

MELANOMA IN FOCUS

Current Developments in Melanoma

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Update on the DREAMseq Trial in Melanoma



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H&O What was the impetus for the DREAMseq trial?

MA In 2015, there were 2 different approaches to treating patients with metastatic *BRAF*-mutant melanoma, both of which had US Food and Drug Administration approval. The first approach was a combination of targeted therapies involving BRAF inhibition and MEK inhibition in the form of dabrafenib (Tafinlar, Novartis) plus trametinib (Mekinist, Novartis). The second approach was a combination of immunotherapies involving the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) inhibitor ipilimumab (Yervoy, Bristol-Myers Squibb) plus the programmed death 1 (PD-1 inhibitor) nivolumab (Opdivo, Bristol-Myers Squibb). The combination of dabrafenib and trametinib had been shown to improve overall survival (OS) compared with single-agent BRAF inhibition, which had in turn been shown to improve OS compared with chemotherapy. Likewise, the CheckMate 067 trial showed improvements in both OS and progression-free survival (PFS) with ipilimumab/nivolumab compared with ipilimumab alone. In 6.5-year results that Wolchok and colleagues published in the *Journal of Clinical Oncology* in 2022, the median OS was 72.1 months in the combination group and 19.9 months in the ipilimumab-alone group. Further, the combination showed a 14% absolute improvement in both 6.5-year landmark OS and PFS compared with single-agent nivolumab.

Given these 2 excellent options that we did not have

before, the first question we had in 2015 was, which option is preferred? The second question we had was, given that patients would have access to both approaches, what is the preferred sequence? The DREAMseq trial was launched 2015 to address these questions. Even in 2021, before the results of the study were announced, half of the patients with metastatic *BRAF*-mutated melanoma were receiving BRAF/MEK inhibitors as their initial therapy and one-quarter of the patients were receiving anti-PD-1 monotherapy.

H&O Could you describe the design of the trial?

MA DREAMseq was a randomized phase 3 trial that enrolled patients with treatment-naive, *BRAF*-mutant metastatic melanoma, and stratified them by Eastern Cooperative Oncology Group (ECOG) performance status and serum lactate dehydrogenase level. In step 1, patients were randomly assigned to receive 12 weeks of induction therapy with ipilimumab/nivolumab followed by up to 84 weeks of nivolumab maintenance vs continuous oral therapy with dabrafenib/trametinib until disease progression. If patients developed progressive disease and were eligible to continue in the study, they were enrolled in step 2 and received the converse therapy.

H&O Could you describe the results?

MA The study was designed with an endpoint of 2-year landmark OS because a crossing of the OS and PFS curves

was expected. We estimated that the 2-year OS rate would be 50% among those who received targeted therapy first and 70% among those who received immunotherapy first. With 300 patients enrolled and 270 patients eligible, the study had 90% power to detect a difference between the sequences of 20% in 2-year OS.

The study was stopped in the early fall of 2021, after the Data Safety Monitoring Committee conducted its fourth interim analysis. The analysis, which reviewed data through July of 2021 on the 265 enrolled patients, revealed a clinically meaningful difference in 2-year OS between the 2 arms, at 52% with targeted therapy first and 72% with immunotherapy first. This finding was consistent with what we had predicted, showing an estimated 20% difference between the groups. This crossed the O'Brien-Fleming boundary, prompting the Data Safety Monitoring Committee to recommend to the ECOG-ACRIN Cancer Research Group and the National Cancer Institute that the study be stopped and that patients in the targeted therapy arm be given the option to cross over to immunotherapy, even if they had not experienced disease progression. These results were practice-changing and prompted the National Comprehensive Cancer Network to change its guidelines in 2023.

H&O What are some possible explanations for why ipilimumab/nivolumab is more effective when used before dabrafenib/trametinib?

MA We gave this a lot of thought, and came up with 3 main reasons. One, the response rates were similar between the 2 approaches, in the 45% range, but the responses were much more durable with ipilimumab/nivolumab than with dabrafenib/trametinib. The durable response rate was 88% among the patients in the ipilimumab/nivolumab group vs approximately 50% among the patients in the dabrafenib/trametinib group.

Two, and this is a component of explanation one, is that immunotherapy tends to work better than targeted therapy in the central nervous system (CNS), particularly in patients with asymptomatic or undetected metastatic disease. In other studies, we have seen response rates with immunotherapy that are as good in the CNS as they are systemically, and as durable. We do not see such durable responses in the CNS with the targeted therapy. The increase in CNS relapses with targeted therapy explains why relapses are more common with targeted therapy than with immunotherapy. Patients who experience a CNS relapse are very difficult to treat in the second-line setting.

Three, the activity of targeted therapy is just about as good in the second-line setting as it is in the first-line setting, and possibly better. In contrast, the activity of immunotherapy is much worse in the second-line setting

than it is in the first-line setting. In the DREAMseq trial, the response rate to immunotherapy was one-third lower when patients received it as second-line rather than first-line treatment, and the median PFS was only about 3 months. All 3 of these reasons contribute to immunotherapy being better as frontline therapy and targeted therapy being better as second-line therapy.

H&O Why was OS initially better with dabrafenib/trametinib?

MA More patients on targeted therapy than on immunotherapy had some degree of tumor shrinkage, so the median OS was better with targeted therapy during the first few months of the trial. The risks crossed by the 4-month point, however, and the median OS became better with immunotherapy, largely because responses were more durable with immunotherapy than with targeted therapy. In addition, the patients who did not benefit from immunotherapy tended to experience toxicities or other issues that made them ineligible for second-line targeted therapy in DREAMseq. As a result, OS was higher with targeted therapy first than with immunotherapy therapy first until the 10-month point.

I would encourage investigators who focus on other tumor types to look at the DREAMseq data and consider whether they might apply to these tumor types.

H&O What is the importance of the crossover of the patients between arms in terms of the survival benefit?

MA This was a very important finding. The use of second-line dabrafenib/trametinib was a critical component of OS in patients who received immunotherapy-first treatment. The OS at 2 years was about 20% to 25% higher than the 2-year PFS curve in the immunotherapy-first arm, supporting the benefit of second-line therapy on 2-year OS.

H&O How did the order of treatment affect toxicity?

MA We did not see any differences in overall toxicity or grade 3/4 toxicity depending on whether the regimen was used in the second-line or frontline setting. The rates of toxicity were also similar between the 2 treatment approaches, although the toxicities themselves were different. The toxicities we worry about with immunotherapy are immune-related adverse events, such as thyroiditis, skin rash, colitis, and hepatitis. Common toxicities with targeted therapy are fevers, nausea, fatigue, joint pain, and abnormalities on liver function tests. Patients who were receiving targeted therapy were more likely to stop treatment because of disease progression, whereas patients who were receiving immunotherapy were more likely to stop treatment because of toxicity. With immunotherapy, only a few of the patients who stopped treatment owing to toxicity while responding to treatment experienced subsequent disease progression.

H&O Would you say that the results of DREAMseq apply to all targeted-therapy combinations?

MA That depends on the disease. For instance, patients have worse outcomes in epidermal growth factor receptor (*EGFR*)-mutated lung cancer if they receive immunotherapy before *EGFR* inhibition because immunotherapy increases the toxicity of subsequent *EGFR* inhibitors. We also know that immunotherapy does not work very well in patients with this type of lung cancer. As a result, we use *EGFR* inhibition first in patients with *EGFR*-mutated lung cancer. For cancers that respond well to immunotherapy, however, such as kidney cancer, immunotherapy can be a reasonable first treatment. I would encourage investigators who focus on other tumor types to look at the DREAMseq data and consider whether they might apply to these tumor types.

H&O Are there any patients with treatment-naïve, *BRAF*-mutant metastatic melanoma in whom targeted therapy should be used first?

MA There may be specific patient groups within the population we looked at in DREAMseq where targeted therapy should be used first. I think that future studies should address the question of who these patients might be.

In addition, patients were not eligible for the study if they had poor ECOG performance status, active brain metastases, or poor organ function. Although we do not have specific data regarding these patients, my advice would be that patients in these high-risk groups should first receive at least a brief course of targeted therapy to get their disease under control. Patients who have brain metastases that are severe enough to require corticosteroids should receive targeted therapy first to try to shrink the brain metastases and should stop taking corticosteroids before receiving immunotherapy. Patients who have serious autoimmune conditions that would flare with immunotherapy should receive targeted therapy instead.

Disclosures

Dr Atkins has served on the advisory board of or as a consultant to Bristol Myers Squibb, Merck, Novartis, Eisai, Aveo Oncology, Pfizer, Werewolf Therapeutics, Fathom, Pyxis Oncology, PACT Pharma, Elpis Biopharmaceuticals, X4 Pharmaceuticals, Valo, Scholar Rock, Surface Oncology, Takeda, Roche, SAB Biotherapeutics, Exelixis, Iovance Biotherapeutics, COTA, Idera Pharmaceuticals, Agenus, Asher Bio, AstraZeneca, Calithera, Seagen, Sanofi, Oncorena, Pliant Therapeutics, and GSK; has received research support to his institution from BMS and Merck; and has stock options in Werewolf Therapeutics, Pyxis Oncology, and Elpis Biopharmaceuticals.

Suggested Readings

Atkins MB, Lee SJ, Chmielowski B, et al. Combination dabrafenib and trametinib versus combination nivolumab and ipilimumab for patients with advanced *BRAF*-mutant melanoma: the DREAMseq Trial-ECOG-ACRIN EA6134. *J Clin Oncol*. 2023;41(2):186-197.

National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guideline®). Melanoma: cutaneous. v.2.2023. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf. Updated March 10, 2023. Accessed April 10, 2023.

Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Long-term outcomes with nivolumab plus ipilimumab or nivolumab alone versus ipilimumab in patients with advanced melanoma. *J Clin Oncol*. 2022;40(2):127-137.