Melanoma: 2021 ASCO Annual Meeting Highlights for the Advanced Practitioner

With coverage from *The ASCO Post*, **Lisa Kottschade, APRN, MSN, CNP**, of Mayo Clinic, reviews data on immune therapy after surgery, the combination of the anti–LAG-3 antibody relatlimab and nivolumab, and a 6.5-year update of combination nivolumab and ipilimumab.

Abstract 9501

High-Dose Interferon or Ipilimumab vs Pembrolizumab for High-Risk Resected Melanoma

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/195948/abstract to read the full abstract and view author disclosures.

Patients with high-risk melanoma who had a course of pembrolizumab had longer recurrence-free survival than patients who received either ipilimumab or high-dose interferon after surgery. These findings of a large SWOG Cancer Research Network clinical trial, S1404, were presented by Grossmann et al during the 2021 ASCO Annual Meeting (Abstract 9501).

Researchers also measured overall survival and found no statistically significant difference in overall survival rates between the two groups of patients at 3.5 years after the last patient enrolled to the trial. They did find, however, that patients taking pembrolizumab had fewer serious side effects than those treated with either high-dose interferon or ipilimumab.

Kenneth F. Grossmann, MD, PhD, of the Huntsman Cancer Institute at the University of Utah Medical Center and Chair of SWOG's Melanoma Committee, was the lead investigator on the study. He commented, "The recurrence-free survival advantage and improved safety profile over the previous standard of care make [pembrolizumab] a continued standard for treating patients with high-risk resected melanoma."

Noting that overall survival measures were not significantly different between the two arms, Dr. Grossmann said, "The overall survival analysis was performed at a predefined time point with only approximately 50% of events needed for a fully powered analysis. We suspect that effective use of PD-1 blockade and other improved therapies for stage IV disease improved outcomes of relapsing patients on the control arm such that overall survival was not different between the two groups."

S1404 Details

The study randomly assigned 1,345 adult patients with stage III or IV melanoma who had undergone surgery to remove their tumors to the pembrolizumab arm or the control arm. Those on the control arm decided with their physicians wheth-

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er to follow a course of high-dose interferon or a course of ipilimumab, both of which are approved by the U.S. Food and Drug Administration for use in treating these patients.

Pembrolizumab, a PD-1 inhibitor, was chosen for the trial because of its comparatively low toxicity and its activity in metastatic disease. Another trial has also since shown a recurrence-free survival benefit for the drug when compared to a placebo. High-dose interferon and ipilimumab, which were standard-of-care treatments for these patients at the start of the study, often come with serious side effects.

As the S1404 researchers had expected, toxicity was lower in patients on the pembrolizumab arm. Among patients taking high-dose interferon, roughly 72% had grade 3 or worse adverse events. The rate of such side effects was about 58% for those on ipilimumab, but it was only about 32% for patients on pembrolizumab.

Dr. Grossmann added that further data to come from this trial will include studies to evaluate pretreatment predictors of whether patients are likely to benefit from treatment and quality-of-life studies to better understand the impact of relapse in patients with high-risk resectable melanoma.

The Advanced Practitioner Perspective

Lisa Kottschade, APRN, MSN, CNP
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The findings of trial S1404 continue to demonstrate the role of immune checkpoint inhibitor (ICI) therapy in resected high-risk melanoma. This evolution of immunotherapy in the treatment of melanoma appears to mirror the progression of agents noted in the metastatic setting and offers patients the opportunity for extended relapse-free survival (RFS).

Prior to the introduction of ICI therapy into the adjuvant setting, patients were relegated to the use of interferon or observation. While interferon improved RFS, in trial after trial, it did not demonstrate significant improvement in overall survival (OS) and was associated with high rates of toxicity. This left oncology providers with few options for their patients, and patients had unacceptable levels of side effects for questionable long-term benefit. With the approval of ICI agents for adjuvant treatment, there are now options to offer patients in this setting.

It is important for oncology advanced practitioners to be aware that, while patients with resected stage IV disease were included in this study, none of the agents utilized (pembrolizumab [Keytruda], ipilimumab [Yervoy], or interferon) are currently approved for resected stage IV disease. Additionally, the lack of a statistically significant difference in OS should be interpreted with caution and doesn't necessarily mean a lack of efficacy in this population. Given the OS benefit of ICIs in the metastatic setting, this may muddy the waters in this patient population, as those who recurred likely went on additional therapy with ICI agents or targeted agents in the metastatic setting, both of which have demonstrated OS benefit.

Disclosure: Ms. Kottschade has served on advisory boards for Bristol Myers Squibb, Immunocore, and Novartis.

Abstract 9503

Targeting LAG-3 and PD-1 With Relatlimab and Nivolumab: A New Option Under Study in Advanced Melanoma

By Caroline Helwick

Visit https://meetinglibrary.asco.org/record/201596/abstract to read the full abstract and view author disclosures.

Immune checkpoint inhibition has been established as an effective treatment for patients with metastatic melanoma. A novel immunotherapeutic combination—this one targeting the LAG-3 (lymphocyte-activation gene 3) and PD-1 immune checkpoints—delayed time to disease progression significantly more than nivolumab (anti–PD-1) alone in a study presented at the 2021 ASCO Annual Meeting.[1]

Initial findings from the global, randomized, registrational phase III RELATIVITY-047 trial[1] were presented at a press briefing prior to the meeting by Evan J. Lipson, MD, Associate Professor of Oncology at the Johns Hopkins Kimmel Cancer Center and Bloomberg-Kimmel Institute for Cancer Immunotherapy in Baltimore.

"Patients who received relatlimab plus nivolumab had a median progression-free survival of 10.1 months—more than double that of patients who received nivolumab alone (4.6 months). This significant improvement meant the study met its primary endpoint, with a hazard ratio of 0.75 and a *P* value of .0055," Dr. Lipson said.

"The progression-free survival benefit appeared relatively early in the course of therapy. The curves separated at 12 weeks, which was when the first on-treatment imaging was performed.

"This is the first phase III study to confirm that targeting the LAG-3 immune checkpoint is a beneficial therapeutic strategy for patients with cancer. Our findings establish the LAG-3 pathway as the third immune checkpoint pathway in history, after CTLA-4 and PD-1, for which blockade has clinical benefit," he added.

Mechanism of Action

LAG-3 is a component of an immune checkpoint pathway that inhibits T-cell activity. Relatlimab, a human IgG4 LAG-3–blocking antibody, restores the effector function of exhausted T cells, "reinvigorating T cells to attack cancer," Dr. Lipson explained.

Relatlimab and the anti–PD-1 agent nivolumab modulate potentially synergistic immune checkpoint pathways and can enhance antitumor immune responses. The two-drug combination has a generally manageable safety profile and can trigger durable tumor regressions in patients with melanoma whose disease has progressed after anti–PD-1 monotherapy, Dr. Lipson said.

About RELATIVITY-047

RELATIVITY-047 is a global, double-blind, randomized, phase III study evaluating this novel immunotherapy approach as a fixed-dose combination in 714 patients with previously untreated, unresectable or metastatic melanoma. Its objective, according to Dr. Lipson, was to test a novel immune checkpoint inhibitor combination "that provides further benefit with manageable risk."

Patients were randomly assigned 1:1 to receive every-4-week intravenous administration of relatlimab at 160 mg plus nivolumab at 480 mg or nivolumab at 480 mg, stratified by LAG-3 expression, PD-L1 expression, *BRAF* mutation status, and disease stage. Median follow-up was 13.2 months.

The study met its primary endpoint, with significantly better median progression-free survival achieved with the combination vs nivolumab alone: 10.12 vs 4.6 months (hazard ratio [HR] = 0.75; $P = .0055$). Progression-free survival rates at 12 months were 47.7% for patients receiving combination therapy vs 36% for nivolumab monotherapy. The combination was favored across key prespecified subgroups.

Dr. Lipson said the median progression-free survival of single-agent nivolumab observed in this study was "in the range" seen in historical studies (ie, 4–7 months). He cautioned against comparing progression-free survival across trials, which often differs in terms of the patient population, timing of scans, and blinded central review vs investigator assessment.

Safety Profile

"In general, treatment-related adverse events associated with relatlimab plus nivolumab were manageable and reflected the safety profile we typically see with immune checkpoint inhibitors. Although the incidence of grade 3 or 4 treatment-related adverse events was higher with the combination (18.9% vs 9.7%), they occurred at a lower rate than we observe with other immunotherapy combinations," Dr. Lipson said.

Treatment-related adverse events led to treatment discontinuation in 14.6% and 6.7% of patients receiving combination and monotherapy, respectively. There were three treatment-related deaths with the combination (hemophagocytic lymphohistiocytosis, acute edema of the lung, and pneumonitis) and two with nivolumab monotherapy (sepsis/myocarditis and worsening pneumonia).

Dr. Lipson called relatlimab plus nivolumab "a potential novel treatment option for patients with previously untreated unresectable or metastatic

melanoma." He noted that forthcoming trial data, including overall response and overall survival rates, will further inform clinical decision-making about the use of this combination in the context of other treatment options, including anti–PD-1 alone or with ipilimumab.

"The first-line treatment choice is a case-by-case decision. We are fortunate in melanoma to have an ever-expanding list of effective standard-of-care therapy options, and I think, at some point, this regimen will be added to that list," he commented.

Reference

1. Lipson EJ, Tawbi HAH, Schadendorf K, et al: Relatlimab plus nivolumab versus nivolumab in first-line advanced melanoma: Primary phase III results from RELATIVITY-047 (CA224-047). 2021 ASCO Annual Meeting. Abstract 9503. Presented June 6, 2021.

The Advanced Practitioner Perspective

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The phase III RELATIVITY-047 study results are an exciting step forward, with prospects of a third immune checkpoint inhibitor (LAG-3) in the treatment of metastatic melanoma. Two important observations were noted in this study. First, there was a significant improvement in median progression-free survival of the combination of relatlimab plus nivolumab in comparison to nivolumab alone. Second, high-grade toxicity (grade 3 or 4) of the combination of relatlimab and nivolumab (18.9%) appears to be less than traditionally seen with anti–CTLA-4/PD-1 combination therapy (58%; Larkin et al., 2019).

We eagerly await further findings, including overall survival and overall response rate, as data continues to be analyzed in this trial. While this combination is not commercially available to patients at this time, oncology advanced practitioners should be aware of this encouraging early phase III data and continue to monitor study updates.

Disclosure: Ms. Kottschade has served on advisory boards for Bristol Myers Squibb, Immunocore, and Novartis.

Abstract 9506

Extended Follow-up of Nivolumab/Ipilimumab for Metastatic Melanoma

By The ASCO Post Staff

Visit https://meetinglibrary.asco.org/record/195983/abstract to read the full abstract and view author disclosures.

In the longest follow-up results from a clinical trial of combination immunotherapy for metastatic melanoma, investigators report that nearly half the patients who received the drugs nivolumab and ipilimumab were alive at a median of 6.5 years after treatment. These long-term results from the CheckMate 067 clinical trial, presented at the 2021 ASCO Annual Meeting by Jedd D. Wolchok, MD, PhD, FASCO, represent a new landmark in survival rates for patients with melanoma treated with immune checkpoint inhibitors (Abstract 9506).

CheckMate 067 Details

The clinical trial compared nivolumab and ipilimumab, alone and in combination, in patients with previously untreated stage III or IV melanoma that could not be removed surgically. Both drugs target proteins on T cells known as immune checkpoints, which some cancer cells exploit to spare themselves from an attack by the T cells. By interfering with these proteins, the drugs essentially release the brakes on such an attack. Nivolumab targets the PD-1 checkpoint protein, and ipilimumab targets the CTLA-4 checkpoint protein.

In the trial, patients were randomly assigned to receive nivolumab and ipilimumab in combination, nivolumab plus a placebo, or ipilimumab alone. Six and a half years after treatment, participants who received the nivolumab/ipilimumab combination were more likely to be alive and to have had no advance of their disease than those who received either drug alone. At the 6.5-year mark, 49% of participants treated with the combination therapy were alive, compared to 42% of those treated with nivolumab alone and 23% of

those treated with ipilimumab alone. Progression-free survival was 34% for the combination therapy group, 29% for the nivolumab-only group, and 7% for the ipilimumab-only group.

Median survival followed the same pattern. For patients treated with nivolumab and ipilimumab, median survival was 72.1 months, or just over 6 years. For those treated with just nivolumab, median survival was 36.9 months, and for those treated with just ipilimumab, it was 19.9 months.

The study authors concluded, "This 6.5-year analysis represents the longest follow-up from a phase III melanoma trial in the modern checkpoint inhibitor combination therapy and targeted therapy era. The results show durable improved outcomes with nivolumab/ipilimumab and nivolumab vs ipilimumab in patients with advanced melanoma. We observed improvement in overall survival, progression-free survival, and objective response rate with nivolumab/ipilimumab over nivolumab alone."

The Advanced Practitioner Perspective

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The CheckMate 067 trial was a landmark trial as the first phase III dual immune checkpoint inhibitor therapy trial, and led to FDA approval of the combination of ipilimumab and nivolumab in the front-line setting for metastatic melanoma. After 6.5 years of follow-up, responses in the combination group continued to be maintained and appeared to translate to prolonged overall survival (OS) as well. While the combination arm and the nivolumab alone arms were not powered to be compared head to head, there was also improved progression-free survival and OS compared to the ipilimumab alone arm. However, with this increased efficacy and survival in the combination arm, toxicity was also significantly increased.

Advanced practitioners who are considering this regimen for their patients need to take this toxicity into consideration when exploring treatment possibilities for their patients. Additionally, it should be noted that for patients in whom the combination arm is not appropriate, single-agent nivolumab could also be considered, given the improved efficacy and survival over that of ipilimumab alone. Advanced practitioners can be instrumental in having thoughtful risk/benefit discussions with their patients prior to initiation of therapy for metastatic melanoma.

Disclosure: Ms. Kottschade has served on advisory boards for Bristol Myers Squibb, Immunocore, and Novartis.