MEETING REPORTER

Society for Melanoma Research Congress

November 18-21, 2015
San Francisco, California

Highlights Include:

- Pembrolizumab/Ipilimumab Combo Shows Promising Efficacy
- James Allison Predicts 'Cures' With Checkpoint Inhibitor Combinations
- Nivolumab Survival Benefit Sustained in Long-Term Data
- Novel Agents, T-VEC Combos Mark Next Phase of Oncolytic Immunotherapy Era
- New Treatments for Novel Targets Next Step in Immuno-Oncology Revolution

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Understanding BRAF Resistance Critical to Advancing Melanoma Care

By Barbara Boughton


Keith Flaherty, MD

While BRAF inhibitors have significantly enhanced melanoma treatment, there is still room for advancement. However, making real strides in devising treatments that provide durable tumor control will require an understanding of BRAF resistance mechanisms, according to Keith Flaherty, MD, associate professor of Medicine at Harvard Medical School and director of Developmental Therapeutics at the Massachusetts General Hospital Cancer Center.

"With BRAF monotherapies and combination therapies, we can extend survival in some patients," Flaherty said in presentation at the 2015 Society for Melanoma Research Congress. "Enhancing patient outcomes also requires understanding the unique genetic wiring in tumors that [do and] do not manifest resistance," he said.

Scientists have now accumulated 5 to 6 years of follow-up data on melanoma patients treated with BRAF inhibitor therapies. "We know that melanoma is not uniformly complex. And there's quite a lot of genetic heterogeneity in terms of amplification and deletion events, and number of mutations in melanoma tumors," Flaherty said.

Flaherty and colleagues have now performed whole genome sequencing on a large cohort of patients who have undergone BRAF inhibitor therapy. "We're now moving toward correlating genetic differences with clinical outcomes," he said.

Right now scientists are attempting to learn the mechanisms of resistance from static biomarkers before deploying patients to therapy. It is important that scientists learn to understand the baseline features of tumors and adaptations of tumors during therapy that make them resistant. With this understanding, patients likely to develop resistance can receive more aggressive treatments, Flaherty said.

Scientists now know that the reengagement of the map kinase signaling pathway plays a part in melanoma treatment resistance, including resistance to BRAF inhibitors. Scientists need to develop therapies that can reengage with the map kinase pathway to try to squelch the mechanisms of reactivation, which can make patients resistant even to combination therapies, Flaherty said. Other baseline tumor features, however, may also play a part in resistance.

MITF expression, which is correlated with BCL2A1 expression, is another potential mechanism for the development of resistance, Flaherty noted. In genetic studies on melanoma tumors, those patients who had upregulated BCL2A1 were more likely to have blunted response to BRAF inhibitor therapy, he added.

Patients low in MITF expression, who also are low in the AXL protein coding gene are also more likely to develop resistance. "Patients with low MITF expression with low AXL expression have been shown to have the shortest duration of tumor control," Flaherty said.

The challenge is to triage patients early in the course of therapy based on the likelihood that their tumors will be resistant. These harder-to-treat patients could then should be treated with doublet therapy, or by adding a MTOR inhibitor or JAK inhibitor to treatment. Both these approaches have shown potential in patient treatment and in the laboratory for overcoming BRAF inhibitor therapy resistance, Flaherty said.

The issue of whether such genetic changes in a tumor could be assessed prior to or during initial therapy has not yet been fully resolved, Flaherty noted. "As we learn more about the genetic mechanisms of resistance, it makes sense to biopsy patient tumors to assess and measure resistance."

"Another question is what drives persistence after maximal response to BRAF inhibitor therapy. And that's more difficult to assess in treated patients," Flaherty said. "In patients who have deep responses to therapy, their metastases are gone in weeks. So biopsies of these tumors are a challenge."

Eventually, researchers hope to develop blood-based biomarkers that could be correlated with genetic changes in tumors that drive resistance, Flaherty noted. Even if the genetics of resistance are not hardwired, assessing baseline tumor biomarkers will eventually play a part in selecting the best therapeutic approach for each patient, Flaherty said.

If genetic signatures or blood-borne biomarkers of resistance could be assessed at baseline or early on in therapy, then oncologists could immediately use more aggressive therapies with these patients, Flaherty said. "As we continue to develop new therapies, we'll find additional solutions to the problem of potential therapy resistance," he added. "Yet there is likely to be no one-size-fits-all approach in terms of overcoming resistance in melanoma patients treated with BRAF inhibitors. ■

Nivolumab Survival Benefit Sustained in Long-Term Melanoma Data

By Silas Inman @silasinman

Victoria Atkinson, MD

Long-term data continue to show sustained improvements in overall survival (OS) with nivolumab (Opdivo) alone or in combination with ipilimumab (Yervoy) as a frontline treatment for patients with advanced melanoma, according to two presentations at the 2015 Society for Melanoma Research Congress.

In the phase III CheckMate-066 trial, the 2-year OS rate with frontline nivolumab was 57.7% compared with 26.7% for dacarbazine.[1] Additionally, in a phase Ib study, the combination of nivolumab and ipilimumab showed an OS rate of 68% at a median follow-up of 32.7 months.[2]

"This trial is the longest follow-up that we have for patients from a phase III trial for a PD-1 antibody. It shows the highest 2-year survival for any PD-1 therapy in advanced melanoma," study author Victoria Atkinson, MD, of Princess Alexandra Hospital and Gallipoli Medical Research Foundation, Queensland, Australia, told Onc at the conference. "Nivolumab is a highly effective treatment, which is significantly improving overall survival for patients with good quality of life."

In the phase III CheckMate-066 trial, 418 untreated patients were randomized in a 1:1 ratio to receive nivolumab at 3 mg/kg every 2 weeks (n = 210) or dacarbazine at 1000 mg/m^2 every 3 weeks (n = 208). Of the patients enrolled, 61% had stage M1c disease and 36.6% had an elevated lactate dehydrogenase level. The primary endpoint of the study was OS. Secondary endpoints included progression-free survival (PFS), objective response rates (ORR), and quality of life.

After a minimum follow-up of 15.1 months, median OS was not yet reached for patients receiving nivolumab compared with 11.2 months in the dacarbazine arm (HR, 0.43; 95% CI, 0.33-0.57; *P* <.001). The 1-year OS rates were 70.7% and 46.3%, for nivolumab and dacarbazine, respectively. Following progression in the dacarbazine arm, 13% of patients (n = 27) went on to receive nivolumab.

Median PFS was 5.4 months with nivolumab versus 2.2 months for dacarbazine (HR, 0.42; 95% CI, 0.32-0.53; *P* <.001). With nivolumab, the 1- and 2-year PFS rates were consistent, at 44.3% and 39.2%, respectively.

The ORR was 42.9% with nivolumab versus 14.4% with dacarbazine. A complete response was achieved by 11% of patients with nivolumab compared with 1% for dacarbazine. At the analysis, 81% of responses in the nivolumab arm remained ongoing.

"This data reassures us that the responses are maintained. Those who do obtain a response with nivolumab have a maintained response," Atkinson said. "With the 2-year overall survival being so high, we're seeing a plateauing of the curve. We hope that with further follow-up we will see maintained responses."

All-grade adverse events (AEs) were similar between each arm but grade ≥3 AEs were less common with nivolumab (13% vs 17%). The most frequently reported all-grade AEs in patients treated with nivolumab were pruritus (22%), diarrhea (18%), and rash (18%). AEs led to discontinuation in just 6% of patients in the nivolumab arm.

"The highest toxicities with nivolumab were fatigue and arthralgias," said Atkinson. "These are very easily managed side effects, and we see that the toxicity profile is better than chemotherapy."

Patient characteristics, such as disease burden, should be utilized to tailor treatment for patients with advanced melanoma, according to Atkinson. Those with a lower burden of disease who are frail are ideal candidates for nivolumab monotherapy. However, patients with high-risk characteristics, for which a rapid response is needed, should receive a combination of nivolumab and ipilimumab. In either scenario, PD-L1 expression did not seem to play a significant role, she advised.

"For melanoma, PD-L1 shouldn't determine whether we give nivolumab monotherapy," she said. "Regardless of PD-L1 status, you live longer with nivolumab."

In the smaller phase Ib study, labeled Study 004, the combination of nivolumab and ipilimumab was explored at various dosing schedules for patients with unresectable or metastatic melanoma. In 3 cohorts that received similar treatment schedules (n = 53), the ORR with the combination was 42% and the median duration of response was 22.3 months. Complete responses were seen in 21% of patients treated with the combination.

In another cohort that received the combination every 3 weeks for 12 weeks followed by nivolumab alone every 3 weeks for 12 weeks (n = 41), the 18-month OS rate was 68%. The ORR was 44%, with complete responses in 17% of patients. The median duration of response was 13.7 months.

This phase Ib study laid the groundwork for a phase II study, which was instrumental in an accelerated approval for the combination of nivolumab and ipilimumab as a treatment for patients with BRAF V600 wild-type unresectable or metastatic melanoma. This accelerated approval marked the first for an immunotherapy combination for patients with cancer.

In the pivotal phase II trial, known as CheckMate-069,[3] the combination reduced the risk of progression or death by 60% compared with ipilimumab alone (HR, 0.40; 95% CI, 0.22-0.71; *P* <.002). Among patients with *BRAF* wild-type tumors, median PFS was 8.9 months in the nivolumab plus ipilimumab group versus 4.7 months in the ipilimumab arm. The ORR was 60% with the combination versus 11% with ipilimumab alone.

On January 23, 2016, the FDA extended the accelerated approval to include those with *BRAF*-mutant melanoma. The application for this approval was based on the phase III CheckMate-067 study,[4] which showed a 59% reduction in the risk of progression or death with the combination versus ipilimumab alone (HR, 0.41; 95% CI, 0.32-0.53). Median PFS with nivolumab/ipilimumab was 11.5 months versus 2.9 months with ipilimumab alone (HR, 0.42; 95% CI, 0.31-0.57; *P* <.001).

"I think immunotherapy is going to have a PD-1 backbone, but it will be combined with other things to see if we can improve that response rate," said Atkinson. "Even with ipilimumab, we're still only looking at response rate of around 55%. We need to look at other therapies to see if we can improve that, so that all patients are achieving a clinically significant response from immuno-oncology." ■

Long G. KEYNOTE-029: Pembolizumab (pembro) + low-dose ipilimumab (ipi) for advanced melanoma. Presented at the Society for Melanoma Research 2015 Congress; November 18-21, 2015; San Francisco, CA.

Pembrolizumab/Ipilimumab Combo Effective in Advanced Melanoma

By Barbara Boughton

A treatment regimen of pembrolizumab (Keytruda) plus low-dose ipilimumab (Yervoy) was tolerable and effective for patients with advanced melanoma, with an overall response rate (ORR) of 56%, according to results from the phase Ib KEYNOTE-029 clinical trial.

The rate of grade 3/4 adverse events (AEs) with the combination was 36%, with a 54% incidence of immune-mediated AEs. These findings were similar to what has been seen with other trials exploring the combination of PD-1 and CTLA-4 inhibition, said lead investigator Georgina Long, BSc, PhD, MBBS, medical oncologist at the Melanoma Institute, Australia, during the late-breaking abstract session at the 2015 Society for Melanoma Research Congress.

The KEYNOTE-029 trial included 72 patients with advanced melanoma followed for 18 weeks. Patients were treated in the United States, New Zealand, or Australia with pembrolizumab at 2 mg/kg and four doses of ipilimumab at 1 mg/kg. Nine of the patients in the study (12%) had been previously treated, but none had been treated with checkpoint inhibitor therapies, said Long.

Most of the patients in the KEYNOTE-029 study were male with a median age of 60 years, and 86% were PD-L1 positive. Only 28% of the patients had *BRAF* V600 mutations. Eighty five percent of patients had a good ECOG performance status of 0, and only 21% had elevated LDH levels.

Among treatment-naïve patients (n = 63), the ORR was 57%. Among those who had been previously treated, the ORR was 44%. The disease control rate (ORR plus stable disease) was 79%, noted Long. "Only 14 patients in the study, or 19%, were diagnosed with progressive disease," she said.

The complete response rate was 4% across the full study. There were no complete responses in those who had undergone previous therapy, said Long.

Thirty-seven patients (51%) had a partial response to treatment. The partial response rates were 52% and 44% in the treatment-naïve and pretreated groups, respectively. Stable disease occurred after treatment in 24% of patients.

Altogether, 72% of the patients received all 4 ipilimumab doses, and only 31% discontinued both treatments before the end of the trial. Most of the discontinuations were due to progression (19%) or AEs (10%), said Long.

"The majority of patients with ongoing adverse events experience thyroid-related side effects," Long said. Ninety three percent of patients experienced treatment-related AEs, but only 22% were rated as "serious" by the investigators. None led to death. Seventeen percent of AEs led to ipilimumab discontinuation before the end of the trial, and 8% of AEs led patients to discontinue both drugs.

The most frequent AE in the KEYNOTE-029 study was rash, which affected 53% of patients. Thirty-one percent of patients experienced fatigue and 28% were diagnosed with pruritis during treatment. Seventeen percent of patients experienced hypothyroidism as a result of treatment.

Grade 3 or 4 immune-mediated AEs affected 17% of patients. The most frequent immune-mediated AEs were hypothyroidism, hypophysitis, and hyperthyroidism. Other common immune-mediated AEs were pneumonitis and colitis, Long noted.

"Hypophysitis was more common in this trial than we've seen in similar studies, but it's difficult to say why that occurred," Long said. "We were very aware of this side effect during the study, and so that may be one explanation."

Georgina Long, BSc, PhD, MBBS

The KEYNOTE-029 phase Ib trial was a continuation of a smaller clinical study with the same study medications at the same dosages. Enrollment in the earlier study also included patients with renal cell cancer, said Long. Since only 6 patients in the earlier study experienced dose-limiting toxicity, the trial was expanded to 72 patients—all with advanced melanoma.

The investigators will continue to evaluate the efficacy and safety data resulting from the treatment regimen used in the KEYNOTE-029 trial, noted Long. They plan to analyze these outcomes and correlate them with tumor biomarkers, using an expanded data set of 153 patients, she added. ■

Long G. KEYNOTE-029: Pembolizumab (pembro) + low-dose ipilimumab (ipi) for advanced melanoma. Presented at the Society for Melanoma Research 2015 Congress; November 18-21, 2015; San Francisco, CA.

More on *OncLive*.com

Jason J. Luke, MD, from the University of Chicago Medicine, discusses the high response rates generated by the combination of anti–CTLA-4 and anti–PD-1 agents and the potential for combining PD-1 inhibitors with oncolytic viruses or IDO inhibitors. In addition to new combinations, other big-picture questions being asked in the field of melanoma are in regard to patient selection for specific agents, as well as determining additional agents that can be combined in the future.

View more, at http://bit.ly/luke-combo

James Allison Predicts "Cures" With Checkpoint Inhibitor Combinations

By Barbara Boughton

James P. Allison, PhD

The FDA approval of ipilimumab (Yervoy) for melanoma in 2011 ushered in a new era of antibodies that target immune checkpoints. Since this milestone, several combinations and monotherapies have gained rapid approval, with continued expansion on the horizon, according to James P. Allison, PhD, at the 2015 Society for Melanoma Research Congress.

"A few years ago, the best you could hope for in advanced melanoma was to improve survival a little bit, but now we have immunotherapies that provide durable responses that last decades," said Allison, professor and chair of immunology at The University of Texas MD Anderson Cancer Center.

"Immunotherapies are successful because they have specificity, memory, and adaptability," he said. "These agents don't just recognize certain peptides on cancer, but can recognize many different mutations—as well as changes in cancer cells—that contribute to the development and persistence of tumors."

The advent of immune checkpoint inhibition has not only altered treatment paradigms for patients with cancer, but it has also changed the way that researchers think about new therapies. Traditionally, targeted therapies and vaccines have been directed against a single mutation or peptide on the cancer cell; however, with the checkpoint inhibitors there are more factors at play.

"Immunotherapies, such as checkpoint inhibitors, don't target tumor cells, and our research work does not involve using vaccines or cytokines to turn on the immune system," Allison said. "Checkpoint inhibitor therapies work by blocking inhibitory pathways, in order to create an anti-tumor response."

In effect, the checkpoint inhibitors that Allison has researched work to unleash or "take the brake off" the immune system. "This approach was a radical departure, so it was at first difficult for us to be taken seriously," he said.

Allison's research was the first to show that CTLA-4 targeted agents, when combined with a GM-CSF tumor cell vaccine, could eradicate melanoma. "It leads to cure in experiments we've now done in thousands of mice. And the cure rate in these experiments is never less than 85%," Allison said.

The fully human antibody ipilimumab has now been used to treat over 50,000 patients with melanoma and other cancers, including those that affect the prostate, kidney, bladder, ovaries, and lungs. The longest surviving patient treated with ipilimumab remains alive 10 years after undergoing initial therapy for melanoma metastasized to the lungs, Allison noted.

Ipilimumab results in objective responses in several tumor types, and the adverse events that accompany treatment—colitis hepatitis, and hypophysitis—can generally be managed with steroids, said Allison.

After follow-up of over 10,000 patients treated with ipilimumab, researchers now know that the use of this agent can lead to long-term survival in about 22% of cases. "I think we can think about starting to apply the word cure to these patients," Allison said.

Allison's work, which led to the approval of ipilimumab, has also illuminated the mechanisms and efficacy of PD-1 inhibitors. Now, just 4 years after the first checkpoint inhibitor was approved, there are two PD-1 inhibitors indicated for metastatic melanoma.

The next step in advancing cancer treatment with checkpoint inhibitors is to expand research into the use of these agents in combination, according to Allison. When checkpoint inhibitors are combined, their efficacy increases and patient survival improves. "The effect of combining these treatments is not synergistic, but additive," Allison said.

In the phase III CheckMate-067 trial, the combination of nivolumab and ipilimumab demonstrated an objective response rate of 57.6% in patients with advanced melanoma. On top of these responses, 13.1% of patients treated with the combination had stable disease.

"With this treatment, two-thirds of patient had some response. And among those who had an objective response, half had 80% or more tumor shrinkage," Allison said.

Researchers now hope to improve available therapies so that 50% of those treated with combination checkpoint inhibitors experience long-term survival, Allison said. Next, these combination strategies are likely to move into other types of cancer, such as lung cancer and renal cell carcinoma.

"Eventually, we expect that these immunotherapies will be combined with more standard therapies in combating tumors such as renal cell cancers—so that we can increase treatment efficacy and improve outcomes," Allison said. "There are many new opportunities for using checkpoint inhibitor therapies outside of melanoma." ■

Allison J. Immune checkpoint blockade in cancer therapy: New insights, opportunities and prospects for a cure. Presented at the Society for Melanoma Research 2015 Congress; San Francisco, CA; November 18-21, 2015.

QoL Similar With Checkpoint Combo Versus Single Agents in Melanoma

By Barbara Boughton

There were few differences in quality of life (QoL), global health, and symptom burden between patients with melanoma who were treated with nivolumab (Opdivo) plus ipilimumab (Yervoy) or either agent alone, according to a recent analysis of patient-reported outcomes from the phase III CheckMate-067 trial.

After 1 year of follow-up, patients in the nivolumab plus ipilimumab arm of the CheckMate-067 trial experienced no clinically meaningful change in health-related QoL—even though they showed significant improvements in survival. Additionally, patients treated with nivolumab alone or ipilimumab alone showed no significant changes in QoL compared to baseline, said Dirk Schadendorf, MD, during a presentation at the 2015 Society for Melanoma Research Congress.

"The nivolumab plus ipilimumab treatment arm had the highest frequency of adverse events, but these adverse events did not seem to affect patient-reported QoL outcomes," said Schadendorf, director of the department of dermatology, the West German Cancer Center at the University Hospital in Essen, Germany.

In the CheckMate-067 study, 945 patients with advanced melanoma were treated with nivolumab alone, ipilimumab alone, or the combination of nivolumab plus ipilimumab. Results revealed that patients in the combination arm showed improved progression-free survival (PFS). The median PFS with the combination was 11.5 versus 6.9 months with nivolumab alone and 2.9 months with ipilimumab alone.

Adverse events (AEs) were more frequent with the combination treatment, with 55% of patients in nivolumab plus ipilimumab having grade 3/4 AEs versus 16.3% with nivolumab alone and 27.3% with ipilimumab. Additionally, over 29% of patients in the combination arm experienced a treatment-related AE leading to treatment discontinuation.

Despite the higher incidence, AEs in the CheckMate-067 study were short-lived. The median time for resolution of grade 3/4 AEs was 1.7 to 4.2 weeks, Schadendorf said.

To assess patient-reported QoL, researchers used the EORTC QLQ30 cancer specific QoL questionnaire and the EQ-5D scale, which assesses health status and global health. The EQ-5D includes a visual analog scale (VAS) in which patient rate their health status on a scale from 0 to 100, as well as a descriptive system which asks participants to rate 5 dimensions of their health in terms of self-care, mobility, usual activities, pain/discomfort and anxiety/depression.

Schadendorf noted that patient characteristics were well balanced among the treatment arms at baseline, suggesting that it is unlikely that pre-existing patient health outcomes affected the results.

Dirk Schadendorf, MD

Reductions were seen in EORTC scores across all arms (P ≤.01); however, these findings were not deemed to be clinically meaningful (≤10 points change). At week 5, there was reduction of 2.7, 4.3, and 3.1 points for nivolumab alone, nivolumab plus ipilimumab, and ipilimumab alone, respectively. Scores returned to baseline levels by week 25 in the nivolumab alone arm and by week 31 in the combination and ipilimumab alone arms.

The EQ-5D scores improved at week 13 with nivolumab alone (P = .042), which persisted throughout the trial. However, in the ipilimumab containing arms, EQ-5D scores initially worsened before returning to baseline by week 13 for the combination and by week 19 for ipilimumab alone. VAS scores were stable for the nivolumab-containing arms and worsened with ipilimumab until week 23.

"Even among patients who suffered severe toxicities such as colitis, treatment did not appear to have a significant effect on quality of life," Schadendorf said. "Do the results in this study indicate that patients don't care about toxicity when they receive a large survival benefit, or is it that QoL wasn't affected because the toxicities were short-lived?" he asked.

One shortcoming of the analysis was that patients who discontinued treatment were not included in QoL assessment, Schadendorf said. To account for this, data are being analyzed that include patients who progressed or discontinued. Additionally, patients will continue to be followed in the study to assess whether the tumor control benefits observed in CheckMate-067 will affect long-term patient QoL outcomes, he said.

"One possible explanation for our findings in this study could be that the tools we have now—utilized in our analysis—are not very useful for assessing QoL in patients treated with newer immunotherapy agents," Schadendorf said. "Yet these are the only instruments we have that are validated, and it could take years to obtain new and better validated tools." ■

Schadendorf D, Long G, Larkin J, et al. Patient reported outcomes (PROs) from a phase 3 study of Nivolumab (NIVO) alone or combined with Ipilimumab (IPI) versus IPI in patients with advanced melanoma. CheckMate 067. Presented at the Society for Melanoma Research 2015 International Congress; November 18-21, 2015; San Francisco, CA.

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Novel Agents, T-VEC Combos Mark Next Phase of Oncolytic Immunotherapy Era in Melanoma

By Barbara Boughton

Robert Andtbacka, MD

With the FDA approval of the first oncolytic immunotherapy—talimogene laherparepvec (T-VEC; Imlygic)—in October, the stage has been set for increased research into these agents, according to Robert Andtbacka, MD, associate professor in the division of Surgical Oncology at the Utah School of Medicine and a research investigator with the Huntsman Cancer Institute.

Oncolytic immunotherapies, such as T-VEC, are genetically modified viruses or plasmids that can invade tumors and replicate—killing cancer cells and spurring an overall immune response as well, Andtbacka said in a presentation at the 2015 Society for Melanoma Research Congress. In research on patients treated with T-VEC and other oncolytic immunotherapies, melanoma patients showed responses in injected and non-injected tumorous lesions, as well as responses at sites of distant metastases, such as the lung and liver.

"Most of us believe these responses are immune-mediated and not virus-mediated," Andtbacka said. Analyses of lesions treated with oncolytic immunotherapies show that these treatments induce antigen-specific immunity with increased levels of CD4 regulatory T cells, CD8 suppressor T cells, and myeloid-derived suppressive T cells. New phase I/II trials also show that oncolytic immunotherapies may enhance the effect of other immunomodulatory agents, such as the checkpoint inhibitor therapy, ipilimumab, Andtbacka noted.

In the phase III OPTiM clinical trial, which led to the approval of T-VEC, durable responses (≥6 months) and objective overall responses in T-VEC–treated stage IIIB-IV melanoma patients were compared to results after treatment with GM-CSF. In the study, 295 patients were treated with intralesional injections of T-VEC and 141 received subcutaneous injections of GM-CSF.

Results revealed that the durable response rate was 16.3% in T-VEC patients vs. 2.1% in GM-CSF patients. The objective response rate was also superior among T-VEC patients—26.4% compared with 5.7% for GM-CSF.

T-VEC also appeared to prompt a global immune response, since 10.8% of patients treated with the agent had a complete response. Although tissue samples from the study were not analyzed, later studies have shed light on the mechanisms through which oncolytic immunotherapies incite a global immune response.

"Treatments such as T-VEC increase the exposure of tumor cell antigens to the immune system—which explains the complete responses seen in the OPTiM clinical trial," Andtbacka said.

Other oncolytic therapies now being investigated include other viruses, as well as plasmids. The phase II CALM trial of CVA21, an oncolytic therapy that utilizes the Coxsackie virus, has also shown promising results in stage IIIC and IV melanoma patients. Among 54 evaluable patients, 38.6% experienced a complete or partial response or stable disease after 24 weeks of treatment. The 1-year survival was 75.4% with no grade 3/4 events. Among patients with lung and liver lesions, the partial response rate was notable—37.5%, Andtbacka said.

The investigators in the CALM trial analyzed the biology of the tumors injected with CVA21, and found that after just 3 injections, the number of lymphocytes within the tumors had significantly increased. Subsequent biopsies also revealed that the tumors showed increased infiltration of T cells. "As a result, these agents are being investigated in combination with checkpoint inhibitor treatments such as ipilimumab [Yervoy] as a means of improving response and survival," Andtbacka said.

Limited data sets in combination trials of T-VEC with ipilimumab or pembrolizumab [Keytruda]—such as the initial results from the MASTERKEY-265 phase Ib study—indicate that these combined regimens improve tumor response. The improved tumor response rates have also been achieved without undue toxicity, Andtbacka said.

In an effort to understand the systemic immunity conferred by oncolytic agents such as T-VEC and CVA21, investigators initiated the phase I STORM study. In the study, patients with advanced non–small cell lung cancer, bladder cancer, prostate cancer, and melanoma were treated with intravenous CVA21—rather than local injections of the oncolytic immunotherapy agent. CVA21 was well tolerated in the study, and most adverse events were grade 1, Andtbacka said. Although it is too soon to assess efficacy, patient tumor and blood samples did shed light on the local and systemic immune effects of CVA21.

The investigators of the STORM study first documented an increase in viral RNAs within tumors. Their results also showed an increased viral load among prostate cancer and melanoma patients in the study, which may indicate that the genetically modified viruses in the bloodstream were able to recognize, hone in, and kill tumor cells, Andtbacka said.

"Agents such as CVA21 have the potential to induce responses in injected and non-injected lesions and to induce an overall immune response that could affect even metastatic lesions," Andtbacka noted. "Since they can increase T-cell infiltration into tumors, oncolytic immunotherapies could be used as a rescue strategy to reconstitute the tumor microenvironment in patients resistant to checkpoint inhibitor therapies," he added. ■

New Treatments for Novel Targets Next Step in Immuno-Oncology Revolution

By Barbara Boughton

Although PD-1 and CLTA-4 checkpoint inhibitors have grabbed the attention of scientists and oncologists in recent years, a wide variety of novel checkpoint and immune blocker/activator therapies may soon hold promise.

"There's a long and growing list of regulatory and activating immunotherapy targets that may hold promise in cancer treatment, although we have yet to develop their potential in the clinic," said Margaret K. Callahan, MD, PhD, assistant attending medical oncologist in the Department of Medicine at Memorial Sloan Kettering Cancer Center.

Scientists are already developing therapies against these novel immunotherapy targets—including agonist antibodies and checkpoint molecules. Many of these immunotherapies are in clinical development, and some have even shown promise in early phase I studies, Callahan said.

Callahan spoke at a lecture on novel checkpoint and immune blockers/activators and tumor immunology at a satellite symposium presented by the Society for Immunotherapy of Cancer (SITC). The SITC satellite symposium took place before the opening of the 2015 Society for Melanoma Research Congress.

Most novel checkpoints and immune blockers/activators known today target T-cell activation, noted Callahan. Yet they drive an immune response, not just through T-cell recognition, but also when a second costimulatory signal occurs through molecules such as CD28 protein antibody or the GITR/GITRL interaction.

Callahan highlighted a few novel checkpoints and immune blockers/activators in her presentation, including the CD137 molecule (4-1BB ligand). CD137 is a positive regulator of T-cell activation, and at least 1 agent is in development that targets CD137. The agent that has the most promise, urelumab, has shown antitumor activity in preclinical data, but also has significant liver toxicities, according to recent research.

"There are a lot of nuances in how these molecules regulate T cells and how they are expressed. So these agents that target these molecules could be quite different, and their effects can be quite different," Callahan said.

Another promising target for cancer therapies is the CD27 molecule, which is expressed on most T cells. Anti-CD27 therapies have shown promise in small clinical trials and have produced patient responses in phase I studies on Hodgkin lymphoma, as well as disease stability in solid tumors, Callahan said.

Preclinical studies on agents that target the LAG3 molecule—a negative regulatory molecule—have also shown potential for reducing unabated cancer growth in mice. In preclinical studies, the power of anti-LAG3 agents has been increased by pairing them with PD-1 inhibitor therapies. In some of these animal studies, a majority of the mice exposed to cancerous cells and then treated with anti-LAG3 agents plus anti–PD-1 inhibitor therapies, were protected against tumor growth.

Margaret K. Callahan, MD, PhD

"In terms of therapies that can rev up the immune system, PD-1 and CLTA-4 checkpoint inhibitor therapies are just the tip of the iceberg," Callahan said. As the number of agents with cancer treatments increase, however, the numbers of combination immunotherapies will also increase, she cautioned.

"There are dozens, if not hundreds, of combinations of therapies that target novel immunotherapy molecules, which we could try out in the clinic. We need to be thinking about the framework that will surround our work in combining these treatments," Callahan said.

Although the biology of many new and novel immunomodulatory agents provides useful information, how they may act in combination with each other during patient treatment can still be unknown.

Even though the action and efficacy of an individual agent can be understood by researchers, and it makes sense theoretically to combine them, such combinations may still not work together well in the clinic, Callahan noted.

"Even though we may know what the individual toxicities are, it can also be a surprise when we get into the clinic, and find that combination treatments have unacceptable complications or adverse events," she added. ■

More on *OncLive*.com

James Allison, PhD, from the MD Anderson Cancer Center, describes promising data on the use of immunotherapies in melanoma, including the combination of anti–PD-1 and BRAF inhibitors.

View more, at http://bit.ly/allison-immuno

Atezolizumab/Vemurafenib Combo Shows Clinical Activity in BRAF+ Melanoma

By Laura Panjwani @OncEditorLaura

Omid Hamid, MD

The combination of atezolizumab (MPDL3280A) and vemurafenib (Zelboraf) yielded durable responses in patients with previously untreated *BRAF V600*–mutated metastatic melanoma in an ongoing phase Ib study.[1]

Atezolizumab, an investigational PD-L1 inhibitor, and vemurafenib, a *BRAF*-targeted agent, produced an objective response rate (ORR) of 76% (95% CI, 50.1%–93.2%). This included 3 complete responses (CR) and 10 partial responses (PR) among the 17 patients evaluable at the time of data collection.

"The targeted therapy has a great initial response rate and a great palliative benefit, but a not so great long-term durable benefit. The immunotherapy has a low initial response rate, but the ability to have a long-term durability," said Omid Hamid, MD, who presented the phase Ib data at the Society for Melanoma Research 2015 International Congress. "The study is still accruing, but as we've brought the cohorts forward, we are seeing higher response rates and durable responses."

In the multicenter, open-label, dose-escalation study, patients received atezolizumab combined with vemurafenib concurrently (n = 3) or after a run-in period with vemurafenib alone for 56 days (n = 8) or 28 days (n = 6). Atezolizumab was administered intravenously every 3 weeks at 20 mg/kg or 15 mg/kg or 1200 mg fixed. Vemurafenib was given twice daily at 960 mg during the run-in period and at 720 mg during the combination.

ORR in the concurrent cohort was 33%, with 1 complete response. ORR was 75% and 100% with 1 CR each in the 56- and 28-day vemurafenib run-in cohorts, respectively. The median duration of response in the overall study population was 20.9 months and the median progression-free survival (PFS) was 10.9 months. Patients in the study will continue to receive treatment until they no longer experience clinical benefit as assessed by the investigators.

Overall, the combination was well tolerated with no dose-limiting toxicities or atezolizumab-related treatment discontinuations.

In the overall study population, grade 3 adverse events (AEs) related to atezolizumab occurred in 41% of patients and grade 3 AEs related to vemurafenib occurred in 59% of patients.

Sixty-seven percent of the concurrent cohort experienced a grade 3 AE, with lower rates of 38% and 33% experienced by the 56- and 28-day vemurafenib run-in cohorts, respectively. Serious AEs included pyrexia and dehydration, which were manageable. There were no treatment-related grade 4 AEs or deaths.

"What we initially saw were toxicities of elevated liver enzymes and rash, but the regimen became more tolerable when we had a run-in period of vemurafenib, and then brought the anti–PD-L1 in," said Hamid, who is chief of Translational Research and Immunotherapy and director of Melanoma Therapeutics at The Angeles Clinic. "We tried very hard to limit the toxicity."

In November 2015, the FDA approved the combination of vemurafenib and MEK inhibitor cobimetinib (Cotellic) as a treatment for patients with *BRAF*-positive metastatic or unresectable melanoma. Because of this approval, the phase Ib study was amended to include the triplet of vemurafenib, atezolizumab, and cobimetinib.

"We are hoping to continue accrual and show greater benefit with the triplet," said Hamid. "This data is extremely positive regarding our ability to take targeted agents and combine them with immune agents and checkpoint inhibitors. I think this is a very viable regimen to take forward. The idea of moving from single-agent targeted or immunotherapy into combinations and now triplets is very exciting."

The vemurafenib/cobimetinib approval was based on the phase III coBRIM study, which found a median PFS of 12.3 months with the combination versus 7.2 months for vemurafenib alone (HR, 0.56; P <.001). At a 17-month analysis, 65% of patients receiving the combination remained alive versus 50% for vemurafenib. The ORR with the combination was 69.6% compared with 50% for vemurafenib alone.[2]

Toxicities with the triplet combination are not expected to be any less tolerable than the doublet combination has shown thus far, said Hamid.

"There are 2 other similar trials going forward with the triplet combination and, in those trials, we've seen toxicity, but it is not significantly higher and there hasn't been any significant toxicity that isn't manageable," said Hamid. ■

Nominations are **now** open online for the 2016 Awards. Visit **Giants. OncLive.com** to nominate a *Giant of Cancer Care.*

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Researchers Seek to Improve Responses With Checkpoint Inhibitors

By Barbara Boughton

Antoni Ribas, MD, PhD

Predictive genetic signatures and novel combination strategies may be the key to improving the often dramatic responses seen with immune checkpoint inhibitors, according to Antoni Ribas, MD, PhD, during a satellite symposium presented by the Society for Immunotherapy of Cancer (SITC) that took place before the opening of the 2015 Society for Melanoma Research Congress.

"It's really remarkable that patients with late-stage melanoma, for instance, would get notable improvements in overall survival from treatments such as nivolumab. But these responders are still in the minority," said Ribas, professor of Medicine, Surgery and Molecular and Medical Pharmacology at the Jonsson Comprehensive cancer Center at the University of California, Los Angeles. "Our job now is to select patients who are poised to respond to PD-1/PD-L1 blockade therapies."

Ribas noted that recent studies have attempted to increase the efficacy of PD-1/PD-L1 blockade by combining treatments. Recent clinical trials have shown improved progression-free survival (PFS) in melanoma with combinations of CTLA-4 and PD-1 agents, but the price has been an increased incidence of serious adverse events, he noted.

> "When we perform the initial decision-making in the use of checkpoint inhibitor therapies in patients, we should be taking biopsies to find out if there are T-cells in the tumor that could be turned off by PD-1/PD-L1 expression,"
>
> –Antoni Ribas, MD, PhD

In the CheckMate-067 trial, for example, patients with advanced melanoma treated with nivolumab plus ipilimumab had a median PFS of 11.5 months versus 6.9 months with nivolumab alone and 2.9 months with ipilimumab alone.

Yet, more patients who underwent the combination therapy suffered serious grade 3/4 adverse events. Grade 3/4 adverse events affected 55% of patients in the combination arm of CheckMate-067, as compared with just 16.3% of those who were administered nivolumab alone and 27.3% of patients who underwent ipilimumab therapy alone.[2]

In a trial published in *The New England Journal of Medicine* (NEJM) in 2011, patients with previously untreated metastatic melanoma also derived survival benefits from the combination treatment of ipilimumab plus the chemotherapy agent dacarbazine.[3]

More recent clinical trials have also highlighted reduced mortality in advanced melanoma with other checkpoint inhibitor therapies. In a clinical trial published in *NEJM* in January 2015, patients with previously untreated melanoma without *BRAF* mutations treated with nivolumab had less risk of mortality than those who underwent treatment with dacarbazine (HR, 0.42).[4]

"There are some patients in these clinical trials who are benefiting from targeting single checkpoints. And by using single checkpoint inhibitor therapies we can also reduce serious adverse events," Ribas said. Yet increasing the number of patients who can benefit from single checkpoint inhibitor therapy requires understanding the biology of tumor response to these treatments, he added.

In patients who don't respond to checkpoint inhibitor therapies, tumors may be able to protect themselves from T-cell infiltration through genetic mutations that trigger an adaptive PD-1/PD-L1 expression, according to recent research by Ribas and others. In other non-responder patients treated with checkpoint inhibitor therapies, T-cells may increase in the patient's bloodstream, but they don't make it into the tumor.

Biopsies of tumors taken before treatment with checkpoint inhibitors could identify genetic signatures that could set off an adaptive PD-1/PD-L1 response, said Ribas. Treatment could then be targeted to those likely to respond to single molecule checkpoint inhibitor therapy. Other methods of improving response to checkpoint inhibitor therapies could include increasing the T-cell infiltration of tumors through immune-activating antibodies, oncolytic viruses, macrophage inhibitors or targeted therapies, Ribas said.

"When we perform the initial decision-making in the use of checkpoint inhibitor therapies in patients, we should be taking biopsies to find out if there are T-cells in the tumor that could be turned off by PD-1/PD-L1 expression," Ribas said. Biopsies after initial treatment can also reveal if there are no T-cells in the tumor, although they may be present elsewhere in the patient's body.

"The idea is to use the right treatment for the right patient by understanding the biology of the tumor and its environment," Ribas said. ■

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Jason Luke on Significance of Biomarker Development for Immunotherapy in Melanoma

By Laura Panjwani @OncEditorLaura

The combination of nivolumab (Opdivo) and ipilimumab (Yervoy) comes with additional toxicity and an increased price tag, warranting its careful use until predictive biomarkers are uncovered, says Jason Luke, MD, assistant professor of Medicine at the University of Chicago Medicine.

"Not all patients respond to these treatments. There are additional toxicities with the combinations, and there are also cost issues because of how catastrophically expensive these drugs are," said Luke. "We really need to know which patients are most likely to respond and which aren't."

At a median follow-up of 9 months, the phase III CheckMate-067 trial found that median progression-free survival (PFS) was 11.5 months with the combination of nivolumab and ipilimumab, 6.9 months for nivolumab monotherapy, and 2.9 months for single-agent ipilimumab. The combination reduced the risk of progression by 58% versus ipilimumab (HR, 0.42; *P* <.0001).

All-grade adverse events (AEs) were 95.5% for the combination, 82.1% for nivolumab, and 86.2% for ipilimumab. Rates of treatment-related discontinuations with the combination and single-agent nivolumab and ipilimumab arms were 36.4%, 7.7%, and 14.8%, respectively.

The FDA granted an accelerated approval to the combination of nivolumab and ipilimumab as a treatment for patients with unresectable or metastatic melanoma, regardless of *BRAF* status, based on findings from the phase II CheckMate-069 study and the phase III CheckMate-067 trial.

To better understand which patients will benefit from nivolumab and ipilimumab as well as other immunotherapy combinations, biomarker development is critical, says Luke.

In an interview with *OncLive*, Luke discusses potential new methods for determining prognostic markers and the challenges of balancing toxicity with efficacy in designing combination regimens.

OncLive: Are there specific approaches to identifying immunotherapy biomarkers that seem promising?

Luke: Several recently presented studies examined the impact of tumor-infiltrating lymphocytes (TILs) as a prognostic marker for immunotherapy, as well as PD-L1. A lot of people are talking about that, and I think it is very important.

Several years ago, our group published a paper showing that the trafficking of CD8-positive T cells in the tumor generates all of the inflammation. We are very interested in a broader look at the tumor microenvironment, and we are doing that through gene expression profiling. Instead of looking at just one gene or one set of cells, we would rather examine the full transcriptome of the tumor and determine which genes are up or down. This provides a much bigger picture of whether immunotherapy is likely to work. We find that those patients who have a T-cell inflamed tumor microenvironment to be much more responsive to immunotherapy. On the flip side, if a patient does not have a T-cell¬–inflamed tumor, immunotherapy basically does not work. This is a better model, but it is just a bit more complicated and has not become a clinical grade diagnostic but, over time, perhaps it could.

Jason Luke, MD

Could this approach help determine which patients may benefit from immunotherapy combinations, such as ipilimumab and nivolumab?

We absolutely think so. If we had a useful clinical grade test, perhaps those patients who are the most highly T-cell inflamed in their tumor might be candidates for an anti–PD-1 antibody alone, as opposed to those who have less inflammation who may perhaps need the combination upfront of CTLA-4 and PD-1 blockades together. As we go forward into the next generation of combination strategies, we are going to be able to better piece out how much push we need to give the patient.

What are the biggest challenges with the use of immunotherapy combinations?

In the frontline setting, the combination of ipilimumab and nivolumab is highly efficacious with more than a 50% response rate. The issue is that there is more than a 50% grade III or IV adverse event rate. In my practice, it really becomes essential to understand who is going to respond to anti–PD-1 alone so we can avoid giving patients the toxicity associated with the combination if they do not need it. We really don't know that yet. The future will likely be trying to look at sequencing of these agents. Could we administer the combination as a second-line therapy? Are there certain patients who will benefit enough? Those will be the future questions.

What drugs are on the horizon that could potentially be used in combination with PD-L1 antibodies?

The combination of CTLA-4 and PD-L1 antibodies has generated a very high response rate and that has been the most recent approval. In clinical trials, however, there are other combinations being investigated, including PD-1 antibodies with oncolytic viruses or IDO inhibitors. Both of these approaches look very promising with much less toxicity. We really don't know which will be the best yet, but there are underpinning rationales for each that suggests that we should pursue them.

What does the future hold for immunotherapy in melanoma?

The future is going to be focused on combination immunotherapy strategies, either with small-molecule inhibitors or other immunotherapeutic agents that, perhaps, we haven't yet seen in the clinic. Despite making so much progress in the past few years in immunotherapy, we have barely scratched the surface on what we can do. Resting our laurels and accepting that the drugs we have are the best we can do is going to do a disservice to our patients. We really need to push forward with these clinical trials to find optimal efficacy with minimal toxicity, and we are not there yet. ■

Novel Pembrolizumab Combos Show Promising Responses in Melanoma

By Silas Inman @silasinman

Roger Dansey, MD

Two separate early phase clinical trials exploring pembrolizumab (Keytruda)-containing immunotherapy combinations have shown objective response rates (ORRs) of over 50% in patients with advanced melanoma, according to findings presented during the late-breaking abstract session at the 2015 Society for Melanoma Research (SMR) Congress.

In a phase I/II trial, the combination of the PD-1 inhibitor pembrolizumab and the IDO-1 inhibitor epacadostat showed an ORR of 53%. In a phase Ib trial, the ORR with pembrolizumab and the oncolytic immunotherapy talimogene laherparepvec (T-VEC; Imlygic) was 56.3%.

"The combination data presented at SMR, including Keytruda combined with epacadostat or Imlygic, may further our goal of improving outcomes without substantial increased toxicity," Roger Dansey, MD, senior vice president and therapeutic area head, oncology late-stage development, Merck Research Laboratories, the company developing pembrolizumab, said in a statement.

In the first ongoing study, labeled KEYNOTE-037, 60 patients with various advanced cancers received the combination of pembrolizumab and epacadostat. At the SMR analysis, data were available from 19 patients with advanced melanoma. Patients received pembrolizumab at 2 mg/kg or a fixed 200 mg dose every 3 weeks. Epacadostat was administered at four doses twice daily (20, 50, 100, or 300 mg).

In addition to responses in the trial, which included 3 complete responses, 21% of patients had stable disease (SD). The disease control rate (ORR plus SD) with the combination was 74%. Data for other efficacy endpoints were not yet available at the time of the analysis.

Treatment-related adverse events (AEs) were consistent with previous reports for pembrolizumab. Across all tumor types, grade 3 AEs were experienced by 15% of patients. The most common grade 3 AEs with the combination were rash (8%), arthralgia (2%), AST increased (2%), mucosal inflammation (2%), and nervous system disorder (2%).

Altogether, 3 patients discontinued treatment due to AEs (grade 3 arthralgia, AST increase, and grade 2 nervous system disorder). There were not any grade 4 treatment-related AEs or deaths with the combination.

Based on earlier assessments of the study, Incyte, which develops epacadostat, and Merck launched a phase III trial to explore the combination as a frontline therapy for patients with advanced melanoma. The study is expected to begin in the first half of 2016.

"The initiation of this large phase III study with Incyte in the first-line advanced melanoma treatment setting is an important addition to our robust immunotherapy clinical development program for Keytruda," said Dansey.

In the second ongoing phase Ib study, efficacy data were analyzed from 16 evaluable patients with previously untreated, unresected advanced melanoma. Pembrolizumab was administered at 200 mg every 2 weeks while T-VEC was given at up to 4 mL of 10^6 PFU/mL for the first dose followed by 10^8 PFU/mL every two weeks.

On top of the responses, which consisted of partial responses and 2 complete responses, 12.5% of patients also had SD. The disease control rate was 68.8% (95% CI, 11-58.7). Other efficacy endpoints were not yet mature at the time of the analysis.

Grade 1/2 AEs occurred in all 21 patients who were evaluable for the safety analysis. The most frequent all-grade AEs were fatigue (52%), pyrexia (48%), chills (43%), rash (38%), headache (33%), and nausea (33%). Grade 3 AEs, regardless of cause, included headache (5%) and diarrhea (5%). No dose-limiting toxicities were reported.

"T-VEC plus pembrolizumab was well tolerated, and we observed no dose-limiting toxicity," investigator Georgina V. Long, BSc, PhD, MBBS, associate professor at the University of Sydney in Australia, said when an initial analysis of safety was presented at the European Cancer Congress. "Treatment-related adverse events were mostly grade 1/2. The combination of T-VEC and pembrolizumab is feasible and warrants further investigation."

Both T-VEC and pembrolizumab are approved as single-agents for patients with melanoma. T-VEC is approved for the local treatment of unresectable cutaneous, subcutaneous, and nodal lesions in patients with melanoma recurrent after initial surgery. Pembrolizumab is approved for patients with advanced or unresectable melanoma following progression on prior therapies.

Based on the findings from the phase Ib study, Merck and Amgen, the developer of T-VEC, are planning a phase III study for the combination in patients with regionally or distantly metastatic melanoma. Additionally, the companies announced plans to explore the combination in a phase I open-label trial for patients with recurrent or metastatic squamous cell carcinoma of the head and neck.

"We believe that talimogene laherparepvec has potential in several cancer types based on its proposed mechanism of action to initiate tumor antigen release and presentation, important steps in activating a systemic anti-tumor immune response," Sean E. Harper, MD, executive vice president of Research and Development at Amgen, said when the collaboration was announced. "We will discuss the design of the phase III melanoma trial with global regulators and look forward to collaborating with Merck on this study." ■

More on *OncLive*.com

Tara C. Gangadhar, MD, from the Hospital of the University of Pennsylvania, discuses preliminary results from an early phase study exploring epacadostat in combination with pembrolizumab.

View more, at http://bit.ly/tara-combo

Vemurafenib/Cobimetinib Shows 30% OS Benefit in BRAF-Mutant Melanoma

By Silas Inman @silasinman

Treatment with the combination of vemurafenib (Zelboraf) and cobimetinib (Cotellic) improved overall survival (OS) by 4.9 months compared with vemurafenib alone for patients with *BRAF* mutation-positive advanced melanoma, according to findings from the phase III coBRIM study presented at the 2015 Society for Melanoma Research (SMR) Congress.

In the updated findings, the median OS was 22.3 months with the combination compared with 17.4 months with vemurafenib alone, representing a 30% reduction in the risk of death (HR, 0.70; 95% CI, 0.55-0.90; *P* = .005). The 1- and 2-year OS rates with the combination were 74.5% and 48.3%, respectively.

"With about half of the people taking Cotellic and Zelboraf alive after two years, these data underscore the progress being made in cancer research toward better patient outcomes," Sandra Horning, MD, chief medical officer and head of Global Product Development at Genentech, the company developing the combination, said in a statement. "Five years ago, the survival rate for BRAF mutation-positive advanced melanoma was measured in months, and now we are measuring it in years."

In the phase III coBRIM study, the MEK inhibitor cobimetinib plus the BRAF inhibitor vemurafenib was compared with single-agent vemurafenib in previously untreated patients with *BRAF* V600E/K mutation-positive unresectable locally advanced or metastatic melanoma. Four hundred and ninety-five patients were randomized to continuous vemurafenib at 960 mg twice daily plus cobimetinib at 60 mg once daily on days 1-21 of a 28-day cycle (n = 247) or placebo (n = 248).

Patient demographics were well balanced across the two arms for age, ECOG performance status, geographic region, and disease stage. More than half of patients had stage IV, M1c melanoma. The primary endpoint for the study was progression-free survival (PFS), with secondary endpoints focused on OS, objective response rate (ORR), and duration of response.

According to earlier assessments, the median PFS with the combination of vemurafenib and cobimetinib was 12.3 versus 7.2 months for vemurafenib alone (HR, 0.56; *P* <.001). The ORR with the combination was 69.6% compared with 50% for vemurafenib alone. The complete response rate in the combination arm was 15.8% versus 10.5% with vemurafenib and placebo (*P* <.001). The median duration of response was 12.98 months versus 9.23 months, with cobimetinib and placebo, respectively.

The most frequently reported adverse events (AEs) of all grades reported in the cobimetinib arm versus the control arm included diarrhea (57% vs 28%), nausea (39% vs 24%), photosensitivity (28% vs 16%), increased ALT (24% vs 18%), increased AST (22% vs 13%), increased CPK (30% vs 3%), vomiting (21% vs 12%), and serous retinopathy (20% vs <1%).

Sandra Horning, MD

Some AEs occurred at lower rates in the combination group, including hair loss (14% vs 29%), hyperkeratosis (10% vs 29%), joint pain (33% vs 40%), cutaneous squamous cell carcinomas (3% vs 11%), and keratoacanthomas (<1% vs 8%). Treatment-related discontinuation rates in the combination and control groups were similar at 13% and 12%, respectively. There were six deaths related to AEs in the cobimetinib arm and three in the control arm.

"The overall survival benefit for Cotellic and vemurafenib observed in the coBRIM trial further underscores the positive impact that the combination of these two therapies can have on the treatment of advanced BRAF V600 mutation-positive melanoma," Michael M. Morrissey, PhD, president and chief executive officer of Exelixis, the developer of cobimetinib, said in a statement.

On November 10, 2015, the FDA approved the combination of vemurafenib and cobimetinib as a treatment for patients with BRAF-positive metastatic or unresectable melanoma, based on an extension in progression-free survival in the phase III coBRIM study. Adding to this, on November 25, 2015, the combination was also approved by the European Commission. The final OS data from the coBRIM study are being submitted to both regulatory agencies for potential label updates for the combination.

Clinical trials continue to assess vemurafenib plus cobimetinib for patients with melanoma, including a phase II study of the combination as a neoadjuvant therapy for patients with melanoma (NCT02036086). Additionally, a phase Ib study is exploring the combination with the PD-L1 inhibitor atezolizumab for BRAF-positive metastatic melanoma (NCT01656642). ■

More on *OncLive*.com

Jeffrey S. Weber, MD, PhD, from the NYU Langone Medical Center, discusses deciding between the combination of dabrafenib plus trametinib and vemurafenib plus cobimetinib as treatments for patients with BRAF-mutant melanoma.

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