EPICS

EPICS CONGRESS COVERAGE: ASCO 2020 – FOCUS ON MELANOMA

June, 2020
On June 12, 2020, following the American Society of Clinical Oncology (ASCO) annual meeting, Aptitude Health brought together a group of scientists and clinical investigators with expertise in melanoma to attend the Emerging Paradigms in Care Series (EPICS) Congress Coverage meeting.

The goal of the expert panel was to critique and debate new evidence in melanoma and gain strategic insight into the most impactful abstracts from the ASCO meeting with respect to shaping current research directions and/or changing the scope of practical clinical care.
MEET THE EXPERTS . . .

Jeffrey S. Weber, MD, PhD
Perlmutter Cancer Center NYU Langone
New York, NY, USA

Michael Atkins, MD
Georgetown-Lombardi Comprehensive Cancer Center
Washington, DC, USA

Alexander Eggermont, MD, PhD
Princess Maxima Center for Pediatric Oncology
Utrecht, The Netherlands

James Larkin, MD
The Royal Marsden
London, UK

Reinhard Dummer, MD
University Hospital of Zurich
Zurich, Switzerland

Caroline Robert, MD, PhD
Institute Gustave-Roussy
Paris, France
<table>
<thead>
<tr>
<th>Time (EST)</th>
<th>Topic</th>
<th>Speaker/Moderator</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.00 PM – 1.05 PM (5 min)</td>
<td>Welcome and Introductions</td>
<td>Moderator: Jeffrey Weber, MD, PhD</td>
</tr>
<tr>
<td>1.05 PM – 1.10 PM (5 min)</td>
<td>Melanoma Adjuvant and Neoadjuvant Therapy</td>
<td>Alexander Eggermont, MD, PhD</td>
</tr>
<tr>
<td>1.10 PM – 1.20 PM (10 min)</td>
<td>Discussion: Melanoma Adjuvant and Neoadjuvant Therapy</td>
<td>Moderator: Reinhard Dummer, MD</td>
</tr>
<tr>
<td>1.20 PM – 1.30 PM (10 min)</td>
<td>Relapsed/Refractory Metastatic Melanoma</td>
<td>Caroline Robert, MD, PhD</td>
</tr>
<tr>
<td>1.30 PM – 1.50 PM (20 min)</td>
<td>Discussion: Relapsed/Refractory Metastatic Melanoma</td>
<td>Moderator: James Larkin, MD</td>
</tr>
<tr>
<td>1.50 PM – 2.00 PM (10 min)</td>
<td>Immunotherapy for Metastatic Melanoma</td>
<td>Michael Atkins, MD</td>
</tr>
<tr>
<td>2.00 PM – 2.20 PM (20 min)</td>
<td>Discussion: Immunotherapy for Metastatic Melanoma</td>
<td>Moderator: Caroline Robert, MD, PhD</td>
</tr>
<tr>
<td>2.20 PM – 2.30 PM (10 min)</td>
<td>\textit{BRAF}-Mutated Metastatic Melanoma</td>
<td>James Larkin, MD/Reinhard Dummer, MD</td>
</tr>
<tr>
<td>2.30 PM – 2.50 PM (20 min)</td>
<td>Discussion: \textit{BRAF}-Mutated Metastatic Melanoma</td>
<td>Moderator: Michael Atkins, MD</td>
</tr>
<tr>
<td>2.50 PM – 3.00 PM (10 min)</td>
<td>Summary and Closing Remarks</td>
<td>Jeffrey Weber, MD, PhD</td>
</tr>
</tbody>
</table>
Melanoma Adjuvant and Neoadjuvant Therapy

ALEXANDER EGGERMONT, MD, PHD
PRINCESS MAXIMA CENTER FOR PEDIATRIC ONCOLOGY
UTRECHT, THE NETHERLANDS
MELANOMA ADJUVANT AND NEOADJUVANT THERAPY: ABSTRACTS (1/4)

> 10015: Twenty-four month RFS and updated toxicity data from OpACIN-neo: A study to identify the optimal dosing schedule of neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in stage III melanoma. Rozeman et al.

The phase II OpACIN-neo study evaluated 3 different dosing schedules of neoadjuvant ipilimumab + nivolumab (IPI/NIVO) in 86 patients with stage III melanoma and measurable lymph node metastasis. Results showed that 2 cycles of ipilimumab 1 mg/kg + nivolumab 3 mg/kg was the most favorable dosing, with 20% grade 3–4 immune-related adverse events (irAEs) and a pathologic response rate (<50% viable tumor cells) of 77% (Rozeman EA, et al. Lancet Oncol. 2019;20(7):948-960).

In the current analysis with 24.6 months of follow-up, only 1 of 64 patients with a pathologic response had relapsed. At 24 months post-surgery, relapse-free survival (RFS) was 84% in the overall population and 97% in patients with a pathologic response, but only 35.5% in patients who did not respond.

The most frequent ongoing irAEs were vitiligo (35%), fatigue (14%), sicca syndrome (11%), rash (10%), arthralgia (7%), and endocrine toxicities (20%). 17 patients required hormone replacement therapy.
10002: First safety and efficacy results of PRADO: A phase II study of personalized response-driven surgery and adjuvant therapy after neoadjuvant ipilimumab (IPI) and nivolumab (NIVO) in resectable stage III melanoma. Blank et al

PRADO is an extension cohort (N = 99) of the OpACIN-neo study designed to confirm the efficacy and safety of neoadjuvant IPI/NIVO with the previously selected dose/schedule. In addition, this study investigated whether patients with a pathologic complete response (pCR) or near-pCR in the index node (largest lymph node metastases) could safely be spared full lymph node dissection.

- The pathologic response rate was 71%, and 61% of patients had a major pathologic response.
- The radiologic response rate was 45%, underestimating the pCR rate.
- Total lymph node dissection was omitted in 60% of patients.
- Of the 28 nonresponders, 7 developed distant metastases before index node resection.
- Grade 3/4 irAEs occurred in 22% of patients during the first 12 weeks.
MELANOMA ADJUVANT AND NEOADJUVANT THERAPY: ABSTRACTS (3/4)

> **10000**: Pembrolizumab versus placebo after complete resection of high-risk stage III melanoma:

The phase III EORTC 1325/KEYNOTE-054 trial compared adjuvant therapy with pembrolizumab vs placebo in patients with resected high-risk stage III melanoma.

- At a median follow-up of 1.25 years, pembrolizumab significantly improved RFS (HR = 0.57; *P* < .0001) (Eggermont AMM, et al. N Engl J Med. 2018;378(19):1789-1801).

The current analysis was conducted at a median follow-up of 3 years:

<table>
<thead>
<tr>
<th></th>
<th>Pembrolizumab</th>
<th>Placebo</th>
<th>HR</th>
<th><em>P</em> Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>64%</td>
<td>44%</td>
<td>0.56</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PD-L1+</td>
<td>65%</td>
<td>46%</td>
<td>0.57</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>PD-L1–</td>
<td>57%</td>
<td>33%</td>
<td>0.45</td>
<td>.002</td>
</tr>
<tr>
<td>Stage IIIA</td>
<td>81%</td>
<td>66%</td>
<td>0.50</td>
<td>.030</td>
</tr>
<tr>
<td>Stage IIIB</td>
<td>66%</td>
<td>47%</td>
<td>0.56</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stage IIIC</td>
<td>54%</td>
<td>32%</td>
<td>0.57</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BRAF mutated</td>
<td>62%</td>
<td>37%</td>
<td>0.51</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BRAF WT</td>
<td>62%</td>
<td>47%</td>
<td>0.66</td>
<td>.003</td>
</tr>
</tbody>
</table>
10017: Final analysis of relapse-free survival in a multicenter, double-blind, placebo-controlled trial of adjuvant seviprotimut-L polyvalent melanoma vaccine after resection of high-risk melanoma.

Slingluff et al. - The MAVIS Part B1 trial compared adjuvant treatment with seviprotimut-L vs placebo in 347 patients with stage IIB–III melanoma following surgical resection.

- In the intent-to-treat analysis, there was no significant difference in RFS between arms (HR = 0.88; P = NS).

- Subgroup analysis identified patient subsets with a trend toward benefit with the vaccine:
  - Stage IIB/IIC subset (HR = 0.65; 95% CI, 0.37–1.17), favoring seviprotimut-L.
  - Age <60 years (HR = 0.64; 95% CI, 0.38–1.08).
  - Stage IIB/IIC patients <60 years (HR = 0.32; 95% CI, 0.12–0.86).
  - Stage IIB/IIC patients <60 years with ulceration (HR = 0.209; 95% CI, 0.07–0.61).

- There was also a trend toward an overall survival (OS) benefit for patients <60 (HR = 0.41; 95% CI, 0.33–1.14).
Regarding the use of anti–PD-1 antibodies in the adjuvant setting for high-risk stage III melanoma based on KEYNOTE-054, some experts expressed concern about delayed long-lasting nonresolving endocrine irAEs, and overtreatment of patients who may not require additional treatment. However, long-term irAE risks might not be very impactful: only 2 additional irAEs were reported between the initial analysis with 1.25 years' follow-up, and the current analysis with 3 years' follow-up.

The most frequent endocrine irAEs affect the thyroid, and the majority of these events are lab abnormalities that do not require replacement therapy. It was suggested that a shorter course of adjuvant anti–PD-1 therapy might reduce irAEs without compromising efficacy, and should be investigated.

The primary debate concerns whether patients with stage IIIa disease really need 2 years of adjuvant therapy, but it was noted that the hazard ratio in this subgroup was 0.50, suggesting substantial clinical benefit. Experts agreed that they would discuss the adjuvant option with their patients, explain the data, and allow their patients to make an informed decision.

It was also noted that the hazard ratio was lower in patients with BRAF-mutated melanomas (HR = 0.51) compared with those with BRAF-WT disease (HR = 0.66), with a 25% difference in RFS at 3 years. For comparison, the difference in RFS at 3 years in the COMBI-AD trial of adjuvant dabrafenib + trametinib in stage III BRAF-mutated melanoma was 20% (HR = 0.51).
Results from the PRADO extension cohort of the OpACIN trial signal a potential shift to come in the management of stage III melanoma, but experts cautioned that the number of patients in this cohort was modest, and results from additional ongoing trials, longer follow-up, and survival data are needed to confirm the safety of omitting extensive lymph node dissection in patients achieving a pCR in the index node following 2 cycles of ipi-nivo neoadjuvant therapy.

At the present time, experts would recommend patients who fit the PRADO criteria be enrolled in these ongoing neoadjuvant clinical trials, rather than adopting the PRADO approach routinely in the clinic.

It was noted that the radiologic response rate underestimated pathologic responses, but radiologic imaging is still considered useful for identifying patients who progress to stage IV disease preoperatively.

After failure of the adjuvant vaccine study, experts believe a path forward might be to study it in combination with a PD-(L)1 inhibitor in high-risk patients.
Relapsed/Refractory Metastatic Melanoma

CAROLINE ROBERT, MD, PHD
INSTITUTE GUSTAVE-ROUSSY
PARIS, FRANCE
10004: Significant antitumor activity for low-dose ipilimumab (IPI) with pembrolizumab (PEMBO) immediately following progression on PD-1 Ab in melanoma (MEL) in a phase II trial. Olsen et al. - 70 patients with advanced melanoma who had progressed on an anti–PD-1 Ab as immediately prior therapy (alone or in a non-CTLA-4 Ab combination) were treated with pembrolizumab (200 mg) + ipilimumab (1 mg/kg) Q3W for 4 doses, followed by pembrolizumab alone for up to 2 years.

- Median time on prior anti–PD-1 therapy was 4.8 months.
- The irRECIST response rate was 27%, including 5 CRs and 14 partial responses (PRs).
- Median duration of response (DOR) was 18.5 months.
- Median progression-free survival (PFS) was 5.0 months.
- Grade 3/4 AEs occurred in 27% of patients; the most common AEs were diarrhea, rash, and transaminase elevation.

Correlative studies show responses with this combination in patients with either a T-cell–inflamed or non–T-cell–inflamed gene expression signature.
10005: Ipilimumab (IPI) alone or in combination with anti-PD-1 (IPI+PD1) in patients (pts) with metastatic melanoma (MM) resistant to PD1 monotherapy. Pires et al

This multicenter retrospective study analyzed 355 patients with metastatic melanoma who received treatment with either ipilimumab plus an anti–PD-1 Ab (n = 193) or with ipilimumab alone (n = 162) after progression on anti–PD-1 monotherapy. Median follow-up was 22.2 months.

The overall response rate (ORR) was 32% with combination therapy and 13% with ipilimumab alone (P = .0021). Stable disease (SD) rates were 9% and 14%, respectively.

Median DOR was 11.6 months with combination therapy vs 9.0 months with ipilimumab alone (P = .0467).

PFS at 1 year was 27% with the combination vs 13% with ipilimumab (P < .01).

Total grade 3/4 AEs were similar between the 2 arms (31% vs 33%), and higher-grade AEs were not associated with response.
**10006: Long-term follow up of lifileucel (LN-144) cryopreserved autologous tumor infiltrating lymphocyte therapy in patients with advanced melanoma progressed on multiple prior therapies.**

Sarnaik et al

The phase II C-144-01 study evaluated the efficacy and safety of lifileucel (autologous tumor infiltrating lymphocytes [TILs]) in patients with metastatic melanoma that had progressed on immune checkpoint inhibitors and BRAF/MEK inhibitors, if BRAFv600 mutant.

- Cohort 2 included 66 patients with 3.3 mean prior therapies (anti–PD-1 100%; anti–CTLA-4 80%; BRAF/MEK inhibitor 23%) and a high baseline tumor burden.

- The objective response rate was 36% (3% CR and 33% PR). The disease control rate (DCR) was 80%.

- Responses appeared to deepen over time.

- Median DOR has not been reached at a median follow-up of 18.7 months (range 2.2–26.9+ months).

- 97% of patients experienced grade 3/4 AEs, primarily related to interleukin-2 (IL-2) infusion and myeloablative therapy, which decreased over time.
10045: Response to immune checkpoint inhibitor (ICI) rechallenge after high-grade immune related adverse events (irAE) in patients (pts) with metastatic melanoma (MM). Shah et al

This retrospective observational study examined a database of 551 patients previously treated with an immune checkpoint inhibitor between January 2014 and January 2020, 180 of whom had experienced a grade 3/4 irAE, and 91 of whom were subsequently rechallenged with the same class of agent.

• Previous grade 3/4 toxicities included colitis or diarrhea 27.5%, hepatitis 23%, skin toxicity 22%, adrenal insufficiency 5.5%, hypophysitis 5.5%, neurological abnormality 4.4%, pancreatitis 3.3%, hematological abnormality 3.3%, arthralgia 3.3%, myalgia 3.3%, pneumonitis 2.2%, insulin-dependent diabetes 1.1%, fatigue 1.1%, vasculitis 1.1%, and hyponatremia 1.1%.

• Median duration between the initial irAE and rechallenge was 9.7 weeks.

• 76% of patients experienced a recurrence of an irAE; 45% were high-grade events and 32% were a different irAE than the initial one.

• There were no rechallenge-related patient deaths.

• 60% of patients experienced a clinical benefit, including 41% CRs, 11% PRs, and 9% disease stabilization.
The data regarding ipilimumab plus an anti–PD-1 antibody in patients with progression on an anti–PD-1 antibody were difficult to interpret. The efficacy of ipilimumab alone in this setting is in the range of 15%–30%, so it is unclear whether the addition of the anti–PD-1 antibody adds significantly to the efficacy. An ongoing SWOG trial is randomizing patients post-progression on an anti–PD-1 antibody to ipilimumab with or without an anti–PD-1 antibody, and this will provide more conclusive data regarding the efficacy of combination therapy in this setting. However, some experts indicated that in the absence of randomized data, they would opt for a combination approach, possibly with lower-dose ipilimumab, following progression on an anti–PD-1 antibody in patients fit enough to tolerate the associated toxicities. Another unanswered question that needs to be addressed through clinical trials is whether treating with single-agent anti–PD-1 first line, followed by ipilimumab (with or without continued anti–PD-1) is as effective as treating with combination therapy in the first-line setting. There is an urgent clinical need for effective therapies for patients who progress on anti–PD-1 and anti–CTLA-4 therapies.
The response and durability data with lifileucel were considered very encouraging, particularly in the heavily pretreated trial population; several experts expressed enthusiasm that TILs could potentially represent a promising new treatment option for patients with advanced melanoma who have progressed on anti–PD-1 and anti–CTLA-4 antibodies. However, this treatment is considered to be challenging initially and requires very careful patient selection: the toxicities associated with the myeloablative treatment and IL-2 infusions require patients to be very fit, and the necessity of waiting 3 weeks between cell collection and treatment requires the disease biology to be slower growing and/or less advanced. Experts indicated that for this therapy to be considered in the second-line setting, a trial comparing lifileucel vs ipilimumab (or ipilimumab + anti–PD-1) in patients with disease progression on first-line anti–PD-1 therapy would be necessary.
The Shah et al data on rechallenging patients who have experienced high-grade irAEs with an immune checkpoint inhibitor after resolution of the irAE support the feasibility of this approach, consistent with other recent reports. Considering the likelihood of clinical benefit, rechallenge should be considered, and risks vs benefits discussed with the patient. Experts also emphasized that rechallenged patients should be monitored very closely. One expert noted that patients who experience toxicity with an anti–PD-1/anti–CTLA-4 combination often do very well with single-agent anti–PD-1 therapy. However, experts indicated they would not rechallenge a patient who had experienced a cardiac or neurologic irAE and would be cautious with those who had experienced pneumonitis.
Immunotherapy for Metastatic Melanoma

MICHAEL ATKINS, MD
GEORGETOWN-LOMBARDI COMPREHENSIVE CANCER CENTER
WASHINGTON, DC, USA
10008: Single-center phase I/Ib study of concurrent intrathecal (IT) and intravenous (IV) nivolumab (N) for metastatic melanoma (MM) patients (pts) with leptomeningeal disease (LMD). Glitza et al.

This single-center study from MD Anderson was designed to evaluate the efficacy and safety of intrathecal administration of nivolumab in patients with metastatic melanoma with leptomeningeal disease (LMD) - 19 patients with radiographic evidence of LMD and neurological symptoms have been treated to date with intrathecal therapy (patients also received IV nivolumab), and represented a very poor prognosis cohort (including patients with performance status ≤2, dexamethasone ≤4 mg/d, prior intrathecal IL-2, prior immune checkpoint inhibitor therapy, prior BRAF/MEK inhibitors, and/or prior radiation therapy).

- There was 1 PR, and 6 patients experienced disease stabilization for >18 weeks.
- Median OS was 19.4 weeks (compared with historical data of OS in the range of 6–12 weeks).
- There were 8 AEs attributable to intrathecal nivolumab, all of which were grade 1, and 3 additional grade 3/4 AEs.
10007: Overall survival and biomarker analysis of a phase Ib combination study of toripalimab, a humanized IgG4 mAb against programmed death-1 (PD-1), with axitinib in patients with metastatic mucosal melanoma. Sheng et al

- 33 patients with metastatic mucosal melanoma received treatment with the anti-PD-1 Ab toripalimab (1 or 3 mg/kg) Q2W in combination with axitinib (5 mg BID).
- The ORR was 48.5% (1 CR, 15 PRs).
- Median PFS was 7.5 months, with 1-year and 2-year PFS rates of 41% and 14%, respectively.
- Median OS was 20.7 months, with 1-year and 2-year OS rates of 65.5% and 45%, respectively.
- 39% of patients experienced grade 3/4 AEs; the most common treatment-related AEs included diarrhea, proteinuria, hand and foot syndrome, and hypothyroidism.
10003: A phase II study to evaluate the need for > two doses of nivolumab + ipilimumab combination (combo) immunotherapy. Postow et al

Patients with unresectable stage III/IV melanoma received 2 doses of nivolumab (1 mg/kg) + ipilimumab (3 mg/kg) followed by a CT scan at week 6. Patients with a CR/PR/SD transitioned to maintenance nivolumab while patients with progressive disease received 2 more doses of nivolumab.

41 of 60 patients (68%) were able to stop nivolumab-ipilimumab at week 6. Best ORRs were 48% at week 12, and 53% at any time afterwards. None of the 19 patients with tumor growth at week 6 who received additional cycles of nivolumab-ipilimumab had a subsequent RECIST response.

57% of patients experienced grade 3/4 AEs, with 3 treatment-related deaths (2 myocarditis, 1 possible adrenal insufficiency).

Correlative studies showed that immunologic effects in the blood (increased Ki67+ and/or ICOS+ CD8 T cells) were observed after the first dose of nivolumab-ipilimumab, but no significant further changes were detected.
10009: Integrative tumor and immune cell multi-omic analyses to predict melanoma response to immune checkpoint blockade. Anagnostou et al

Tumor samples from 40 patients treated on the CheckMate-038 trial with either nivolumab alone (n = 9) or nivolumab + ipilimumab (n = 31) were analyzed with whole exome sequencing, RNAseq, and TCRseq, to develop a multiomics model predictive of clinical outcome.

A higher number of Ig rearrangements was observed in baseline samples of responders (P = .0016), suggesting differential B-cell infiltration may be linked to clinical response. Deconvolution of RNA seq data confirmed an enrichment of tumor-associated B cells in baseline tumor samples from responding patients.

A multiomic model differentiated between low- and high-risk patients in the overall population (PFS: 29.01 months vs 1.43 months; HR = 5.92; P = 9.07 × 10^-5) and in the subset of patients treated with nivolumab + ipilimumab (PFS: 29.01 months vs 1.43 months; HR = 8.09; P = 7.05 × 10^-5).

The risk score incorporated Ig rearrangements, TCR productive clones, PD-L1 expression, and expressed tumor mutational burden.
10010: Using machine learning to predict immunotherapy response in advanced melanoma.

Researchers used neural networks to analyze H&E stained slides and accurately discriminated between tumor, lymphocytes, and connective tissue (AUCs 0.886 – 0.984). A logistic regression classifier was developed that combined neural network output with clinicodemographic variables to predict response to immune checkpoint inhibitor therapy. When tested on an independent cohort of 32 patients, the classifier alone predicted benefit with an accuracy AUC of 0.712. When clinicodemographic variables were added, accuracy increased (AUC = 0.790).
10011: Autoantibodies as predictors for survival and immune-related adverse events in checkpoint inhibition therapy of metastatic melanoma. Hassel et al

Luminex AutoAb profiling was used to retrospectively analyze pretreatment serum samples from 333 patients with metastatic melanoma who received immune checkpoint inhibitor therapy at 5 European centers.

Antibodies were detected to 832 distinct autoimmune or tumor antigens. Regression analysis of autoantibodies revealed an association with both irAEs and better clinical outcome. Specific autoantigens that correlated with irAEs and survival included anti-MAGEB4 and anti-FGFR1.

- Elevated pretreatment levels of anti-MAGEB4 were associated with longer overall survival (HR = 0.77; P = .002) and the development of irAEs (HR = 1.27; P = .002) in patients treated with ipilimumab ± nivolumab.
- Higher pretreatment anti-FGFR1 antibodies were associated with shorter survival (HR = 1.27; P = .008) and a lower frequency of irAEs (HR = 0.69; P = .04).
> **10030**: Surrogate endpoints for overall survival in anti-programmed death-1 and anti-programmed death ligand 1 trials of advanced melanoma. Nie et al

A meta-analysis of 8 randomized controlled trials was used to evaluate ORR, DCR, and PFS, as surrogates for predicting for OS in anti–PD-1/PD-L1 trials in patients with metastatic melanoma.

- The correlation of ORR/DCR and OS was relatively weak (nonsignificant).
- The correlation of PFS and OS was strong ($R^2$ of 0.82 in sample size, 0.75 in fixed effect, and 0.72 in random effect model weighting).
- A future anti–PD-1/PD-L1 trial would need an HR <0.78 for PFS to predict an OS benefit.
Experts believe that it will be possible to reduce the number of cycles of ipilimumab plus an anti–PD-1 antibody for some patients by identifying the good responders who derive ≥90% of benefit from 1–2 cycles. Evolving data from both the metastatic and neoadjuvant settings will help to fine-tune patient selection.

The correlative data from the Postow et al study suggest that one dose of combination therapy may be sufficient to start the immune response, which may then be maintained with single-agent anti–PD-1 treatment. For patients who do not respond to 2 cycles of combined immunotherapy, an alternative treatment is likely to be necessary.

Current imaging techniques are considered inadequate for evaluating responses to immunotherapies; conventional CT scans likely underestimate the amount of tumor that has been eliminated, and may detect residual abnormalities such as scars from the immune system attack. For this reason, CR based on CT scan was not considered a reliable surrogate marker for OS.

Better imaging tools that can distinguish tumor from artifacts of the immune attack on the tumor are needed to help guide treatment decision.

Experts advised a more extensive evaluation, including PET imaging for patients with ≥80% tumor shrinkage to evaluate metabolic activity, as well as repeat biopsy, to determine if a patient can stop therapy.

Liquid biopsies may eventually be able to be used in place of traditional radiographic procedures to monitor patients, but these would need to be able to detect tumor-specific mutations at a high level of sensitivity.
Ipilimumab plus an anti–PD-1 antibody is considered the most efficacious therapy currently available for advanced melanoma, and should be considered the comparator for new investigational agents.

The problem of leptomeningeal disease is growing, particularly in patients treated with BRAF/MEK inhibitors, which are extending survival but do not penetrate the central nervous system (CNS), and this is a clear unmet clinical need. The results from the study of intrathecal nivolumab demonstrate the feasibility of this approach, but experts advised that more data based on more patients treated at institutions other than MD Anderson would be needed to understand the potential of this strategy. It was noted that immunotherapies, particularly combination regimens, appear to be effective, and using these regimens earlier in the course of disease, such as in the neoadjuvant setting, may help to reduce the number of patients who ultimately relapse with leptomeningeal disease.

The ORR and PFS from the study of toripalimab + axitinib in patients with mucosal melanoma were considered promising, particularly compared with historical data in this patient subgroup, but it was noted that there does not appear to be a tail on the PFS curve, unlike what is seen with other immune checkpoint inhibitor regimens, and 2-year PFS was only 14%. Experts indicated that they would not be comfortable adopting this approach based on the current data, and recommended a randomized trial comparing this regimen with a standard PD-1 or PD-1/CTLA-4 regimen.
While the emerging data with novel biomarkers is considered interesting and encouraging, none have been validated for routine clinical use. Machine-based learning was considered potentially interesting, and after the initial setup, requires low resource utilization, but does not provide any insight into the underlying biology driving responses. The most useful biomarkers at the current time would be those that could be used to identify patients who will do well with an anti-PD-1 antibody alone. While biomarkers to identify patients who will not respond to ipilimumab plus an anti-PD-1 antibody should also be developed, it was noted that currently, there are no other treatment options to offer these patients. However, this could help to identify patients for clinical trials of new investigational agents.

PFS may be an appropriate surrogate for OS in trials of immune checkpoint inhibitors, but it depends on the comparator used in a phase III trial, and may not apply to combination checkpoint inhibitor therapies. Further, prediction of median OS may be less important than landmark OS with these agents. In contrast, ORR was not considered to be a useful surrogate marker for OS.

Many of the studies presented at ASCO this year have focused on de-escalation of therapy, and there is value in identifying lower intensity, less toxic, less expensive regimens that are just as good as current standards. However, there remains a strong need for new agents that can further improve outcomes and push 5-year OS beyond the landmark of 52% achieved with nivolumab + ipilimumab.
BRAF-Mutated Metastatic Melanoma

JAMES LARKIN, MD
THE ROYAL MARSDEN
LONDON, UK

REINHARD DUMMER, MD
UNIVERSITY HOSPITAL OF ZURICH
ZURICH, SWITZERLAND
10001: Long-term benefit of adjuvant dabrafenib + trametinib (D+T) in patients (pts) with resected stage III BRAF V600-mutant melanoma: Five-year analysis of COMBI-AD. Hauschild et al.

The phase III COMBI-AD trial randomized patients with resected stage III BRAF V600E/K-mutant melanoma to 12 months of adjuvant therapy with dabrafenib + trametinib vs placebo.

- Previous results showed a significant improvement with combination therapy in RFS (3-year RFS: 58% vs 39% (HR = 0.47; P <.001) and OS (3-year OS: 86% vs 77%; HR = 0.57; 95% CI, 0.42–0.79) (Long et al. N Engl J Med. 2017;377(19):1813–1823).

- The current analysis was conducted with a median follow-up of 5 years.

- Median RFS had not been reached in the combination arm (95% CI, 47.9–NR) vs 16.6 months (95% CI, 12.7–22.1 months) with placebo (HR = 0.51 [95% CI, 0.42–0.61]).

- 5-year RFS was 52% with dabrafenib + trametinib vs 36% with placebo.

- The RFS benefit with BRAF/MEK therapy was evident across all AJCC 7 substages (HR [95% CI]: IIIA, 0.61 [0.35–1.07]; IIIB, 0.50 [0.37–0.67]; IIIC, 0.48 [0.36–0.64]).

- Median distant metastasis-free survival was not reached in either arm but favored dabrafenib + trametinib (HR = 0.55, 95% CI, 0.44–0.70).

- Benefit was observed in all subgroups examined.

- OS was not updated in this analysis.
10012: Update on overall survival in COLUMBUS: A randomized phase III trial of encorafenib (ENCO) plus binimetinib (BINI) versus vemurafenib (VEM) or ENCO in patients with BRAF V600-mutant melanoma. Gogas et al

In part 1 of the COLUMBUS trial, 577 patients with advanced/metastatic BRAF V600-mutant melanoma, untreated or with progression after first-line immunotherapy, were randomized 1:1:1 to encorafenib + binimetinib vs single-agent therapy with vemurafenib or encorafenib

This updated analysis was performed with 60.6 months of follow-up

- Median OS was 33.6 months with the combination, 23.5 months for encorafenib, and 16.9 months for vemurafenib.
- The HR was 0.62 [95% CI, 0.49–0.79] for the combination vs vemurafenib
- 4-year OS was 39%, 37%, and 26% for the combination, encorafenib, and vemurafenib, respectively
- 4-year PFS was 26%, 22%, and 12% for the combination, encorafenib, and vemurafenib, respectively
10022: A phase II, multicenter study of encorafenib/binimetinib followed by a rational triple-agent addition for patients with BRAF V600-mutated advanced melanoma (LOGIC2).

Dummer et al. 

Patients with BRAF-mutated advanced melanoma were treated with encorafenib + binimetinib. At time of progression, FoundationOne next-generation sequencing (NGS) was performed on a baseline sample and on a progressive disease sample. Based on the genetic evolution between the biopsy at baseline and at progression and clinical considerations, patients entered part II and received 1 of 4 third-agent additions to encor/bini: A. LEE011 (CDK4/6 inhibitor), B. BKM120 (PI3K inhibitor), C. INC280 (c-Met inhibitor), or D. BGJ398 (FGFR inhibitor).

58 patients were enrolled into part II (group A = 38; B = 6; C = 13; D = 1), and 29 patients were assigned to treatment based on results of the biopsy on progressive disease.

Patients assigned to the CDK4/6 inhibitor had mutations in genes including CDKN2A, KRAS/NRAS/HRAS, BRAF, CDK4, or MAP2K1.

Patients assigned to the PI3K inhibitor had mutations in PTEN or PIK3CA.

Patients assigned to the c-Met inhibitor had mutations in MET.

No patients were assigned to the FGFR inhibitor.

With LEE011, the ORR was 5% (1 PR), DCR was 26%, and median PFS was 2.1 months.

With BKM120, there were no responses, DCR was 17%, and median PFS was 1.6 months.

With INC280, there were no responses, DCR was 15%, and median PFS was 2.2 months.
10039: Association of prior immune checkpoint blockade (ICB) with longer progression-free survival (PFS) in patients treated with intermittent versus continuous dabrafenib and trametinib: A post-hoc analysis of S1320. Algazi et al.

The phase II SWOG S1320 trial demonstrated that continuous dosing of dabrafenib + trametinib yielded longer PFS than intermittent dosing of these agents in patients with BRAF V600E/K-mutated metastatic melanoma (Algazi et al. 2020 AACR annual meeting).

This post-hoc analysis investigated the association between prior exposure to immune checkpoint inhibitor therapy and PFS in patients randomized to either intermittent or continuous dosing.

- 37% of the 206 randomized patients had received prior immunotherapy.
- PFS was longer in patients with prior immune checkpoint inhibitor exposure (median PFS = 6 months vs 9 months from randomization, 8 months vs 11 months from starting treatment; HR = 0.60; 95% CI, 0.41 – 0.98).
- There was no difference in the association between prior immune checkpoint inhibitor therapy and PFS between arms (interaction P-value = .62).
10021: The IMPemBra trial, a phase II study comparing pembrolizumab with intermittent/short-term dual MAPK pathway inhibition plus pembrolizumab in melanoma patients harboring the \textit{BRAFV600} mutation. Rozeman et al

The aim of this study was to identify the optimal duration of MAPK inhibition with dabrafenib + trametinib in combination with pembrolizumab in terms of safety, feasibility, and immune-activating capacity.

32 patients with \textit{BRAFV600E/K}-mutated advanced melanoma initiated pembrolizumab 200 mg Q3W and were randomized in week 6 to continue pembrolizumab only (cohort 1) or to receive in addition intermittent dabrafenib 150 mg BID + trametinib 2 mg QD for 2×1 week (cohort 2), 2×2 weeks (cohort 3), or continuously for 6 weeks (cohort 4). All cohorts continued pembrolizumab for up to 2 years.

Grade 3/4 AEs were observed in 12%, 12%, 50%, and 62% of patients in cohort 1, 2, 3, and 4, respectively. All planned BRAK/MEK inhibitor therapy was given in 88%, 63%, and 38% of patients in cohort 2, 3, and 4.

Most patients needed to interrupt or discontinue dabrafenib + trametinib due to fever or elevated liver enzymes.

ORR at week 18 was 62% in cohort 1, 75% in cohort 2, 75% in cohort 3, and 50% in cohort 4.

Median PFS in patients treated with pembrolizumab monotherapy was 10.6 months compared with 27.0 months for patients treated with pembrolizumab and short-term/intermittent dabrafenib + trametinib (\textit{P}= .13).
10023: Time to central nervous system (CNS) metastases (mets) with atezolizumab (A) or placebo (P) combined with cobimetinib (C) + vemurafenib (V) in the phase III IMspire150 study. Ascierto et al

The phase III IMspire150 study randomized 514 patients with previously untreated BRAF V600-mutated advanced melanoma to first-line treatment with cobimetinib + vemurafenib with or without atezolizumab; results showed improved PFS with the addition of atezolizumab (15.1 months vs 10.6 months; HR = 0.78; \( P = .0249 \)) (McArthur et al. AACR 2020 annual meeting)

The cumulative incidence of CNS metastases as first site of progressive disease at 24 months was 21% with triplet therapy vs 25% with BRAF/MEK inhibition alone (HR = 0.83; 95% CI, 0.57–1.19)

Estimated CNS metastasis-free survival rates were 69% with atezolizumab vs 62% with the doublet at 24 months (HR = 0.79; 95% CI, 0.55–1.14)
10028: The anti–PD-1 antibody spartalizumab in combination with dabrafenib and trametinib in advanced BRAF V600–mutant melanoma: Efficacy and safety findings from parts 1 and 2 of the Phase III COMBI-i trial. Long et al

- The phase III COMBI-i trial is comparing first-line therapy with dabrafenib + trametinib with or without spartalizumab in patients with unresectable or metastatic BRAF V600–mutant melanoma.
- The current results are based on 36 patients enrolled in the safety run-in and biomarker cohorts.
- The confirmed ORR was 78% in 28 evaluable patients, with 16 CRs (44%) and 12 PRs (33%).
- Median DOR was not reached, and the 24-month DOR rate was 53%.
- Median PFS was 22.7 months, and the 24-month PFS rate was 41%.
- Median OS had not been reached, with a 24-month OS rate of 74%.
- In patients with elevated lactate dehydrogenase, ORR was 67%, with 4 CRs (27%); median PFS was 10.7 months, and median OS was not reached. The estimated 24-month PFS and OS rates in these patients were 27% and 52.5%, respectively.
Experts expressed some surprise that with longer-term follow-up of the COMBI-AD trial, the survival curves have not come together, and there appears to be a tail in the dabrafenib + trametinib arm, suggesting that targeted therapy may be able to cure some patients with BRAF-mutated melanoma, at least in the adjuvant setting. However, it is not clear that this approach is superior to, or even equivalent to, what would be expected with an anti–PD-1/anti–CTLA-4 approach. Some investigators indicated they would consider the BRAF/MEK-targeted approach, rather than immunotherapy, for younger patients with stage IIIa melanoma, for whom the risk of long-term endocrine irAEs may be of greater concern.

It was also noted that the hazard ratio for RFS for the stage IIIa population of patients did not quite reach significance in the COMBI-AD trial (AJCC 7 stage IIIa; HR = 0.61; 95% CI, 0.35–1.07), while the hazard ratio was significant in the KEYNOTE-054 trial with adjuvant pembrolizumab (AJCC 7 stage IIIa; HR = 0.50; P = .030). Moreover, using AJCC 8 classification in the COMBI-AD trial, the RFS curves come together at 5 years for patients with stage IIIa disease (5-year RFS: 71% vs 70%; HR = 0.85; 95% CI, 0.36–1.91).

PFS and OS results from the COLUMBUS trial suggest that the efficacy of encorafenib + binimetinib is very similar to that of dabrafenib + trametinib and vemurafenib + cobimetinib. In clinical practice, the choice between BRAF/MEK inhibitor combinations is usually made based on side effect profiles.
The optimal strategy for using BRAF/MEK inhibition and immune checkpoint inhibition (triplet combination vs sequential) in BRAF-mutated metastatic melanoma remains uncertain, and data from ongoing randomized trials will be necessary to get clarity.

Experts indicated that results from current studies of triplet therapy are difficult to interpret because the control arm was the BRAF/MEK inhibitor doublet, rather than an anti–PD-1/anti–CTLA-4 combination, which is considered the standard to beat in terms of OS.

The data with vemurafenib + cobimetinib + atezolizumab are expected to be submitted to the FDA and may gain approval, but experts are not convinced that this triplet is superior to ipilimumab + nivolumab.

The EORTC 1612-MG phase II study is prospectively evaluating whether a sequential approach with an induction period of 12 weeks with encorafenib + binimetinib followed by combination immunotherapy with nivolumab + ipilimumab improves PFS compared with nivolumab + ipilimumab alone in patients with BRAF-mutated unresectable or metastatic melanoma.
Unfortunately, the pilot study investigating the use of NGS-detected molecular alterations to direct the addition of a third agent to a BRAF/MEK inhibitor backbone following progression on the doublet did not show clinical benefit with the agents tested, but the study did demonstrate the feasibility of monitoring molecular alterations throughout the course of therapy. Potential reasons for the disappointing results include molecular alterations key to resistance missed by NGS, the limited number of therapeutic agents available to target detected mutations, and a limited understanding of resistance mechanisms as well as pharmacodynamic interactions between drugs.

The preliminary results from the initial cohorts enrolled in the phase III trial of spartalizumab + dabrafenib and trametinib showed a very promising ORR and PFS, but it was noted that these patients were a highly selected subset who were likely younger than the overall population, and were suitable for repeat biopsies in the biomarker cohort. It is unclear why the waterfall plot showed CRs with tumor reductions less than 100%, but experts speculated that these may be patients with lymph node metastases (up to 10 mm remaining is considered a CR by radiology) or they may have nonmetabolically active scars on CT scan, which are presumed to be CRs but imaging is not definitive.
US Headquarters
5901-C Peachtree Dunwoody Road NE
Suite 200, Atlanta, GA 30328, US

EU Headquarters
Wilhelmina van Pruisenweg 104
2595 AN The Hague, the Netherlands

aptitude-health.com