through the trial the bortezomib route of administration was changed from intravenous to subcutaneous, and the rate of Grade 3 peripheral neuropathy decreased from 16% to 3% after the change.

Evens AM et al. Proc ASCO 2016;Abstract 7507.

Effect of bortezomib on complete remission (CR) rate when added to bendamustine-rituximab (BR) in previously untreated high-risk (HR) follicular lymphoma (FL): A randomized phase II trial of the ECOG-ACRIN Cancer Research Group (E2408)
The complete response rate in the BR treated patients was 58%, while the complete response rate in the BVR treated patients was 74%, and that difference is statistically significant. These results suggest the addition of bortezomib to the BR induction therapy can substantially improve the complete response rate. The next step is to see whether this improvement in complete response rate translates into better disease control as shown by improvement in progression-free survival. The question then becomes, is bortezomib a novel agent that investigators would continue to build upon in follicular lymphoma? Possibly, as there have not been any groundbreaking new drugs in follicular lymphoma in the past few years. Of course we are very interested in the maintenance portion of this trial, which is testing the combination of lenalidomide when added to maintenance rituximab therapy.

Dr Flinn
Bendamustine and rituximab (BR) has emerged as a standard front-line therapy for patients with follicular lymphoma due to its favorable toxicity and efficacy results seen in 2 randomized Phase III trials (BRIGHT and StiL). Unfortunately, patients continue to relapse, and new agents are needed for these patients. ECOG-E2408 was a 3 arm randomized Phase II trial looking at the addition of bortezomib to BR in induction as well as alternative maintenance strategies. The primary endpoint of the study was complete response rate. The CR rate of BVR (74%) was superior to BR (58%; \( p = 0.016 \)). This superiority was consistent across FLIPI subgroups. However, this improvement came at the expense of increased toxicity, predominantly sensory neuropathy. The degree of sensory neuropathy appeared lower in patients in whom bortezomib was administered subcutaneously versus IV. The major issue for all Phase II studies in follicular lymphoma is whether CR rates are surrogates for PFS and OS. The CR rates of BR seen in this trial are roughly double those seen in the BRIGHT trial, highlighting the degree of subjectivity of response assessments in investigator assessment of response in follicular lymphoma. However, the results of this trial are consistent, both in terms of CR rate and increased neurotoxicity, with a single arm Phase II trial of a similar regimen previously presented.

Given the increased toxicity, I do not think this regimen should be used as a standard therapy until Phase III trials demonstrate its superiority. The development of several new proteasome inhibitors with superior toxicity profiles raises the question of whether they are better drugs to combine with BR.

Dr Leonard
Bendamustine + rituximab has become the standard chemoimmunotherapy for initial treatment of follicular and other indolent lymphomas. Various studies have added bortezomib to chemotherapy, including BR in indolent lymphoma. Evens and colleagues demonstrated that bortezomib + BR improves CR rates from 58% to 74% in high risk (by FLIPI or high tumor burden) follicular lymphoma patients. Toxicities included neuropathy and slightly worsened cytopenias. Historically CR rates have been of modest value in FL. However, this study incorporated PET CR as an endpoint and there is some evidence that PET CR rate may correlate with longer term outcome.
Dr Smith

Mantle cell lymphoma (MCL) remains incurable. Lenalidomide is active in MCL and is approved in the US (as are ibrutinib and bortezomib) to treat relapsed MCL based on the single-arm Phase II MCL-001 EMERGE trial in patients who had previously received bortezomib. There is pre-clinical rationale, and indication by comparing across Phase II trials but not proven in a randomized trial, that adding rituximab to lenalidomide (R2) enhances efficacy.

The SPRINT trial, designed pre-ibrutinib, randomized patients (2:1) to receive lenalidomide alone (25 mg days 1-21/28) vs investigator choice (rituximab, chlorambucil, cytarabine, fludarabine, gemcitabine). ORR (40% vs 11%), PFS (median 8.7 vs 5.2 months) and response duration (median 16.1 vs 10.4 months) favored lenalidomide. Quality of life showed no decline while on lenalidomide. SPRINT confirms and extends EMERGE (ORR 28%, median TTP 4 months, median DoR 17 months), with better outcomes in SPRINT, having less heavily pre-treated patients. Lenalidomide, generally with empiric addition of rituximab, is active in relapsed MCL.

The pilot front-line trial of R2 in MCL included 38 patients, median age 65 and ~1/3 each with MIPI low, intermediate and high. Toxicity was as expected, with 11% “flare” reaction. Results are impressive, with ORR 92% (64% CR) and 85% progression-free at 2 years. High MIPI patients in particular are doing better than expected. This regimen merits further investigation. The US intergroup front-line MCL trial E1411 does have an R2 maintenance arm after BR or BVR induction.

Therefore, these results are encouraging in that there may be long term benefit from this maneuver.

Ultimately, however, several studies in FL have shown PFS benefit but not OS benefit. Therefore, longer term follow-up is needed to determine whether the short term CR effects of adding bortezomib translate into longer term benefit — measured primarily by overall survival and quality of life. Additionally this study includes maintenance rituximab for all subjects, and lenalidomide added to maintenance in one arm — whether or not bortezomib is of benefit (with respect to efficacy and toxicity) versus the other options for use in daily practice will be determined by longer follow-up.

References:

Dr Kahl
This was a Phase II randomized multi-center trial published in The Lancet Oncology in 2016. Lenalidomide is an immunomodulatory drug that has been shown to have single agent activity in mantle cell lymphoma. The EMERGE trial was a single trial that revealed a response rate of around 30% for single agent lenalidomide. This SPRINT trial was designed to compare lenalidomide to standard therapy in relapsed/refractory mantle cell lymphoma. The treatment was lenalidomide 25 mg orally on days 1-21 of each 28-day cycle. Treatment was given until progressive disease, intolerability, or patient preference. It was compared against investigator’s choice of rituximab, gemcitabine, fludarabine, chlorambucil, or cytarabine. All of these drugs were given as single agents. 254 patients were enrolled in this trial.

The median age was 68.5 years and patients had a median of 2 prior regimens. With a median follow-up of 15.9 months, lenalidomide was found to significantly improve the progression-free survival compared to investigator’s choice, with a median of 8.7 months versus 5.2 months. The response rate for lenalidomide came in at 40% on this study compared to 11% with investigator’s choice. The majority of these responses were partial. There was no difference in the overall survival between the 2 arms. Toxicities were consistent with prior reports of lenalidomide. 44% of patients experienced at least Grade 3 neutropenia while on lenalidomide. Grade ≥3 non-hematologic toxicity was rare, however. Patients who received lenalidomide reported Grade 1 and 2 fatigue at a frequency of 20% and diarrhea at a frequency of 19%.

So this trial shows that lenalidomide has reasonably good single agent activity in relapsed/refractory mantle cell lymphoma with a response rate of around 40% and progression-free survival of almost 9 months. This validates the approval of lenalidomide for recurrent mantle cell lymphoma. I think of particular interest is the notion of combining lenalidomide with rituximab. Investigators from MD Anderson have studied this combination and have reported on this. The combination of the 2 agents seems to improve the response rate to over 60% and resulted in approximately doubling the response ratio. Given those data, I would be inclined to use rituximab in combination with lenalidomide when opting for this particular therapy in relapsed or refractory mantle cell lymphoma.

The New England Journal of Medicine paper looking at the combination of lenalidomide and rituximab as initial treatment of mantle cell lymphoma was done by a group of investigators at Cornell Medical Center in conjunction with Moffit Cancer Center, University of Pennsylvania and University of Chicago. This study focused on patients with previously untreated mantle cell lymphoma. 38 patients were enrolled at the 4 centers over a period of 3 years. The median age was 65. Patients received lenalidomide at a dose of 20 mg daily on days 1-21 of each 28-day cycle for a total of 12 cycles. Rituximab was administered once weekly for the first 4 weeks and then every other cycle until disease progression.

The primary endpoint of the study was the overall response rate. It appeared to be a fairly typical mantle cell population, with the median age of 65. Most patients had advanced-stage disease and 1/3 of the patients had high risk by MIPI scoring. The overall response rate in the intent to treat population (n = 38) was 87%, with 61% of patients judged to be in complete response. The 2-year progression-free survival is
85%, indicating some durability. Of note, the median follow-up on the trial is relatively short at less than 3 years. It will be particularly interesting to see if these promising early results hold up to longer follow-up.

Overall I think the regimen is definitely worthy of additional study, and I hope to see this regimen compared against other standard mantle cell therapies in the future, such as the bendamustine/rituximab regimen, which is a very active regimen in older mantle cell lymphoma patients.

**Dr Flinn**

Mantle cell lymphoma is a heterogeneous disease with varied biology and therapies. When initially described, mantle cell lymphoma was thought to have a universally dismal prognosis. It is now recognized that while for most this an aggressive disease, there are varied outcomes and a subset of patients have a better prognosis. Initial therapies range from aggressive chemotherapy and stem cell transplantation to observation. There are now multiple reports of a non-chemotherapy based approach to mantle cell lymphoma with lenalidomide. The first data were in refractory mantle cell lymphoma, in which 3 Phase II studies demonstrated the activity of lenalidomide, including in patients previously treated with bortezomib. Most recently, the SPRINT trial compared lenalidomide to investigator choice.

This study clearly demonstrated the superior PFS of lenalidomide compared to other monotherapy choices and highlighted the poor alternative therapy choices where the most popular choice was single agent rituximab. This study was conceived and executed before the availability of ibrutinib, which now also is indicated in mantle cell lymphoma. It is not clear in what sequence these agents should be used. The study of Ruan et al, in which lenalidomide/rituximab is used in the front line, is provocative. However, other front-line studies with lenalidomide have not been able to reproduce these results.

**Dr Leonard**

Lenalidomide either alone or in combination is clearly active in mantle cell lymphoma. The Trněný study demonstrates that lenalidomide has meaningful activity in relapsed patients in comparison to other agents that are currently options. The overall response rate was 40% with lenalidomide versus 11% with investigator choice, and the progression-free survival was also substantially improved. These data show that lenalidomide is a useful agent in relapsed MCL and support its use in clinical practice. Ruan and colleagues report that lenalidomide plus rituximab can be an effective regimen (without chemotherapy) as initial treatment in MCL across a broad spectrum of patients.

The regimen was generally well tolerated, and quality of life improved over the course of the study. Given the wide array of agents/regimens used in up-front MCL, with the choice often based on patient/physician preference, it seems reasonable to consider lenalidomide plus rituximab use for some patients with MCL needing therapy who prefer a lower-intensity approach. How this regimen compares to commonly used strategies (chemotherapy based) in MCL will await further studies and longer follow-up.
Ibrutinib and the mTOR inhibitor temsirolimus are the 2 agents approved in Europe for treatment of relapsed mantle cell lymphoma (MCL). This is the first Phase III randomized trial comparing approved single agents in relapsed/refractory MCL. Strengths of the study include Phase III design, international cooperation and rapid accrual (280 patients in <1 year). The median age of 68 years and median 2 prior regimens suggest “real-world” patients, although all had PS 0 or 1. Not surprisingly, outcomes favored ibrutinib vs temsirolimus: ORR 72% vs 40%, primary endpoint PFS median 14.6 vs 6.2 months, DoR at 18 months 58% vs 20%. Improved outcomes with ibrutinib also improved patient-reported quality of life.

ORR, PFS and DoR ibrutinib outcomes match previous Phase Ib/II data; no new safety signals were observed. Temsirolimus’ 40% ORR is significant, implicating PI3K/AKT/mTOR as useful targets.

Supplementary data on PFS2, time from start of therapy on this trial to progression after the next therapy, suggest ibrutinib “failure” does not necessarily confer dismal prognosis. Still, MCL in 1/3 of patients does not respond to ibrutinib, ibrutinib is not curative and blastoid MCL remains an unmet need. Trials exploring earlier use of ibrutinib and combinations are in progress.

Ibrutinib is approved for patients with relapsed/refractory mantle cell lymphoma on the basis of a single arm Phase Ib/II study. Ibrutinib is known to have a response rate of 60%-70% in mantle cell lymphoma with reasonably good durability, typically 12-18 months. The trial under discussion was the confirmatory Phase III study in which ibrutinib was compared to temsirolimus, an mTOR inhibitor that is approved for use in relapsed/refractory mantle cell lymphoma in Europe. In this particular trial, patients were randomly assigned to daily ibrutinib therapy at 560 mg per day versus intravenous temsirolimus given at a dose of 175 mg days 1, 8 and 15 of cycle 1 and then 75 mg on days 1, 8 and 15 of subsequent 21-day cycles. 280 patients were enrolled in this trial.

The patients were well balanced for important baseline characteristics. The median progression-free survival in the ibrutinib treated patients was 14.6 months versus 6.2 months in the temsirolimus treated patients. Ibrutinib was also better tolerated, with fewer Grade 3 or higher adverse events. In summary, this trial confirms that ibrutinib is a highly active single agent for relapsed/refractory mantle cell lymphoma with response durations of over 12 months. Ibrutinib remains the single agent of choice for relapsed/refractory mantle cell lymphoma. It will be particularly interesting to see how ibrutinib does in combination.
**Dr Flinn**

In this study, Dreyling and colleagues evaluate ibrutinib compared to temsirolimus in patients with relapsed mantle cell lymphoma. Two-hundred and eighty patients were randomized to 1 of the 2 arms. Ibrutinib was clearly superior. This study confirmed the efficacy of ibrutinib in patients with mantle cell lymphoma who had a median of 2 prior therapies. However, temsirolimus is not approved in the US and as a consequence is not a relevant control. This leaves unsettled the issue of sequencing. While no difference in overall survival was demonstrated in this study, the magnitude of PFS benefit with ibrutinib seen in this study and in the Phase II trial would lead many clinicians to use ibrutinib in first relapse instead of other available therapies. Studies looking at ibrutinib in front-line mantle cell regimens are under way, where it is most likely to make a difference in survival.

**Dr Leonard**

Temsirolimus has activity and regulatory approval in Europe for recurrent mantle cell lymphoma. This study compared ibrutinib to temsirolimus in this patient population. This was one of the larger (and few) randomized trials in recurrent MCL (280 subjects) and demonstrated clear advantages with ibrutinib in this setting. Ibrutinib was better tolerated, and progression-free survival was markedly better in the ibrutinib arm by comparison to temsirolimus. Since temsirolimus is generally not used in the US for MCL, this study does not “change” my practice. However, these data provide additional information on ibrutinib in the relapsed MCL patient population and give added justification for its routine use in this group. A substantial number of patients had durable remissions (>12-18 months) after ibrutinib treatment. Additionally ibrutinib therapy was associated with a more favorable quality of life assessment.

Further studies, particularly of combination approaches, will better define the optimal setting for the use of ibrutinib in the MCL patient population.

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**Ibrutinib in combination with rituximab in relapsed or refractory mantle cell lymphoma: A single-centre, open-label, phase 2 trial**


**Dr Smith**

Ibrutinib is the most active approved agent in relapsed MCL, but a significant percentage of relapsed MCL does not respond, relapse is inevitable and ibrutinib is not very active against blastoid MCL. Combinations are under investigation. While rituximab almost always enhances B-cell lymphoma therapeutics, there were theoretical and pre-clinical data of concern for potential antagonistic effects with rituximab + ibrutinib. Fortunately, such antagonism has not been seen clinically. This report includes 50 patients with relapsed/refractory MCL treated on a single-center Phase II trial with ibrutinib + rituximab. No new toxicities were reported, though Grade 3 atrial fibrillation (12%) was higher than in prior reports of ibrutinib alone.
Lymphocytosis, common with ibrutinib, was abrogated by adding rituximab. ORR was 88%, CR 44%. The caveats of cross-trial comparisons suggesting that this regimen is better than ibrutinib, ORR 68%, CR 21%, are illustrated in this trial having only ECOG PS 0/1 patients and only 12% high MIPI vs 49% in the original trial. Nonetheless, rituximab does not appear to have been detrimental and no unexpected toxicity was seen. At median follow-up of 16 months, only 21 (42%) remain on treatment, and patients with Ki-67 ≥50% did not do well, so there remains room for improvement.

Dr Kahl
This was a single center study done at MD Anderson. This was published in *The Lancet Oncology* in 2016. Because ibrutinib often results in a peripheral blood lymphocytosis, it was hypothesized that the addition of rituximab would be a useful agent to help clear circulating lymphocytes and possibly improve the overall response rate with ibrutinib in mantle cell lymphoma. This group of investigators enrolled 50 patients with recurrent mantle cell lymphoma over the span of a year. Median age was 67 and the median number of prior regimens was 3. The follow-up was relatively short in this trial with only 16.5 months. Of note, however, is that 88% of the patients experienced an objective response to the combination regimen, which appears to be better than the historical comparison of about 65% for single agent ibrutinib.

Median follow-up is relatively short to comment whether the durability is increased, but at 12 months over 70% of patients remained in remission. There were adverse events that led to discontinuation of therapy in 5 patients, which included atrial fibrillation in 3, liver infection in 1 and bleeding in another. So the take-home message from this single institution Phase II trial is that the combination of ibrutinib and rituximab may be more efficacious than ibrutinib alone. Certainly other agents have benefited by combination with rituximab. Based upon these data, I think it would be very reasonable to give rituximab in combination with ibrutinib therapy in relapsed or refractory mantle cell lymphoma.

Dr Flinn
Wang et al evaluate the efficacy of the combination of ibrutinib and rituximab in relapsed/refractory mantle cell lymphoma. At first glance, the results are quite impressive. In 50 patients this combination produced an ORR of 88% and a CR rate of 44% compared to an ORR of 68% and CR rate of 21% in a previous multi-center Phase II trial of single agent ibrutinib. However, the trials are quite different — single center versus multicenter. There are also significant differences in the patients, best demonstrated by differences in the MIPI score. Finally, the follow-up is quite short so it is hard to compare PFS between the 2 studies, which is a more relevant endpoint. In CLL it is not clear what the addition of rituximab adds to ibrutinib.

I believe the same is true in this setting. It is unlikely we will ever see a randomized trial of ibrutinib with or without rituximab. There are more important issues to study. The addition of rituximab adds little in the way of toxicity and thus this combination will likely become popular. However, it is not yet clear how much it adds. Perhaps with further follow-up the differences will become more evident.
Dr Smith

This KEYNOTE-013 study has demonstrated anti-PD-1 monoclonal antibody pembrolizumab activity in relapsed Hodgkin lymphoma (HL) with objective response rate (ORR) ~65%. PMBCL is more like HL than non-Hodgkin lymphoma by gene expression profiling, and similarly frequently contains abnormal 9p24.1, site of PD-L1 and PD-L2 genes. The KEYNOTE-013 results for the relapsed/refractory PMBCL cohort (N = 16), ineligible for or relapsed after SCT, are reported here. Pembrolizumab dosing changed from 10 mg/kg every 2 weeks (N = 11) to 200 mg every 3 weeks (N = 5) during the study. Median age was 30 (22-62); 44% ≥4 prior therapies; 31% prior autoSCT. Median follow-up is 5 months.

No unexpected toxicity was noted, with 1 treatment-related Grade 3 neutropenia and no treatment-related Grade 4-5 events. ORR is 6/16 (38%), including 1 complete response, 5 ongoing (<1+ to 17+ months). Longer follow-up is needed, as is biomarker development, but PD-1 inhibition is promising in PMBCL and may be used in earlier lines of therapy.

Dr Kahl

This is a Phase Ib study of pembrolizumab in patients with relapsed/refractory primary mediastinal large B-cell lymphoma. This study was presented at the EHA meetings in the summer of 2016. The rationale here is that primary mediastinal large B-cell lymphoma can exhibit 9p24 alterations similar to Hodgkin lymphoma, resulting in the overexpression of PD-1 ligands. Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands and has shown tumor activity in solid tumors and
in classical Hodgkin lymphoma. This abstract focuses on a small cohort of patients with primary mediastinal large B-cell lymphoma. Patients needed to have relapsed/refractory disease and be considered ineligible for autologous stem cell transplantation.

They received pembrolizumab at a dose of 10 mg per kg every 2 weeks or 200 mg every 3 weeks. The primary endpoint was the overall response rate. At the time of this presentation 16 patients had been enrolled with primary mediastinal large B-cell lymphoma. The first 11 patients received pembrolizumab at 10 mg per kg every 2 weeks while the next 5 patients received the fixed dose of 200 mg every 3 weeks. The patients were fairly heavily pre-treated, with ≥4 prior lines of therapy. 4 patients experienced serious adverse events, including Grade 3 pneumonia in 3 patients. No patients discontinued treatment for toxicity. Among the 16 treated patients, the overall response rate was 37.5% with 6 of 16 patients achieving an objective response.

The median duration of response has not been reached, with the longest responder out to 17 months. This is the first data set suggesting that immune checkpoint inhibition is a promising strategy in primary mediastinal B-cell lymphoma. Because of genetic alterations that are frequently seen in this lymphoma subtype, there is a good biologic basis for testing checkpoint inhibition in this patient population, and this promising response rate in this highly refractory patient group provides evidence that further study is needed to define the response duration and response quality. I think it is likely that combination studies will be evaluated testing checkpoint inhibition with other immunomodulatory therapies and possibly with combination chemotherapy.

Dr Flinn
In this study, Zinzani et al evaluate PD-1 blockade with pembrolizumab in primary mediastinal large B-cell lymphoma (PMBCL). PMBCL frequently exhibits 9p24.1 alterations, leading to overexpression of the PD-1 ligands, PD-L1 and PD-L2. This provides a possible mechanism of immune escape and target for therapy.

In 16 heavily pre-treated patients, the objective response rate (ORR) was 37.5% (6/16), including 1 patient with CR and 5 with PR. A nearly 40% response rate is impressive in this disease, with what appears to be modest toxicity. However, these results are not as impressive as results with Hodgkin lymphoma, another disease with 9p24.1 alterations.

The key will be understanding the durability of this approach. CAR T cells are also very active in this population, in whom high CR rates have been seen. Combining PD-1 blockade with CAR T cells would be attractive if toxicity could be managed.

Dr Leonard
There is strong rationale for the evaluation of pembrolizumab in primary mediastinal large B-cell lymphoma (PMBCL) given the presence of 9p24 alterations in this lymphoma subtype. This trial demonstrated that this agent is well tolerated in this patient population. It is a small study, but 6 out of 16 subjects responded. This is encouraging given that relapsed patients with this histology tend to otherwise have relatively poor outcomes and refractory disease. This suggests to me that further evaluation of this agent, potentially in combination with chemotherapy or other targeted approaches, makes sense in PMBCL.
PD-1 ligands (PD-L1 and PD-L2) expressed by tumors, or their microenvironment, bind to PD-1 on T cells to suppress T-cell killing. Checkpoint inhibitors interrupt this binding and re-activate T-cell cytotoxicity. The anti-PD-1 monoclonal antibody nivolumab was granted FDA accelerated approval for post-SCT relapsed Hodgkin lymphoma (HL) based in part on data from this Phase Ib trial. This report focuses on the 81 patients with B-cell (N = 31) and T-cell (N = 23) non-Hodgkin lymphoma and myeloma (MM, N = 27). The recommended dose is 3 mg/kg IV every 2 weeks. Grade ≥3 toxicity occurred in 18% and was similar to prior reports, with 3 Grade ≥3 pneumonitis (including the only Grade 5 toxicity).

Response rates were lower than in HL — 4/10 FL, 4/11 DLBCL, 0/10 other B-cell histologies, 4/23 T cell, 1/27 MM — but most responses were durable. In a limited number of tissue samples available, immunohistochemistry for PD-L1 and PD-L2 and FISH for 9p24, commonly altered in HL, were not useful biomarkers for response. Phase II trials in specific subtypes are under way to further define single agent activity and provide framework for combinations. Identification of a biomarker for response would be very useful.

Dr Kahl
Nivolumab in patients with relapsed/refractory hematologic malignancy: preliminary results of the Phase 1b study. The background here is that cancer cells can exploit the programmed death-1 immune checkpoint pathway, allowing them to avoid immune surveillance. These so-called checkpoint inhibitors have shown promising activity in Hodgkin lymphoma. Of course, a high proportion of Hodgkin lymphoma cases have genetic alterations within the 9p24.1 locus, leading to high PD-L1 expression and making HL a logical target for immune checkpoint inhibition. Whether non-Hodgkin lymphoma, which less frequently has this genetic alteration, would still respond favorably to checkpoint inhibition was the subject of this study. This was a Phase Ib study with cohort expansions.

Patients received the anti-PD-1 monoclonal antibody nivolumab at doses of 1 mg per kg or 3 mg per kg every 2 weeks. Patients would receive therapy until disease progression or until unacceptable toxicity. 81 patients were enrolled. 10 patients had follicular lymphoma, 11 patients had diffuse large B-cell lymphoma, 10 patients had other
Hodgkin and Non-Hodgkin Lymphoma

B-cell lymphomas, 13 patients had mycosis fungoides, 5 patients had peripheral T-cell lymphoma, and 5 patients had other T-cell lymphomas. The patients were heavily pre-treated with a median of 3 prior therapies and a range from 1 to 12. Overall the treatment was reasonably tolerated, with Grade 3 toxicity being infrequent. Of note, there were 9 cases of pneumonitis of which 3 were at least Grade 3.

With regard to efficacy, 36% of patients with diffuse large B-cell lymphoma responded, and 40% of patients with follicular lymphoma responded. None of the other patients with B-cell lymphomas responded to nivolumab. 40% of patients with peripheral T-cell lymphomas responded, while 15% of patients with mycosis fungoides responded. Complete responses were rare. Response duration could not be accessed in this cohort due to the relatively short follow-up. Individual responses have persisted for as long as 80 weeks in individual patients. Attempts were made to correlate response with genetic alterations in the 9p24.1 locus. Only 3 patients in the cohort had such abnormality and no correlations could be made.

In addition, PD-L1 overexpression was largely not seen by immunohistochemistry and does not appear to predict response to checkpoint inhibition in these different lymphoma subtypes. This study provides proof of concept that checkpoint blockade can result in objective responses in follicular lymphoma, diffuse large B-cell lymphoma, and some T-cell lymphomas. Unfortunately a reliable biomarker was not identified, but the study provides early evidence to support ongoing investigation of checkpoint blockade in different lymphoma subtypes. I think it is likely that we will see combination therapy approaches with other immunological agents such as anti-CD20 therapy or possibly other immunomodulators such as agents like lenalidomide or CAR T-cell therapy in the future.

Dr Flinn

In this study, Lesokhin and colleagues evaluated the activity of the anti-PD-1 antibody nivolumab in patients with refractory lymphoma and other hematologic malignancies. These investigators saw significant activity that was sometimes durable in patients with FL and DLBCL. However, the response rates were considerably lower than those seen in Hodgkin lymphoma. In addition, alterations of 9p24 were rare. Immune related events were seen in 34% of patients. Fifteen percent of patients discontinued therapy due to drug related AEs. These results are somewhat better than what was seen with ipilimumab where the ORR was 11% in a small of number patients.

However, it seems unlikely these agents will be used as single agents. Their ultimate use will likely be in combination. It is also interesting to contrast these results with another T-cell directed treatment, CAR T-cell therapy, with which very high response rates are seen in DLBCL.

Dr Leonard

This study presents initial data from nivolumab in patients with a variety of non-Hodgkin lymphomas (and myeloma). Certainly this agent has meaningful activity in a variety of tumor types (outside of lymphoma), and in particular its efficacy in Hodgkin lymphoma is quite important. It is important to note that while the total number of
subjects in this study is reasonable, within each lymphoma subtype the numbers are much smaller (in the area of 10 subjects or less). Definitive conclusions about response rates will require much larger numbers of patients. The fact that there were responses in 4 patients each (out of about 10) with DLBCL and FL is encouraging, and responses in T-cell lymphoma are also notable.

Durability seems reasonable (over 6 months in some cases) and tolerability seems consistent with prior experience in other tumor types. To me this suggests that this agent warrants further evaluation in FL, DLBCL and T-cell lymphoma in particular. I will await such data before using nivolumab commonly for these patients in my practice, with the possible exception of occasional patients in quite challenging situations who lack other potential options.

**Hodgkin Lymphoma**

**PD-L1 and PD-L2 genetic alterations define classical Hodgkin lymphoma and predict outcome**


**Dr Moskowitz**

Classical Hodgkin lymphoma is defined by few Reed Sternberg cells admixed with a significant mixed inflammatory background. Recent evidence has determined that the most common genetic abnormalities in HL are on chromosome 9p24.1 where the PD-1 ligands, PD-L1 and PD-L2, and Janus kinase 2 signal transducers are. The prognostic significance of PD-L1/PD-L2 alterations in HL was unknown and was the purpose of this study.

A fluorescence in situ hybridization assay (FISH) evaluated CD274/PD-L1 and PDCD1LG2/PD-L2 alterations in 108 biopsy specimens from patients with newly diagnosed HL who were treated with the Stanford V regimen (not the optimal regimen), and these alterations were correlated with outcome.

60% had early stage disease where the cure rate is extremely high, and abnormalities in this pathway had no impact on outcome.

The incidence of 9p24.1 amplification increased by clinical risk group (ES-Favorable, 24%; ES-Unfavorable, 34%; AS, 50%; \( p = .024 \)).

The authors are suggesting that since patients with AS disease had a worse outcome with higher levels of 9p24.1 amplification, this is a platform for combination studies of chemotherapy and checkpoint inhibitors.

This may or may not be true; it is unclear if the same results would occur if ABVD, BEACOPP or BV-AVD were the regimen studied.
**Dr Flowers**

PD-1 blockade has activity in multiple malignancies and is demonstrated to be exceptionally active in Hodgkin lymphoma as described in the studies below. PD-1 ligands engage the PD-1 receptor on T cells, induce PD-1 signaling and produce T-cell exhaustion by reversibly inhibiting T-cell activation and proliferation. Cancer cells that express PD-1 ligands on their surface appear to use the PD-1 pathway to evade antitumor immune responses. This study examines the genetic basis of PD-1 ligand dysregulation and association with classical Hodgkin lymphoma.

The authors used a fluorescence in situ hybridization (FISH) assay to evaluate PD-L1 and PD-L2 alterations in patients with newly diagnosed classical Hodgkin lymphoma who had long-term follow-up after initial therapy. This study indicates that PD-L1/ PD-L2 copy number alterations are a defining feature of classical Hodgkin lymphoma, with 97% of all evaluated samples having concordant alterations; 56% had 9p24.1 copy gain and 36% had 9p24.1 amplification. There was strong association between PD-L1 and PD-L2 protein expression and 9p24.1 genetic alterations. These alterations may explain the activity of PD-1 blockade in HL.

**Dr Nastoupil**

Management of relapsed/refractory classical Hodgkin lymphoma (cHL) has been therapeutically challenging, with new optimism surrounding the clinical activity of immune checkpoint inhibitors in relapsed/refractory cHL.

This was a multi-center collaborative effort using paraffin-embedded samples from 108 patients uniformly treated and with long term robust clinical data, in which a FISH assay was used to determine the incidence and prognostic significance of 9p24.1, PD-L1 and PD-L2 alterations and EBV-encoded small RNA (EBER) status in patients diagnosed with cHL at Stanford University. Central review of the samples confirmed the diagnosis. Patients were treated on 3 concurrent clinical protocols of the Stanford V chemotherapy regimen plus modified involved field RT.

The median age of patients was 30 years, 68% were limited stage (I/II), and 86% had nodular sclerosis HL. Almost all cases had concordant alterations in PD-L1 and PD-L2 loci. The highest level of 9p24.1 alterations (amplification) was more common in advanced stage disease. This suggests that PD-1-mediated immune evasion may foster tumor spread.

This study uses a FISH assay to identify alterations in PD-L1/PD-L2, which is a more practical approach to profiling these tumors than what has been done previously. The common alterations in the PD-L1/PD-L2 loci may explain the activity of PD-1 blockade in cHL.

The application of this methodology suggests this may be clinically available and utilized to guide therapy or incorporated into trial design to predict response, particularly when exploring PD-1 blockade in this disease.
This is the Phase Ib study of pembrolizumab in classical HL. All patients previously had progression of disease on brentuximab vedotin (BV), making this a different patient population compared to the nivolumab Phase Ib study, a more favorable cohort. The dose of pembrolizumab was 10 mg/kg every 2 weeks until disease progression occurred. (This dose is excessive; now patients receive a fixed dose of 200 mg every 3 weeks on all pembrolizumab clinical trials, and higher dosing or shorter intervals do not correlate with efficacy for either CPI.) Response to treatment was assessed at week 12 and every 8 weeks thereafter.

Thirty-one patients were enrolled; all heavily pretreated and BV failures. The CR rate was 16%, and 48% of patients achieved a partial remission for an overall response rate of 65%. The progression-free survival rate was 69% at 24 weeks and 46% at 52 weeks. Biomarker analyses demonstrated a high prevalence of PD-L1 and PD-L2 expression, treatment-induced expansion of T cells and natural killer cells, and activation of interferon-g, T-cell receptor, and expanded immune-related signaling pathways.

Most common side effect requiring intervention was thyroid dysfunction. CPI use should also be cautioned for patients with a previous history of pneumonitis.

This publication examined patients with classical Hodgkin lymphoma who experienced relapse following brentuximab vedotin in the Phase Ib study KEYNOTE-013 that evaluated the safety and efficacy of the anti-PD-1 antibody pembrolizumab in patients with hematologic malignancies. 31 patients with classical Hodgkin lymphoma were heavily pretreated, with the majority receiving more than 4 lines of prior therapy and more than two thirds having received relapse after autologous stem cell transplant. Patients received pembrolizumab 10 mg/kg given every 2 weeks, and response assessments were performed by PET/CT at 12 weeks and every 8 weeks thereafter.

Patients with radiographic progressive disease at week 12 who were clinically stable could remain on therapy if they were experiencing clear clinical benefit despite PD. The most common treatment-related AEs were hypothyroidism (16%), diarrhea (16%), nausea (13%), and pneumonitis (10%). With a median follow-up for surviving patients of 17.6 months (range, 10.6 to 22.5 months), 15 patients discontinued pembrolizumab because of PD, 2 because of an AE (pneumonitis and nephrotic syndrome), and 6 for other reasons. Twenty patients responded and 70% had a duration of response ≥24 weeks. Nearly all samples available at baseline for patients in the study demonstrated evidence of PD-L1 on the tumor cells.
This study provides preliminary evidence of the tolerability and efficacy of pembrolizumab in a heavily pretreated population of patients with classical Hodgkin lymphoma. It is consistent with the biological data described above and with studies of other PD-1 inhibitors in the treatment of Hodgkin lymphoma, such as nivolumab.

Dr Nastoupil

Genetic analyses have shown that Reed-Sternberg cells in cHL frequently exhibit amplification of 9p24.1, leading to increased activity of the JAK/STAT pathway, and overexpression of PD-L1 and PD-L2. In addition, EBV can lead to PD-L1 expression. Taken together, HL tumor cells may rely heavily on PD-1 and evading immune surveillance for survival. With available monoclonal antibodies that target PD-1, PD-1 blockade may be a favorable approach for patients with relapsed/refractory cHL.

This is a report on the patients with relapsed/refractory HL from the Phase Ib study of pembrolizumab in hematologic malignancies (KEYNOTE-013). The study included adult patients with relapsed/refractory HL without a curative option, including those who were not transplant candidates or had relapsed after ASCT. In addition, patients were required to have received brentuximab vedotin.

31 patients were enrolled between 12/13 and 9/14. Median age was 32 years. 71% had previously undergone ASCT. The most common treatment-related AEs included hypothyroidism (16%), diarrhea (16%), nausea (13%), and pneumonitis (10%). There were no Grade 4 treatment-related AEs and no deaths due to study treatment. The ORR was 65%, 16% achieved a CR and 48% a PR. The median follow-up was 17.6 months. PFS at 24 weeks was 69% and OS was 100%.

Correlative studies were done, including 19 patients with available paired samples. Despite findings that pembrolizumab increased circulating immune cell subsets (expansion of T cells and NK cells) and upregulated IFN-γ pathways, gene signatures did not appear to predict response in this small cohort.

This study demonstrated that pembrolizumab, an anti-PD-1 monoclonal antibody, was effective in relapsed/refractory cHL and was associated with an acceptable safety profile. Further clinical development is warranted.

Dr Moskowitz

Phase II “registration study”

3 cohorts:

• 1. R/R cHL after ASCT and subsequent BV therapy (cohort 1)
• 2. Ineligible for ASCT due to chemo-resistance (no response to salvage chemotherapy and BV therapy failure)
• 3. R/R cHL after ASCT, not treated with BV after ASCT but may have received BV as part of initial or salvage therapy

Pembrolizumab administered at a fixed dose of 200 mg intravenously every 3 weeks. Primary endpoint was ORR.

Results: Very short follow-up, 60 patients were evaluable for cohorts 1 and 2.

ORR among 30 patients in cohort 1 was 70%, 6 CRs.

ORR among 30 patients in cohort 2 was 80%; 8 patients (27%) achieved CR.

This was an unexpectedly high CR rate.

There were 7 Grade 3 TRAEs in 3 patients: neutropenia, colitis, diarrhea, cytokine release syndrome, herpes zoster infection, increased amylase, and lichen planus, and only 1 Grade 4 TRAE, increased lipase. There were no treatment related deaths.

I will present the final results of a study with >200 patients at ASH in December.

Dr Flowers
This Phase II study of pembrolizumab (KEYNOTE-087) enrolled 2 evaluable cohorts of patients with classical Hodgkin lymphoma: relapsed and refractory patients after autologous stem cell transplantation and brentuximab vedotin therapy (cohort 1) and patients ineligible for autologous stem cell transplantation due to lack of response to salvage chemotherapy who had also failed brentuximab vedotin (cohort 2). All patients received pembrolizumab 200 mg IV every 3 weeks. The most common treatment-related adverse events were fever, diarrhea, fatigue, thrombocytopenia, dry skin, and cough.

The overall response rate for the 30 patients in cohort 1 was 70% with 6 patients achieving complete response, and the overall response rate for the 30 patients in cohort 2 was 80% with 8 patients achieving complete response. These preliminary data support the findings described above for the activity of pembrolizumab in patients with relapsed and refractory classical Hodgkin lymphoma in the overall concept of the value of PD-1 blockade in this disease.

Dr Nastoupil
These are the preliminary findings of the Phase II study of pembrolizumab (anti-PD-1 monoclonal antibody) in relapsed/refractory chHL (KEYNOTE-087). The aims of this study were to determine the ORR and safety of 200 mg of pembrolizumab every 3 weeks in R/R chHL in 3 cohorts: (1) chemo-resistant, transplant ineligible and after brentuximab vedotin (BV), (2) after ASCT and subsequent BV, and (3) after ASCT but no prior BV.

60 subjects were included. 35% had primary refractory disease, 67% received ≥4 prior lines of therapy, and 100% had failed prior BV. ORR among 30 patients in cohort 1 was 70%. 6 patients (20%) achieved CR, 15 (50%) PR, and 6 (20%) stable disease as best response.
ORR among 30 patients in cohort 2 was 80%. 8 patients (27%) achieved CR, 16 (53%) PR, and 4 (13%) stable disease as best response. The most common treatment-related AEs were pyrexia (13%), diarrhea (8%), fatigue (7%), thrombocytopenia (7%), dry skin (7%), and cough (7%). No treatment related deaths had occurred.

The Phase II study of pembrolizumab in R/R cHL demonstrated similarly favorable efficacy and safety as the Phase I study. Additional follow-up, including more data from cohort 3, is in progress.

Nivolumab for classical Hodgkin’s lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: A multicentre, multicohort, single-arm phase 2 trial


Dr Moskowitz
Phase II “registration trial”

Patients were given nivolumab 3 mg/kg every 2 weeks until progression, death, unacceptable toxicity, or withdrawal from study.

The primary endpoint was objective response by an independent radiological review.

The number of patients who achieved an objective response was 53 (66.3%, 95% CI 54.8-76.4); the best overall responses were complete remission in 7 (9%) patients and partial remission in 46 (58%) patients.

Concordance between IRRC and investigator assessments was only 76.3% for objective response and 53.8% for best overall response.

Discordance in complete remission between IRRC and investigator assessments was largely based on the interpretation of 18F-FDG PET scans. In my opinion I see very little difference between CR and PR in patients treated with CPI for HL; response duration/ PFS is very similar.

Six patients stopped nivolumab treatment and proceeded to stem cell transplantation (5 allogeneic stem-cell transplantation and 1 ASCT). Well-tolerated treatment, typical side effects.

Update will be presented at ASH.

Dr Flowers
This Phase II study examined heavily pretreated patients who relapsed following autologous stem cell transplantation and had either relapsed following or failed to respond to brentuximab vedotin given after autologous stem cell transplantation. The median number of prior therapies was 4; 49% had 5 or more lines of therapy, and 93% had at least 1 prior autologous stem cell transplant. All 80 patients received nivolumab at 3
mg/kg IV every 2 weeks until progression, death, unacceptable toxicity, or withdrawal from study. The most common treatment-related adverse events were fatigue (25%), infusion-related reactions (20%), rash (16%), arthralgia (14%), fever (14%), nausea (13%), diarrhea (10%), increased lipase (9%), and neutropenia (9%).

Grade 3/4 adverse events were uncommon. Among 80 patients evaluated by independent review, 9% experienced complete remission, 58% experienced partial remission, 23% experienced stable disease, and 8% experienced progressive disease. The median time to first objective response was 2 months. The median duration of follow-up was only 9 months, but the median duration of objective response was evaluable at 8 months for this population. Interestingly, in a post hoc analysis none of the patients with progressive disease had 9p24.1 amplification, and none of the patients with complete remission had polysomy.

Overall this study demonstrated reduction in tumor burden in most patients in this heavily pretreated population of Hodgkin lymphoma. These data further demonstrate the value of PD-1 inhibition in patients with Hodgkin lymphoma and motivate future studies evaluating the use of these agents in earlier lines of therapy and in combination with chemotherapy.

**Dr Nastoupil**

This is a multi-center, single arm, Phase II study to examine the efficacy defined as ORR of nivolumab (anti-PD-1 monoclonal antibody) in relapsed HL. Eligibility included adult patients with relapsed/refractory cHL who had failed ASCT and subsequent BV. Patients received nivolumab at 3 mg/kg every 2 weeks until disease progression, unacceptable toxicity, or study end.

80 subjects were enrolled. Median age was 37. Median number of prior lines of therapy was 4. Median time from most recent BV was 0.7 years and median time from ASCT was 3.4 years.

The most common drug-related adverse events were fatigue (25%), infusion-related reaction (20%), rash (16%), arthralgia (14%), pyrexia (14%), nausea (13%), diarrhea (10%), and pruritus (10%). The majority of these were Grade 1-2 with the exception of 1 case of Grade 3 rash.

In this registrational study, nivolumab resulted in durable responses and an acceptable safety profile in heavily pre-treated patients with HL and without a good standard of care option. This study continues to enroll, and additional cohorts including BV naïve patients and patients who received BV prior to ASCT continue to explore the efficacy of nivolumab in cHL.
Brentuximab vedotin and AVD followed by involved-site radiotherapy in early stage, unfavorable risk Hodgkin lymphoma

Kumar A et al.  
**Blood** 2016;128(11):1458-64.

**Dr Moskowitz**

A multicenter Phase II study of BV-AVD followed by 30 Gray (Gy) involved site radiation therapy (ISRT). HL patients with unfavorable risk features including bulky disease were treated with 4 cycles of BV and AVD. Patients who achieved a negative PET scan (Deauville score of 1-3) received 30 Gy ISRT.

No clinically significant non-infectious pneumonitis was observed. Serious adverse events, neuropathy was manageable.

After 2 and 4 cycles of BV + AVD, 90% (26 of 29) and 93% (27 of 29) of patients achieved a negative PET scan, respectively. Two patients with biopsy-proven primary refractory HL were treated off-study.

With a median follow-up of 18.8 months, by intent to treat, the 1-year progression free survival is 93.3% (95% CI 84-102). This is the first report of BV-AVD in early stage HL and suggests that the treatment can be given safely with consolidation radiotherapy.

This is a 4-cohort study; only cohort one has been reported.

Cohort 2: Complete BV-AVD and 20 Gy RT

Cohort 3: BV-AVD and residual site radiotherapy (defined as the post-chemotherapy PET-negative residual CT volume) at 30 Gy

Cohort 4: BV-AVD alone

**Dr Flowers**

Brentuximab vedotin has been demonstrated to be a useful agent for patients with relapsed and refractory Hodgkin lymphoma following failure of autologous stem cell transplantation and as consolidation following autologous stem cell transplantation for high-risk patients. The activity of this antibody-drug conjugate in patients with Hodgkin lymphoma which uniformly expresses the CD30 antigen has motivated the incorporation of brentuximab into earlier lines of therapy and into combinations with chemotherapy. This study evaluated the use of BV in combination with the AVD chemotherapy regimen and radiation in patients with unfavorable-risk early-stage Hodgkin lymphoma.

Among 30 patients enrolled, 47% had bulky disease defined by CT measurement of >10 cm, 67% had an elevated ESR, 47% had B symptoms, and 47% had extranodal involvement. 25 patients completed 4 cycles of BV plus AVD followed by 30 Gray of radiation. Peripheral neuropathy was observed in 40% of patients (12 of 30 patients), with Grade 1 neuropathy occurring in 10 of 12 and Grade 3 neuropathy occurring in 2
of 12 patients. Serious adverse events occurred in 6 patients, including 3 patients with febrile neutropenia (Grade 3) and 2 patients admitted with fever without neutropenia. Ninety percent of patients (26 of 29) achieved a negative PET scan after 2 cycles; 93% (27 of 29) achieved a negative PET scan after 4 cycles, and all 25 patients completing therapy achieved PET-negative complete response.

With a median follow-up of 19 months no patients had relapsed. This study demonstrated the ability to safely combine brentuximab vedotin with chemotherapy and radiation in high-risk patients with early-stage Hodgkin lymphoma. This may provide a backbone for future studies examining this combination in randomized trials.

**A phase 2 trial of ABVD followed by consolidation in limited stage non-bulky Hodgkin lymphoma**


**Dr Moskowitz**

Primary endpoint is no RT consolidation necessary; however, an expensive substitute is being added, BV.

We already know based upon multiple studies that a PET 2 negative rate of 80%-82% happens after 2 cycles of ABVD for ESHL-unfavorable and ASHL. In this study 35/40 patients were PET 4 negative and would do extremely well with no additional therapy.

The addition of BV consolidation converted 3 additional patients to PET negativity.

The follow-up is very short and durability is unknown. It is unclear to me if this is a viable treatment approach in ESHL, especially since there is no mention of the size of the single largest nodal mass; the most important risk factor for PFS. In addition, the cost of 6 doses of BV for patients already in remission is suspect.

**Dr Flowers**

This multicenter study evaluated the use of brentuximab vedotin given at 1.8 mg/kg every 3 weeks for 6 cycles and administered 6 weeks after induction therapy with ABVD for patients with previously untreated limited-stage non-bulky Hodgkin lymphoma as a means to avoid radiation in this patient population. The primary objective of the study was to estimate the proportion of patients who achieved PET-negative disease (Deauville score ≤2) after ABVD followed by BV consolidation. The number of cycles of ABVD given was determined by the patient’s baseline risk factors and the interim PET scan result; 28% of patients received 2 cycles of ABVD and 65% of patients received 4 cycles of ABVD.

Among 40 evaluable patients, 73% of patients achieved PET-negative status after 2 cycles of ABVD, 88% of patients achieved PET-negative status following completion of ABVD, and 94% of patients were PET-negative after the completion of BV. Given that the majority of the patients were PET negative after 2 cycles of ABVD, it is unclear
how much additional value brentuximab provided in this setting. Neutropenia (Grade 3) occurred in 3 patients in this trial and there was one sepsis-associated death, which may raise some concerns about the safety of this regimen in this population. Further study is needed to understand the potential value of brentuximab consolidation for patients with limited-stage disease and to clarify the role that it may play in previously untreated patients with Hodgkin lymphoma.

**Dr Nastoupil**

This is a Phase II study examining ABVD followed by BV in patients with limited stage, non-bulky HL. The hypothesis is that BV may be a safe and effective alternative to consolidative radiation in patients with non-bulky Stage I/II disease.

Patients received 2-6 cycles of ABVD and an interim PET scan. Approximately 6 weeks after the induction therapy, 1.8 mg/kg of BV was given every 3 weeks for 6 cycles. 40 subjects were evaluable, with a median age of 29, and 55% had unfavorable disease. The vast majority (>90%) received 4 or fewer cycles of ABVD and 1 subject received XRT due to disease progression.

Grade ≥3 toxicities associated with BV included neutropenia in 3 patients and peripheral neuropathy and rash in 1 patient each. There was 1 death due to sepsis and hepatic failure. With a median follow-up of 12 months, 90% of patients were PET negative after completion of BV (72% PET negative after ABVD). Estimated 1-year PFS and OS were 91% and 97%.

With relatively short follow-up, BV consolidation following ABVD was associated with good clinical efficacy and expected safety profile. Longer follow-up is necessary to judge whether the late side effects of XRT can be overcome with the use of BV as consolidation for non-bulky limited stage HL.

**Brentuximab vedotin in combination with dacarbazine or bendamustine for frontline treatment of Hodgkin lymphoma in patients aged 60 years and above: Interim results of a multi-cohort Phase 2 study**

Yasenchak CA et al. Proc ASH 2015;Abstract 587.

**Dr Moskowitz**

This Phase II, front-line, open-label study examines the efficacy and durability of response of brentuximab vedotin as monotherapy and in combination with DTIC or bendamustine in HL patients aged ≥60 yrs (NCT01716806).

63 patients have been treated (n = 26 monotherapy, 21 DTIC combination, 16 bendamustine combination). Median age for all patients was 76 yrs (range, 62-92), and 70% were deemed ineligible for conventional chemotherapy; it is unclear to me why patients were not candidates for curative therapy. One must remember that C-MOPP
is curative and can be given to patients with poor cardiac function, and I commonly administer this easy treatment to the elderly.

A total of 50/63 patients have discontinued therapy. Discontinuations were due to adverse event (n = 18, including 15 for Grade 2 or 3 peripheral neuropathy), progressive disease (PD) after complete or partial remission (CR or PR; n = 13).

For patients treated with the DTIC combo, the ORR was 100% (67% CR). The median PFS has not been reached (median observation time 9.8 mo) and 18/21 patients remain alive without PD.

For patients treated with the bendamustine combo, the starting dose of bendamustine was reduced from 90 to 70 mg/m² to improve tolerability after the first 10 patients were enrolled.

The ORR was 100% (78% CR) in the first 9 patients; with limited observation time (median 3.6 mo), 8/9 patients remain alive without PD.

Again, one must decide whether patients should be treated with curative intent, and strict parameters need to be used.

**Dr Flowers**

Older patients with Hodgkin lymphoma have inferior outcomes compared to younger patients, tolerate standard chemotherapy regimens such as ABVD poorly, and have no clear standard of care therapy. The activity of brentuximab vedotin in relapsed Hodgkin lymphoma has motivated attempts to integrate it into earlier lines of therapy and to utilize it in populations unable to tolerate traditional chemotherapy regimens, like elderly individuals with Hodgkin lymphoma. This study examined the safety and efficacy of brentuximab vedotin as monotherapy and in combination with DTIC or bendamustine in patients with classical Hodgkin lymphoma who were ≥60 years old. Brentuximab was administered at 1.8 mg/kg every 3 weeks for up to 12 cycles with DTIC and for up to 6 cycles with bendamustine (given 90 or 70 mg/m²).

Adverse events leading to treatment discontinuation occurred in 11 of the 27 (41%) patients treated with BV monotherapy. Of the 26 evaluable patients, 24 experienced response and 19 (73%) experienced complete response. Based on the prior publications describing this cohort in *Blood* in 2015, the most common adverse events were peripheral sensory neuropathy (78%), fatigue (44%), and nausea (44%), and toxicities were Grade ≤2 for most patients. However, the incidence of Grade 3 peripheral neuropathy events was relatively high (about 30% overall). With a median follow-up of 20 months, 11 patients (41%) experienced progression of disease after CR or PR.

Of 22 patients treated with BV plus dacarbazine, 9 patients experienced adverse events (41%), 21 of 21 evaluable patients responded, and 14 patients experienced complete response (67%). With a median follow-up of 9.8 months, 2 patients (9%) experienced progression of disease after CR or PR. These data remain quite preliminary but offer alternative options for elderly patients with HL who are not candidates for traditional chemotherapy.
**Dr Nastoupil**

The optimal therapy for elderly patients with HL is not well defined. Intensive chemotherapy is often tolerated poorly. New options that are effective and well tolerated for this population are needed. BV has durable activity and is tolerable. BV has been investigated in untreated patients with HL in patients aged ≥60 years and was associated with high ORR but short PFS (10.5 months). To enhance the durability of BV in untreated patients, the investigators explored BV in combination with dacarbazine or bendamustine in elderly patients with HL.

Preliminary findings were presented. 69 previously untreated patients ≥60 years with HL were enrolled (27 monotherapy; 22 dacarbazine + BV; 20 bendamustine + BV). Median age was 76 years.

68% had advanced stage, 25% had an ECOG PS of 2-3. 72% were deemed poor candidates for chemotherapy. The ORR was high with either combination (100%), 67% CR with dacarbazine and BV and 81% CR with bendamustine and BV. With a relatively short follow-up, median PFS has not been reached, with a median observation time of 9.8 months in the dacarbazine + BV group.

Treatment-related AEs Grade ≥3 were not infrequent and occurred in 36%, SAEs were reported for 9% with dacarbazine and BV. 41% of patients receiving BV monotherapy discontinued therapy due to AEs, as did 41% of patients receiving dacarbazine + BV.

Longer follow-up is necessary to examine whether BV in combination with either dacarbazine or bendamustine has durable responses that would challenge the current standard of care for elderly patients. An alternative combination such as BV + anti-PD-1 antibody may be a more promising combination as it may be associated with a more favorable safety profile.

**US Intergroup trial of response-adapted therapy for Stage III to IV Hodgkin lymphoma using early interim fluorodeoxyglucose-positron emission tomography imaging: Southwest Oncology Group S0816**

Adapted treatment guided by interim PET-CT scan in advanced Hodgkin’s lymphoma


**Dr Moskowitz**

Advanced stage HL PET-adapted study

2 cycles of ABVD followed by interim PET-CT and if negative, randomization to ABVD or AVD
If PET+, Phase II directed therapy with BEACOPP variants

A total of 1,214 patients; 937 of the 1,119 patients (83.7%) who underwent interim PET-CT had a negative result, and after randomization there was no difference in 3-year PFS between ABVD and AVD, and bleomycin can be omitted for cycles 3-6 (finally!).

172 patients with positive findings on the interim scan: 3-year PFS rate was 67.5% and the overall survival rate 87.8%. This is 25%-30% better than continuing ABVD, but this was not randomized.

Southwest Oncology Group S0816

PET-adapted study of ABVD for 2 cycles and if negative interim scan continue, if positive switch to escalated BEACOPP

(Deauville score 1 to 3 was considered negative)

336 of the enrolled patients were evaluable.

271 (82%) PET 2-negative and 60 (18%) PET 2-positive.

2-year estimate for progression-free survival (PFS) was 79% (95% CI, 74% to 83%) in PET-negative patients

The 2-year estimate for PFS in the subset of patients who were PET 2-positive after 2 cycles of ABVD was 64%.

Similarities of 2 studies

PET-negative rate after ABVD x 2 is >80% and is the benchmark.

Most failing patients by definition are in the PET-negative group based upon absolute numbers.

Switching to BEACOPP was safe and efficacious.

The reason that RATHL results look better is that unfavorable ESHL was also included and SWOG had only Stage III/IV.

When looking at results of ECHELON 1: BV-AVD vs ABVD, the endpoint I am most interested in is the PET 2-negative rate after BV-AVD.

Dr Flowers

The German Hodgkin Study Group intensified regimen of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escalated-dose BEACOPP) appears to be a highly active regimen that may cure incrementally more patients than standard ABVD in the first-line setting, but this regimen is more markedly toxic, it causes infertility in most recipients, and a substantial fraction of patients who would relapse following ABVD (but not escalated BEACOPP) can be cured with salvage stem cell transplantation. Thus, this aggressive approach is likely only appropriate for patients at substantially increased risk.
The Southwest Oncology Group S0816 study led by Dr Press used early interim PET imaging after 2 cycles of ABVD to determine the utility of response-adapted therapy for Stage III to IV classic Hodgkin lymphoma. PET2-negative patients (Deauville score 1-3) received an additional 4 cycles of ABVD, whereas PET2-positive patients (Deauville score 4 or 5) were switched to escalated BEACOPP. Among 331 evaluable patients who had central review of the interim PET2 scan, 271 (82%) were PET2-negative and 60 (18%) were PET2-positive; 49 switched to escalated BEACOPP as planned and 11 declined. The 2-year progression-free survival in patients who were PET2-positive was 64%, which compares favorably to historical controls (15% to 30%).

In a second trial, patients with advanced stage Hodgkin lymphoma also underwent PET following 2 cycles of standard ABVD. PET2-negative patients (Deauville score 1-3) were randomly assigned to continue ABVD or receive the same regimen without bleomycin (AVD) for 4 cycles, whereas PET2-positive patients (Deauville score 4 or 5) were switched to BEACOPP, BEACOPP-14 or escalated BEACOPP as determined by the treating center. Among 1,119 patients who underwent central review of an interim PET-CT, the Deauville score was 1 in 111 patients (9.9%), 2 in 483 (43.2%), 3 in 343 (30.7%), 4 in 144 (12.9%), and 5 in 38 (3.4%).

For the PET2-negative patients, the 3-year progression-free survival was 85.7% (95% CI, 82.1 to 88.6) in the ABVD group and 84.4% (95% CI, 80.7 to 87.5) in the AVD group. 15 patients (3%) experienced pulmonary adverse events during the latter 4 cycles of ABVD vs 3 patients (1%) in the latter 4 cycles of AVD. Among the 182 PET2-positive patients, 172 received BEACOPP, and the 3-year progression-free survival rate for the group as a whole was 67.5%. These results suggest PFS benefit for PET2-positive Stage III to IV patients switched to escalated BEACOPP compared to the historical experience with continued ABVD in PET2-positive patients. The second study suggests that dropping bleomycin may slightly reduce the risk of pulmonary toxicity for PET2-negative patients, with substantially different expected efficacy.

**Dr Nastoupil**

Outcomes for HL have improved over the past several decades, with ongoing discussions about whether the toxicity profile associated with BEACOPP is acceptable given the possibility of overtreatment of many patients with the goal of curing more than 70% of patients. This was a collaborative study among the 4 major US cooperative groups (SWOG, CALGB/Alliance, ECOG, AIDS malignancy consortium) to assess the use of interim PET for intensifying chemotherapy in patients for whom continued treatment with ABVD may not result in cure.

Eligible patients included adults (18-60) with advanced stage HL and good performance status. Patients completed an interim PET scan after 2 cycles of ABVD (PET2). Those that were PET2 negative received an additional 4 cycles of ABVD and those that were PET2 positive were switched to eBEACOPP for 6 cycles.

336 patients were eligible and evaluable. PET review was centralized with Deauville scores provided and completed within 2-4 days. 82% were PET2 negative and completed ABVD. 60 (18%) were PET2 positive, but only 49 actually received eBEACOPP: 5 refused to receive BEACOPP and did not continue on study, 3 received
ABVD, and 3 declined therapy. 96% in the ABVD arm achieved a complete remission. In the ABVD escalated to eBEACOPP group, 55% achieved a CR. The 2-year PFS was 79% (82% for PET2 negative; 64% for PET2 positive).

The relative dose delivery was greater for the ABVD treated patients. eBEACOPP was associated with higher toxicity than ABVD: 86% vs 37% Grade ≥4 toxicity. There were 3 treatment related deaths (1 ABVD, 2 eBEACOPP). Second cancers were also higher with eBEACOPP (6% vs 1%).

This study reports higher than anticipated PFS for the entire group and more favorable outcomes for the group with positive PET, suggesting that intensifying therapy with an early PET response assessment may successfully salvage some patients while reducing the exposure of a large number of patients to the more toxic BEACOPP regimen.

Longer follow-up is still desirable to examine late events. A randomized study is necessary to result in adoption of risk adapted therapy based on preliminary PET. In addition, would a more intensive approach with de-escalation be superior, starting with BEACOPP and after 2 cycles de-escalating those who are PET2 negative to ABVD? Would this have resulted in better outcomes for the entire cohort? The Europeans have explored this approach, and the PFS may be more favorable. Lastly, is there a better tool than PET to risk stratify patients?
Lung Cancer

Current and Future Use of Checkpoint Inhibitors


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Publications

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Lee MS et al. *Association of primary site and molecular features with progression-free survival and overall survival of metastatic colorectal cancer after anti-epidermal growth factor receptor therapy.* Proc ASCO 2016;Abstract 3506.


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**Gastroesophageal Cancer**


Pancreatic Cancer


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Melanoma

Talimogene Laherparepvec

Current and Future Use of Checkpoint Inhibitors


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Genitourinary Cancers

Prostate Cancer


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