MELANOMA IN FOCUS

Current Developments in Melanoma

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Nivolumab and Relatlimab as Frontline Therapy in Advanced Melanoma

Nikhil I. Khushalani, MD
Senior Member and Vice Chair, Department of Cutaneous Oncology
Assistant Center Director for Clinical Research Review and Partnerships
H. Lee Moffitt Cancer Center and Research Institute
Tampa, Florida

H&O What makes the combination of nivolumab and relatlimab a good choice in advanced melanoma?

NK We already have a wealth of data on monotherapy with the programmed death 1 (PD-1) inhibitors nivolumab (Opdivo, Bristol Myers Squibb) and pembrolizumab (Keytruda, Merck). We also have extensive data regarding combination checkpoint inhibition with nivolumab plus the anti–cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) agent ipilimumab (Yervoy, Bristol Myers Squibb). The newest combination consists of the PD-1 inhibitor nivolumab and the lymphocyte activation gene 3 (LAG-3) inhibitor relatlimab-rmbw, administered together in one intravenous injection (Opdualag, Bristol Myers Squibb).

The main rationale for combining PD-1 inhibition with LAG-3 inhibition is that both PD-1 and LAG-3 contribute to a tumor microenvironment that leads to T-cell exhaustion and allows tumor growth. Targeting these immune checkpoints can lead to rejuvenation of the T cells in the immune microenvironment. Preclinical studies demonstrated synergy between PD-1 inhibition and LAG-3 inhibition, which led to further research with this combination.

H&O What is the most important study to examine this combination for first-line treatment of patients with advanced melanoma?

NK The pivotal study for nivolumab plus relatlimab is RELATIVITY-047. This large phase 2/3 trial enrolled patients aged 12 or older with unresectable or metastatic melanoma. Although patients could have received prior adjuvant or neoadjuvant therapy, they were not eligible if they had received treatment for unresectable or metastatic disease. The fact that patients were as young as 12 years was important because most trials of immune checkpoint inhibitors have enrolled only patients aged 18 years or older. After the phase 2 portion of the trial met predefined efficacy criteria, the trial proceeded to phase 3, in which a total of 714 patients were randomly assigned in a 1:1 ratio to either nivolumab (480 mg) plus relatlimab (160 mg) or nivolumab alone (480 mg). The primary endpoint was progression-free survival (PFS) as determined by blinded independent central review, and the secondary endpoints were overall survival (OS) and objective response rate (ORR). The study employed a statistical hierarchical design in which OS was examined only if PFS was statistically significant and ORR was examined only if OS was statistically significant.

H&O Could you discuss the results of this study?

NK When interim results were presented by Dr Evan Lipson at the 2021 annual meeting of the American Society of Clinical Oncology (ASCO), the median PFS at a median follow-up of 13.2 months was significantly longer in the combination arm than in the nivolumab-alone arm, at 10.1 vs 4.3 months, respectively (hazard ratio [HR], 0.75; 95% CI, 0.6-0.9; *P*=.0055). In the most-recent results,

which were presented by Dr Georgina Long at the March 2022 ASCO monthly plenary series, the median PFS at a median follow-up of 19.3 months was 10.2 months with combination therapy vs 4.6 months with nivolumab alone (HR, 0.78; 95% CI, 0.6-0.9). So what we are seeing is a 22% improvement in PFS with the addition of relatlimab to nivolumab.

Dr Long also presented the first data on OS, showing that the median OS was not reached with the combination vs 34.1 months with nivolumab alone at a median of 19.3 months (HR, 0.80; 95% CI, 0.6-1.0; *P*=.0593). The OS rates were 77.0% vs 71.6% at 12 months and 63.7% vs 58.3% at 24 months, respectively; neither of these differences was statistically significant. An estimate of OS at 3 years also showed a trend toward improvement with the combination but failed to reach statistical significance; only time will tell if there is a statistically significant and clinically meaningful difference in OS with the addition of relatlimab to treatment. The confirmed ORR was 43.1% with the combination vs 32.6% with nivolumab alone; this difference was statistically significant. Complete responses occurred in 16.3% of the patients on combination treatment vs 14.2% of those on nivolumab alone.

I would like to caution that the trial was designed to have its first restaging for patients performed at 12 weeks, with subsequent imaging performed every 8 weeks thereafter—thus making the second follow-up assessment take place approximately 20 weeks from initiation of therapy. Several prior studies of checkpoint inhibitor monotherapy have shown a median PFS of approximately 6 to 7 months, whereas the median PFS in this trial was less than 5 months. Could the timing of follow-up in this trial explain the lower-than-expected PFS rate in the nivolumab-only arm?

H&O What were the adverse effects of treatment in the 2 groups?

NK Nivolumab is very well tolerated as monotherapy, and the combination of nivolumab and relatlimab is considered well tolerated as well. Despite these conclusions, we must not forget that checkpoint inhibitors come with a risk for treatment-related adverse events, and that combining checkpoint inhibitors increases that risk. Some of the toxicities seen in the combination arm were quite notable, particularly the endocrinopathies, such as adrenal insufficiency and hypophysitis. As described in the 2022 publication of RELATIVITY-047, patients in the combination arm were 5 times as likely than those in the nivolumab-alone arm to experience adrenal insufficiency of any grade, and 3 times as likely to experience hypophysitis of any grade. Similarly, patients in the combination arm were more than twice as likely as those in the nivolumab-alone arm to experience immune hepatitis or immune-related colitis. The rate of myocarditis, which may be related to the LAG-3 molecule, was 1.7% in the combination arm vs 0.6% in the nivolumab-alone arm. Fortunately, most of the cases of myocarditis in this study were considered reversible. Still, the rate of discontinuation owing to treatment-related adverse events was more than twice as high in the combination group as in the nivolumab-alone group, at 15% vs 7%, respectively. The rate of discontinuation owing to grade 3 or 4 treatment-related adverse events was nearly 3 times as high in the combination group as in the nivolumab-alone group, at 9% vs 3%, respectively. There were 3 treatment-related deaths in the combination group and 2 treatment-related deaths in the nivolumab-alone group. So there is definitely more toxicity with the nivolumab/relatlimab combination, which is something we need to discuss with our patients because these adverse events can affect quality of life. Still, nivolumab/relatlimab does seem to be better tolerated than ipilimumab/nivolumab, the other combination approved for use in melanoma. The rate of grade 3 or 4 treatment-related adverse events is 19% for nivolumab/relatlimab vs approximately 55% for ipilimumab/nivolumab.

H&O What has been the effect of RELATIVITY-047?

NK The major effect has been the approval of nivolumab/relatlimab by the US Food and Drug Administration in March 2022 for patients with unresectable or metastatic melanoma based on the strong positive results for PFS. This is an especially important approval because it applies to patients aged 12 years or older, and we do have pediatric patients who develop advanced melanoma. The label does not specify that patients need to be therapy-naive, so I can see this combination being used in both the frontline and refractory settings, which is encouraging.

H&O Where does this approval leave the role of PD-1 monotherapy in advanced melanoma?

NK The way I look at it is that we have 3 buckets of patients based on clinical risk stratification. The first bucket is patients who previously would have received anti–PD-1 therapy as frontline therapy and will now receive nivolumab/relatlimab instead. The second bucket is high-risk patients who previously would have received ipilimumab/nivolumab and will still receive this combination. These high-risk patients are those with poor prognostic factors, including elevated lactic dehydrogenase, bulky disease, asymptomatic brain metastases, liver

disease, and advanced mucosal melanoma. The third bucket is patients who have relative contraindications to immune checkpoint inhibition, such as those with autoimmune disease. In these patients, I would prefer to use anti–PD-1 monotherapy in order to reduce the risk of causing a flare in the underlying autoimmune disease. What we still do not know is whether nivolumab/relatlimab will perform as well as the ipilimumab/nivolumab combination for the poor-prognosis patients; longer follow-up from RELATIVITY-047 should help in this assessment.

I do not believe that nivolumab/relatlimab needs to be used for everyone in that first bucket, especially given that we do not yet have confirmatory OS data. Furthermore, the combination does come with a slightly higher toxicity rate than monotherapy. As a result, I think it is still reasonable to use anti–PD-1 monotherapy at this time.

> The main disadvantage of a single infusion is that we do not know which agent is responsible if the patient develops a hypersensitivity during treatment.

H&O Can biomarker data be used to determine which patients are more likely to benefit from nivolumab/relatlimab?

NK Biomarker data from RELATIVITY-047 show that virtually every patient subgroup benefited from the combination over nivolumab alone, although the differences were not always statistically significant. For example, this study suggested that patients with low expression of programmed death ligand 1 (PD-L1) and those with high expression of LAG-3 were more likely to respond to nivolumab/relatlimab than to nivolumab alone. Based on what future trials show, I could potentially see using anti–PD-1 monotherapy in patients with high tumor cell expression of PD-L1, ipilimumab/nivolumab in someone with low PD-L1 and low LAG-3, and nivolumab/relatlimab in patients with low PD-L1 and high LAG-3. Another factor is *BRAF* mutational status; results from DREAMseq that Dr Michael Atkins recently presented at an ASCO monthly plenary series showed that 2-year OS was better when ipilimumab/nivolumab was given first than when dabrafenib (Tafinlar, Novartis)/trametinib (Mekinist, Novartis) was given first in the therapy-naive, *BRAF* V600–mutated advanced melanoma population.

H&O What makes nivolumab/relatlimab different from other immune checkpoint inhibitor combinations?

NK Not only is relatlimab the only approved agent we currently have that targets LAG-3, the combination of nivolumab/relatlimab is provided at a fixed dose in a single vial. As a result, the combination is given as a single infusion rather than as sequential infusions of checkpoint inhibitors. This has advantages and disadvantages. The main advantage, of course, is that a single infusion is simpler and faster. The main disadvantage of a single infusion is that we do not know which agent is responsible if the patient develops a hypersensitivity during treatment. Another notable difference is that the ipilimumab/nivolumab regimen consists of 4 doses of ipilimumab/nivolumab followed by nivolumab maintenance, whereas the nivolumab/relatlimab regimen does not have a specific endpoint besides progression or toxicity.

H&O What other studies are looking at the use of nivolumab/relatlimab?

NK In melanoma, an ongoing study has been looking at nivolumab/relatlimab in the refractory setting for patients whose disease has progressed on previous immune checkpoint inhibitor or targeted therapy. Preliminary results that Dr Paolo Ascierto presented at the 2017 European Society for Medical Oncology annual meeting have shown a response rate to nivolumab/relatlimab of just 11% to 16% in these patients. In addition, a large, ongoing adjuvant trial called RELATIVITY-098 is randomly assigning patients with resected melanoma who are at high risk for recurrence to either nivolumab/relatlimab or nivolumab alone (NCT05002569).

Research on nivolumab/relatlimab is being conducted in other solid tumors as well. One phase 2 study is looking at the addition of nivolumab/relatlimab to chemotherapy vs nivolumab plus chemotherapy as frontline therapy in recurrent or metastatic non–small cell lung cancer (NCT04623775). A phase 2 trial is comparing nivolumab/relatlimab vs nivolumab alone as second-line study treatment in advanced hepatocellular carcinoma (NCT04567615). Another study is being conducted in patients with gastroesophageal and gastric cancers (NCT04062656). Finally, research is looking at the use of nivolumab/relatlimab in patients with B-cell

malignancies and Hodgkin's disease (NCT05255601). I suspect these are just a few studies of many more to come across the spectrum of cancer therapy.

H&O Are any other immune checkpoint inhibitor combinations being studied for use as first-line treatment in advanced melanoma?

NK A variety of immune checkpoint inhibitors are being studied in phase 1 and 2 trials, including inhibitors of T cell immunoreceptor with Ig and ITIM domains (TIGIT), TNFR-related protein (*GITR*), T-cell immunoglobulin and mucin domain 3 (TIM-3), OX40, and CD137. Phase 3 studies are looking at combinations of anti–PD-1 agents with other agents, such as intralesional therapy, anti–vascular endothelial growth factor therapy, and histone deacetylase inhibitor therapy.

Disclosure

Dr Khushalani has served on the advisory board of Bristol Myers Squibb, Regeneron, Merck, Jounce Therapeutics, Iovance Biotherapeutics, Genzyme, Novartis, Castle Biosciences, Nektar, and Instil Bio; has been a steering or scientific committee member for Nektar, Regeneron, Replimune, Bristol Myers Squibb, and the National Comprehensive Cancer Network via Pfizer; has served on the data safety monitoring committee of AstraZeneca and Incyte; has received institutional research support from Bristol Myers Squibb, Merck, Celgene, Regeneron, Replimune, Novartis, HUYA Bioscience, and GSK; and has common stock in Bellicum, Amarin, and Asensus Surgical.

Suggested Readings

Ascierto PA, Bono P, Bhatia S, et al. Efficacy of BMS-986016, a monoclonal antibody that targets lymphocyte activation gene-3 (LAG-3), in combination with nivolumab in pts with melanoma who progressed during prior anti–PD-1/PD-L1 therapy (mel prior IO) in all-comer and biomarker-enriched populations [ESMO abstract 4998]. *Ann Oncol.* 2017;28(5)(suppl).

Atkins MB, Lee SJ, Chmielowski B, et al. DREAMseq: a phase III trial—ECOG-ACRIN EA6134 [ASCO Plenary Series abstract 356154]. *J Clin Oncol.* 2021;39(36)(suppl).

Lipson EJ, Tawbi H, Schadendorf D, et al. Relatlimab (RELA) plus nivolumab (NIVO) versus NIVO in first-line advanced melanoma: primary phase III results from RELATIVITY-047 (CA224-047) [ASCO abstract 9503]. *J Clin Oncol.* 2021;39(15)(suppl).

Long GV, Hodi FS, Lipson EJ, et al. Relatlimab and nivolumab versus nivolumab in previously untreated metastatic or unresectable melanoma: overall survival and response rates from RELATIVITY-047 (CA224-047) [ASCO Plenary Series abstract 360385]. *J Clin Oncol.* 2022;40(36)(suppl).

Tawbi HA, Schadendorf D, Lipson EJ, et al; RELATIVITY-047 Investigators. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. *N Engl J Med.* 2022;386(1):24-34.