MELANOMA IN FOCUS

Current Developments in Melanoma

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Update on LAG3 and Immunotherapy Combinations in Melanoma

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H&O How does the mechanism of action of LAG3-targeted therapies differ from that of other immune checkpoint inhibitors?

HT LAG3-targeted therapy unlocks an entirely new pathway that we were unable to target before. Checkpoint inhibitors affect different phases of T-cell activation, ranging from antigen recognition to T-cell receptor activation and then exhaustion. LAG3 seems to be very important for the regulation of T-cell exhaustion. Programmed death 1 (PD-1) is the first marker of both T-cell activation and T-cell exhaustion, and LAG3 appears to be the immediate second marker. If you look at a double-positive T cell that has both PD-1 and LAG3, it is likely to be a lot more exhausted than a T cell that is positive for just PD-1. Signs of exhaustion include decreased cytokine production, decreased cytolytic activity, and decreased proliferation. Targeting LAG3 allows the T-cell receptor repertoire to expand, increasing CD8 T-cell activity and promoting an antigen-specific immune response.

H&O What have the clinical data shown about the efficacy of combining LAG3 inhibitors with PD-1 inhibitors in melanoma treatment?

HT Preclinical models and experience with patients have shown that LAG3 inhibition is not effective on its own; it is really the combination with PD-1 inhibitors that makes it effective. The original phase 1 trial of the PD-1 inhibitor nivolumab plus relatlimab (Opdualag, Bristol Myers Squibb) in nearly 560 patients with melanoma, RELATIVITY-020, showed that the rate of response to treatment in the second line was only 12%. The responses were deep and durable, but 12% is relatively low. The fact that LAG3 inhibitors are often ineffective as part of second-line treatment led to the idea that they should be investigated as part of first-line treatment, before the T cells become terminally exhausted.

H&O Could you discuss the results of the RELATIVITY-047 trial that you conducted, and how nivolumab plus relatlimab has changed the treatment landscape?

HT When we compared nivolumab plus relatlimab vs nivolumab alone (Opdivo, Bristol Myers Squibb) in a randomized, double-blinded fashion, it was very clear that the combination was more effective than the single agent.[1] The median progression-free survival (PFS) by blinded, independent review, which was the primary endpoint of the study, was almost twice as long with the combination as with nivolumab alone, at 10.1 vs 4.6 months, respectively. The hazard ratio for progression or death was statistically significant, at 0.75. The median overall survival (OS) was not reached, and the overall response rate (ORR) was 43.1% with nivolumab/relatlimab vs 32.6% with nivolumab alone.

The 3-year data from this trial showed that the median PFS was 10.2 months with combination treatment vs 4.6 months with nivolumab alone, with a statistically significant hazard ratio of 0.79.[2] We were also able to see an effect of combination treatment on survival, with a

median OS of 51.0 months for the combination and 34.1 months for nivolumab alone. The ORR was 43.7% with nivolumab/relatlimab vs 33.7% with nivolumab alone—an absolute improvement of 10%.

The median age of patients in phase 3 trials of metastatic melanoma is generally in the mid-60s, so that many of the deaths over the next 5 to 10 years may be from causes other than melanoma. As a result, the endpoint of melanoma-specific survival is very important. That endpoint was even more impressively in favor of nivolumab/relatlimab, with a hazard ratio of 0.75 in our 3-year results.[3] The confidence intervals for this hazard ratio did not cross 1.0.

> Because nivolumab/relatlimab is a relatively safe combination, I would eventually like to see it used as the basis for other triplet regimens and even quadruplet regimens.

H&O What safety concerns are seen with nivolumab plus relatlimab?

HT Regarding safety, we know that the combination of nivolumab and the cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) inhibitor ipilimumab (Yervoy, Bristol Myers Squibb) leads to a high rate of grade 3 or 4 toxicity, at nearly 55%. By contrast, the rate of grade 3 or 4 toxicity with a combination of nivolumab and relatlimab is 22%, which is approximately 10% higher than that seen with nivolumab alone. The median number of grade 3 or 4 toxicities is just 1 for patients on nivolumab/relatlimab vs 2 or 3 for patients on ipilimumab/nivolumab.

The types of adverse effects seen with nivolumab/relatlimab are very similar to those seen with single-agent nivolumab, with one exception being that we see an increased incidence of adrenal insufficiency. Adrenal insufficiency tends to begin during the first 1 to 2 months of treatment with nivolumab/relatlimab, whereas it is most likely to begin during the first 3 to 9 months with ipilimumab/nivolumab. Patients present with symptoms such as fatigue, headache, and hypotension. Adrenal insufficiency can be tricky to diagnose, and the treating physician should be on the alert for it. Fortunately, it is easy to manage if you suspect it early and diagnose it properly.

H&O What patient populations benefit the most from LAG3-targeted combination approaches?

HT It is difficult to pick out a patient population that derives more benefit than others. When we conducted subgroup analyses in RELATIVITY-047, we saw the same increases in efficacy with nivolumab/relatlimab regardless of patient characteristics such as *BRAF* mutation status, tumor mutational burden, and a diagnosis of acral or mucosal melanoma. Instead, I look at the totality of the patient characteristics, such as the disease pace and the disease burden. We do not have data right now regarding nivolumab/relatlimab in patients with brain metastases, so ipilimumab/nivolumab remains the standard of care for them.

We are currently conducting the phase 2 BLUEBONNET trial at MD Anderson to see if nivolumab/relatlimab has the same activity in the brain that we have seen elsewhere in the body (NCT05704647).

H&O What biomarkers are emerging to help identify patients with melanoma who might respond best to LAG3-targeted combination therapy?

HT We do not have good biomarkers for response at present. Although we stratified the RELATIVITY-047 study for LAG3 expression status, this did not end up predicting response. LAG3 positivity was a positive prognostic sign; these patients did better than those who were LAG-negative, but that was true regardless of whether patients received combination therapy or nivolumab alone.

H&O Have the recent negative results of nivolumab/relatlimab in the adjuvant melanoma setting in the RELATIVITY-098 trial raised any questions in your mind about the efficacy of this combination in the metastatic setting?

HT Not at all. We have not yet seen the full data from RELATIVITY-098, but these results support the idea that the presence of the tumor is important. In research that we published in *Nature*, we saw a major pathologic response rate of 63% with just 2 doses of neoadjuvant nivolumab/relatlimab.[3] If anything, RELATIVITY-098 highlights that LAG3 blockade may be even more appropriate in the neoadjuvant setting than in the adjuvant setting.

H&O What novel LAG3 combination approaches beyond PD-1 pairing are showing promise in clinical trials?

HT It is important to highlight the combination of fianlimab and cemiplimab (Libtayo, Sanofi-Aventis/Regeneron), which target LAG3 and PD-1, respectively. Fianlimab works similarly to relatlimab, but it is being studied at a much higher dose than what has been used in studies of relatlimab—nearly 10 times higher. Early data from single-arm trials suggest that the fianlimab combination may be more effective than the relatlimab combination.[4] Two phase 3 trials of fianlimab and cemiplimab are ongoing (NCT05608291, NCT06246916), including a trial I am working on that is comparing fianlimab/cemiplimab with nivolumab/relatlimab in the first-line metastatic setting.

Beyond those studies, I would like to see studies that look at inhibiting all 3 checkpoints: PD-1, LAG3, and CTLA-4. The only study to look at this combination so far is the phase 1/2 RELATIVITY-048 trial.[5] Results reported at the 2024 American Society of Clinical Oncology Annual Meeting on 46 patients showed an ORR of 58.7% for the combination of ipilimumab, nivolumab, and relatlimab. The dosage of ipilimumab was very low, at just 1 mg/kg every 8 weeks, which is very unusual. As a result, we are in the process of conducting a phase 1 dose escalation study called TRINITY at MD Anderson (NCT06683755). We want to determine the best dose of ipilimumab to use in this triplet regimen, and we are using an every-4-week schedule.

Because nivolumab/relatlimab is a relatively safe combination, I would eventually like to see it used as the basis for other triplet regimens and even quadruplet regimens. That is a very exciting prospect.

H&O How do you choose between a LAG3/PD-1 combination and a CTLA-4/PD-1 combination in the frontline setting?

HT The data are very comparable. An indirect comparison between ipilimumab/nivolumab and nivolumab/relatlimab in the CheckMate-067 and RELATIVITY-047 trials, respectively, showed that the PFS, ORR, and melanoma-specific survival with the combinations were fairly similar once the baseline characteristics had been matched.[6] When I have relatively equally effective combinations and one of those causes 3 times the toxicity of the other, I will generally look for reasons to use the less toxic combination. Still, some specific patient characteristics still make me use ipilimumab/nivolumab. If the patient is having pain or other symptoms and an immediate response is required, ipilimumab/nivolumab can still be a reasonable choice. A 2% to 5% increase in the response rate may be worth the toxicity if the patient is having a problem such as organ blockage that requires an immediate response. On the other hand, I choose nivolumab/relatlimab if the patient has metastases to the brain. Overall, I end up treating approximately one-third of my patients with ipilimumab/nivolumab and two-thirds with nivolumab/relatlimab.

Disclosures

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