PD-1 or PD-L1 Blockade Adds Little to Combination of BRAF and MEK Inhibition in the Treatment of BRAF V600–Mutated Melanoma

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Most melanomas are driven by activation of the extracellular regulated kinase (ERK) pathway. In approximately 40% of cutaneous melanomas, this activation is due to a BRAF V600E or K mutation and these tumors are generally quite sensitive to treatment with the combination of a RAF inhibitor (RAFi) and a MEK inhibitor (MEKi). There are now three US Food and Drug Administration (FDA)–approved RAFi plus MEKi combinations, which have revolutionized the treatment of BRAF V600–mutated melanomas. They induce responses in 60%-80% of patients and are associated with improved overall survival (OS). Unfortunately, up to 80% of melanomas will develop resistance and progress at a median time of 12-15 months.

Checkpoint inhibitors have, at the same time, also revolutionized the treatment of metastatic cutaneous melanoma. Two inhibitors of the programmed cell death protein 1 (PD-1) checkpoint have been approved for the treatment of melanoma, and three inhibitors of programmed death ligand 1 (PD-L1) have been FDA-approved for treatment of a variety of solid tumor indications.[1] These drugs are associated with response rates of 35%-40% in patients with melanoma, and many of these responses are long-lived. PD-1 and PD-L1 inhibitors are active in melanoma treatment regardless of the mutational status of the *BRAF* gene. Although there are not strong data directly comparing inhibitors of PD-1 and PD-L1, these agents appear to have broadly similar response rates and toxicity profiles.

There were many reasons to think that combining RAFi and MEKi with PD-1 or PD-L1 blockade would result in synergistic therapeutic effects. Clinically, the combinations of RAFi plus MEKi resulted in high response rates but of relatively short duration. The PD-1 or PD-L1 blockers, in contrast, were associated with lower response rates but more durable responses. Combination RAFi and MEKi have largely nonoverlapping toxicities with PD-1 and PD-L1 inhibitors and different mechanisms that drive toxicities. As such, it was assumed that combining them would be tolerable. In addition, there was evidence that combination RAFi and MEKi resulted in increased melanoma antigen expression,[2] increased T-cell infiltration in tumors,[3] and could make the tumor microenvironment more favorable for immune activation by neutralizing immunosuppressive myeloid-derived suppressor cells[4] or enhancing dendritic cell function.[5]

On the other hand, there were indications that combining RAFi and MEKi with checkpoint inhibitors might not be straightforward. Preclinical data indicated that MEK inhibition might suppress T-cell function,[6] and recent data suggest that combination RAFi plus MEKi can inhibit dendritic cell maturation and T-cell activation.[7] Furthermore, the first combination clinical trials adding ipilimumab (anti–cytotoxic T-cell lymphocyte-4) to either the RAFi vemurafenib[8] or the RAFi plus MEKi combination of dabrafenib/trametinib[9] were both stopped early in dose escalation because of toxicity, hepatotoxicity in the former and gastrointestinal toxicity in the latter.

Two trials have been published in which patients with BRAF V600–mutated melanoma were randomly assigned to treatment with combination RAFi plus MEKi with or without anti–PD-1 or anti–PD-L1 antibodies. IMspire150 randomly assigned patients with BRAF V600–mutated melanoma to treatment with vemurafenib and cobimetinib with or without atezolizumab, an anti–PD-L1 antibody.[10] The primary end point was investigator-assessed progression-free survival (PFS), and the addition of atezolizumab showed a small, statistically significant benefit (hazard ratio = 0.78), leading to FDA approval of this triplet combination. It was noteworthy that the difference in PFS between the two cohorts as assessed by an independent review committee (a secondary end point) was not statistically significant. KEYNOTE-022 tested combination dabrafenib plus trametinib with or without pembrolizumab, an anti–PD-1 antibody. There was not a statistically significant difference in the primary end point of investigator-assessed PFS[11] although a nonprotocol-specified second analysis with longer follow-up did show improved PFS with the triplet compared with the doublet.[12] In neither of these trials, did it appear that anti–PD-1 or PD-L1 therapy contributed to the objective response rate; response rates ranged from 63% to 72%, consistent with the expected response rate for combination RAFi plus MEKi therapy alone. There was no improvement in objective response rates for triplet therapy over doublet therapy.

ASSOCIATED CONTENT

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THE TAKEAWAY

In the article that accompanies this editorial,[13] the addition of the anti–PD-1 antibody spartalizumab to combination dabrafenib plus trametinib in a randomized trial did not improve PFS, response rate, or 24-month OS in previously untreated patients with metastatic BRAF V600–mutated melanoma. Consistent with two previous randomized trials, the addition of anti–PD-1 or anti–PD-L1 antibodies to combination RAFi plus MEKi is not associated with a significant clinical benefit and should not be studied further in melanoma.

In the article that accompanies this editorial,[13] a third trial (COMBI-I) is published, which tested dabrafenib plus trametinib with or without spartalizumab, an anti–PD-1 antibody that is not FDA-approved. As with the first two trials, the primary end point was investigator-assessed PFS, and at a median follow-up of 27.2 months, the difference in PFS between the two treatment arms was not statistically significant. As with IMspire150 and KEYNOTE-022, there were no statistically significant differences in the secondary end points of overall response rate or in 24-month OS. The authors conclude that "…the results of this primary analysis do not support first-line use of Sparta-DabTram in patients with BRAF V600-mutant metastatic melanoma."

One possible explanation for these negative results is that the triplet was not well tolerated. Patients in the triplet arm required more dose interruptions and dose reductions of dabrafenib and trametinib. In the triplet arm, only 32% of patients received full-dose dabrafenib compared with 54% of patients in the doublet arm. Beyond this, alternative explanations could include the possibility that RAFi plus MEKi combinations impede the full benefits of PD-1 or PD-L1 blockade or vice versa.

We now have three randomized trials testing whether adding either PD-1 or PD-L1 blockade to RAFi plus MEKi combinations in BRAF V600–mutated metastatic melanoma improved investigator-assessed PFS. Two trials were negative; one (IMspire150) was positive; although when PFS was assessed by an independent review committee, the difference in PFS was not statistically significant. In none of these trials, did the triplet treatment show a statistically significant improvement in response rate or 24-month OS.

We believe that there are sufficient data now to be confident that the addition of anti–PD-1 or anti–PD-L1 antibodies to combination RAFi plus MEKi is not associated with a significant clinical benefit and should not be studied further in melanoma. Moreover, there is some evidence of harm, as the additional toxicity of triplet combination limited the delivery of combination RAFi plus MEKi therapy in COMBI-I. Focus should turn instead to (1) optimizing doses and schedules of combination RAFi plus MEKi and checkpoint inhibitors, (2) developing treatment strategies to overcome resistance to these therapies, and (3) determining how best to sequence combination RAFi plus MEKi therapy and checkpoint inhibitors. Regarding the latter point, there are several sequential therapy trials currently underway in previously untreated patients with BRAF V600–mutated melanoma. Patients are randomly assigned to begin treatment either with combination RAFi plus MEKi therapy or with checkpoint inhibitor immunotherapy and are crossed over at progression or, in some cases, at a specified time point. Preliminary data from two of these trials—the Secombit trial and the DREAMseq trial—have been presented at recent meetings. In both these trials, patients who initially received ipilimumab plus nivolumab had better PFS than patients who received RAFi plus MEKi as their first treatment. We eagerly await the publication of these results in peer-reviewed journals since, if these data are correct, they will be practice-changing for oncologists taking care of patients with newly diagnosed metastatic BRAF V600–mutated melanoma.

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