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ASO PERSPECTIVES

Spoiled for Choice: Do We Finally Have Clarity on Optimal Treatment Sequencing for Patients with Metastatic Melanoma Harboring an Actionable BRAF Mutation?

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More than a decade has now passed since the tide turned in the management of patients with metastatic melanoma. After long years of despair, with hundreds of treatments and treatment combinations failing to improve survival for patients with unresectable advanced disease, in 2010 success was finally achieved with a phase III randomized controlled trial (RCT) demonstrating improved overall survival (OS) for patients receiving the immune checkpoint inhibitor (ICI) ipilimumab compared with those receiving a glycoprotein vaccine.[1] Remarkably, it was less than 12 months later that a second phase III RCT comparing the BRAF inhibitor vemurafenib with dacarbazine[2] also demonstrated an improvement in OS for patients whose metastatic melanoma harbored a BRAF V600 mutation. These two unrelated treatments targeting vastly different mechanisms heralded a revolution in the management of patients with advanced melanoma. The last decade has seen dramatic improvements in the efficacy of ICIs, with combination ipilimumab and nivolumab now the standard first-line immunotherapy combination.[3] Meanwhile, mitogen-activated pathway kinase inhibitors (MAPKi) targeting both BRAF and MEK have improved survival for patients with actionable BRAF mutations.[4] However, the question of optimal sequencing and whether patients with advanced/unresectable BRAF-mutant melanoma should receive a first-line ICI or MAPKi has until recently remained largely unanswered.

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The ECOG-ACRIN EA6134 (DREAMseq) trial randomized 265 patients with treatment-naïve BRAF V600-mutant advanced melanoma to either dabrafenib/trametinib or ipilimumab/nivolumab.[5] At the time of disease progression, patients were switched to the alternative regimen and the trial sought to answer which sequence of treatments improved OS at 2 years. The trial was ceased early after the fourth interim analysis demonstrated that patients receiving first-line ipilimumab/nivolumab had a 2-year OS of 72% (95% confidence interval [CI] 62–81%) compared with 52% for first-line dabrafenib/trametinib (95% CI 42–62%; log-rank $p = 0.0095$). Adverse events were similar in both groups, with grade 3 or higher toxicity seen in 60% of patients receiving ipilimumab/nivolumab compared with 52% receiving dabrafenib/trametinib.

These results are consistent with results from previous series[6] as well as early data from the SECOMBIT study, which had a similar study question and showed a trend to improved survival with ICIs compared with MAPKi at 2 years.[7] For patients with rapidly progressive, symptomatic disease, MAPKi therapies are likely to be preferable due to their rapid onset of action. However, it is now clear that for the vast majority of treatment-naïve patients presenting with metastatic or unresectable melanoma, ICIs are preferable first-line treatments to MAPKi-targeted therapy.

Recruitment to the DREAMseq trial commenced in July 2015 and 86% of patients were treatment-naïve at enrolment. Of the 14% of patients who received prior treatment, this was almost exclusively adjuvant interferon, with no patients receiving adjuvant ICI- or MAPKi-targeted therapy. Patients were not stratified by whether they received adjuvant therapy. In the intervening years, adjuvant therapy has become standard of care for many patients with stage III melanoma[4] and recent data even suggest an

improvement in survival for adjuvant therapy in patients with stage II melanoma.[8] In 2022, many patients presenting with a new diagnosis of advanced melanoma have progressed on or soon after receiving adjuvant systemic therapy with either ICIs or MAPKi. It is unclear whether the results of the DREAMseq trial apply in this setting and how adjuvant therapies affect the tumor microenvironment at relapse and therefore influence subsequent response.

Furthermore, the results of DREAMseq do not answer the important question of direct relevance to patients at the time of consulting with surgical oncologists, i.e. whether adjuvant ICI therapy is preferable to adjuvant MAPKi therapy for patients with resected stage III BRAF-mutant melanoma. A head-to-head trial comparing MAPKi with ICIs in the adjuvant setting has not occurred and is unlikely to ever be run given the likely cost of such a trial. Therefore, currently, decision making is influenced by differences in adverse event profiles between classes, the fact that MAPKi have demonstrated OS benefit (unlike ICIs where data continue to mature), as well as institutional biases. The low tumor burden and differences in host–tumor interactions in patients treated in the adjuvant setting suggest that ongoing studies and novel biomarkers are required to help clarify which class of treatment is preferable for particular subgroups of patients.

For many patients with advanced melanoma, contemporary therapies allow for long-term disease control and even the possibility of cure. The DREAMseq and SECOMBIT studies highlight the importance of understanding how first-line systemic therapies influence the responses to subsequent lines of treatment and, by extension, patient OS. Similar to the DREAMseq study, the recently published RCT comparing combination relatlimab/nivolumab with nivolumab alone as first-line treatment for advanced melanoma included 8% of patients with prior adjuvant therapy.[9] As this percentage inevitably increases, future trials of first-line systemic therapy for metastatic melanoma will need to carefully control for prior adjuvant therapies to better inform real-world practice.

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