MELANOMA IN FOCUS

Current Developments in Melanoma

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What Will Be the Next Partner for Combination Immunotherapy With Nivolumab and Ipilimumab?

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H&O Which patients with melanoma are eligible for treatment with the combination of nivolumab (Opdivo, Bristol Myers Squibb) plus ipilimumab (Yervoy, Bristol Myers Squibb)?

JL The frontline treatment of advanced melanoma with nivolumab plus ipilimumab is based on the results of the CheckMate 067 trial. In the most recent results from this trial, the overall survival rate at a minimum of 7.5 years of follow-up was 48% in the combination group vs 22% in the ipilimumab-alone group.[1] This has become the standard by which we judge all other treatments in melanoma.

Earlier this year, we saw a big shift in melanoma treatment that was based on the results of the NADINA trial, which were presented at the 2024 American Society of Clinical Oncology (ASCO) Annual Meeting and published in the *New England Journal of Medicine*.[2] NADINA showed that the addition of neoadjuvant treatment with nivolumab/ipilimumab to standard surgery and adjuvant therapy led to a 68% relative reduction in the risk of disease recurrence or death. The results of this study led to neoadjuvant nivolumab/ipilimumab becoming a standard therapy for patients who have stage III or IV melanoma with clinically detectable lymph nodes.

H&O What are the limitations of dual immunotherapy in these patients?

JL One limitation is that, as with every type of cancer, we cannot cure everybody. We can achieve durable responses in 50% to 60% of patients who have metastatic melanoma, which really is amazing because we had no real treatment for melanoma before the development of immune checkpoint blockade in 2012 or so. Melanoma was one of the worst kinds of cancer people could get. But even with all our advances in treatment, 40% to 50% of patients do not experience a long-term benefit.

The other important limitation is toxicity, which can be problematic to manage. What is interesting is that the use of immune therapies has changed the way we think about toxicity because patients experience immune activation toxicities rather than chemotherapy-like toxicities. Immune activation toxicities are concerning, with more than half of patients experiencing one or more high-grade events that require a hospitalization or major medical intervention. The good news is that the patients in whom severe toxicity develops almost always experience a long-lasting response. Oncologists who take care of patients with melanoma have been using immune checkpoint inhibitors for a long time; we are familiar with managing the toxicities of these agents and see how they benefit patients in the long run. We understand that although a hospitalization early in treatment may seem like a problem, it is often followed by a lasting remission. The argument can be made that a week in the hospital with severe colitis, for example, followed by a long or permanent treatment-free interval, is more patient-friendly than a regimen that causes milder side effects but continues for years. As bad as high-grade toxicity

seems when a patient is going through it, the potential of avoiding future treatment is profound. So maybe we need to start embracing the idea of accepting short-term pain in exchange for long-term gain and better outcomes for patients. This is the idea behind using treatment-free survival as an outcome measure for the effects of immune checkpoint inhibition.[3]

H&O What is the concept behind adding other agents to nivolumab/ipilimumab?

JL Monotherapy with nivolumab or pembrolizumab (Keytruda, Merck) is approved as adjuvant treatment in melanoma, which led to the idea that combining 2 immune checkpoint inhibitors might work even better for these patients. Unfortunately, the CheckMate 915 trial showed that adding ipilimumab to nivolumab did not improve outcomes vs nivolumab alone in advanced or metastatic melanoma.[4] A major limitation of this trial is that in 2015, when the study began, we did not have any real information about how best to combine these agents, so the dosage of ipilimumab—1 mg/kg once every 6 weeks—was designed to reduce side effects rather than being optimized for the combination. A colleague and I wrote about this limitation in an editorial that appeared in the same issue as the article.[5] In contrast, the CheckMate 067 trial used ipilimumab at a dosage of 3 mg/kg every 3 weeks for 4 treatments.[6]

We run the risk of losing the potential benefit of the triplet if we do not give enough ipilimumab.

H&O What agents have been examined in combination with nivolumab/ipilimumab?

JL One of the high-profile agents to be examined in combination with nivolumab/ipilimumab is granulocyte-macrophage colony-stimulating factor (GM-CSF), also known as sargramostim (Leukine, Partner Therapeutics). The phase 2/3 EA6141 trial from ECOG-ACRIN, which started accruing patients in 2015 (NCT02339571), was undertaken after a previous study suggested that GM-CSF might reduce the toxicity of ipilimumab.[6]

Another agent that has been studied in combination with nivolumab/ipilimumab is the LAG-3 antibody relatlimab, which is approved for use in combination with nivolumab (Opdualag, Bristol Myers Squibb). Data from the single-arm, phase 1/2 RELATIVITY-048 study, which were presented at the 2024 ASCO Annual Meeting, suggested that the triplet regimen had encouraging efficacy, with a confirmed overall response rate of 59%.[7] This number is not much different from what we see with the regular dose of nivolumab/ipilimumab, however. The problem is that the trial employed a reduced dose of ipilimumab to reduce the toxicity seen with the addition of relatlimab. In my opinion, the goal should not be to reduce toxicity but to maximize the early response rate and then let the patient halt treatment. Oncologists should accept that the increase in toxicity is part of the deal, and it should not be a barrier.

The third agent of interest that is being studied in combination with nivolumab/ipilimumab is a UV1 vaccine against telomerase. A single-arm trial looking at this agent has produced some preliminary data that appear somewhat intriguing. In the context of a treatment that already has a response rate of approximately 60%, however, it is hard to determine from a single-arm trial whether the combination might represent an advance.

Regardless of what we combine with nivolumab/ipilimumab, we need to be cognizant of the dose and schedule of ipilimumab. We run the risk of losing the potential benefit of the triplet if we do not give enough ipilimumab.

H&O What should the next step be in research?

JL The next step should be to do thorough dose- and schedule-finding studies of nivolumab/ipilimumab plus other agents. That will never happen, however, because ipilimumab is coming off patent in a couple of years, so there is no incentive for the manufacturer to conduct such studies. To be done properly, these types of trials require more than 1000 patients, which is very expensive. The cooperative groups should be able to conduct randomized trials that compare triplet vs doublet combinations, but these will be smaller trials of more limited value.

H&O What do you see as the future of triplet therapy in melanoma?

JL I think that the concept of triplet therapy is sound, but its use will be severely hampered by the dearth of clinical trials. Manufacturers have little incentive to promote a switch from long-term to short-term treatment, which is not attractive from a commercial perspective. This is unfortunate, but it is the world we live in. As a result, I see triplet therapy having very limited use clinically.

Disclosures

Dr Luke has served on the data and safety monitoring boards of AbbVie, Agenus, Evaxion Biotech, Immutep, and Shionogi; has served on the scientific advisory boards (no stock) of 7 Hills Pharma, Affivant, BioCytics, Bright Peak Therapeutics, Exo Therapeutics, F-star Therapeutics, Inzen Therapeutics, RefleXion, and Xilio Therapeutics, plus (stock) Actym Therapeutics, Alphamab Oncology, Arch Oncology, Duke Street Bio, Elipscience, Kanaph Therapeutics, NeoTx, Onc.AI, OncoNano, physIQ, Pyxis Oncology, Saros Therapeutics, Stipe Therapeutics, and Tempest Therapeutics; has been a paid consultant to AbbVie, Agenus, Alnylam Pharmaceuticals, AstraZeneca, AskGene Pharma, Atomwise, Bayer, Bristol Myers Squibb, Castle Biosciences, Checkmate Pharmaceuticals, Codiak BioSciences, Crown Bioscience, Cugene, Curadev Pharma, Day One Biopharmaceuticals, Eisai, EMD Serono, Endeavor Biomedicines, Flame Biosciences, G1 Therapeutics, Genentech, Geneos Therapeutics, Gilead, Glenmark Pharmaceuticals, HotSpot Therapeutics, Kadmon, KoBioLabs, Krystal Biotech, KSQ Therapeutics, Janssen, Ikena Oncology, Inzen Therapeutics, Immatics, Immunocore, Incyte, Instil Bio, IO Biotech, LegoChem Biosciences, Lyvgen Biopharma, MacroGenics, Merck, Mersana Therapeutics, Nektar Therapeutics, Novartis, Partner Therapeutics, Pfizer, Pioneering Medicines, PsiOxus Therapeutics, Regeneron, Replimune, Ribon Therapeutics, Roivant Sciences, Servier Pharmaceuticals, Stingthera, Storm Therapeutics, Sumitomo Pharma, Synlogic Therapeutics, Synthekine, and Teva; and has received research support (all to institution) from AbbVie, Astellas, AstraZeneca, Bristol Myers Squibb, Corvus Pharma, Day One Biopharmaceuticals, EMD Serono, F-star Therapeutics, Genmab, HotSpot Therapeutics, Ikena Oncology, Immatics, Imugene, Incyte, Janux Therapeutics, Kadmon, KAHR, MacroGenics, Merck, Moderna, Nektar Therapeutics, NextCure, Novartis, Numab Therapeutics, Palleon Pharmaceuticals, Pfizer, Replimune, Rubius Therapeutics, Servier Pharmaceuticals, Scholar Rock, Synlogic Therapeutics, Takeda, Trishula Therapeutics, Tizona Therapeutics, TScan Therapeutics, Werewolf Therapeutics, and Xencor.

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