Melanoma Treatment Advances: 2018 in Review

New, more effective and better tolerated options make doctors' decision to recommend adjuvant therapy—and patients' to start it—easier.

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By Marc Hurlbert, PhD, MRA Chief Science Officer

The Melanoma Research Alliance knows the majority of patients, along with their loved ones, are passionate about advancing research to end suffering and death due to melanoma. In support of this, MRA has invested more than $101 million towards cutting-edge research, including the study of more than 96 unique treatment approaches.

Adjuvant Therapy Approvals in 2018

Options for patients with surgically resected (removed) Stage III or Stage IV melanoma

- FDA approved the expanded use of the combination of dabrafenib (Tafinlar) and trametinib (Mekinist) for the adjuvant treatment of patients with surgically resected melanoma with a BRAF mutation, who also have lymph node(s) involvement. (April 2018)
- FDA approved the expanded use of nivolumab (Opdivo) to the adjuvant setting in some patients with melanoma, specifically for the adjuvant treatment of patients with melanoma with involvement of lymph nodes, and also for patients with metastatic disease who have undergone complete resection. (December 2017)

Advanced Melanoma Treatment Approval in 2018

For patients with unresectable (not surgically removable) Stage IV melanoma that has a BRAF mutation

- FDA approved the combination of encorafenib (Braftovi) and binimetinib (Mektovi) for patients with advanced melanoma with a BRAF mutation as detected by an FDA-approved test. (June

2018)

Adjuvant Therapy Approvals. Adjuvant therapy helps to further reduce the risk of melanoma returning after surgery that has removed all detectable disease. While surgery can be curative for many patients, a risk of relapse remains particularly high for patients with melanoma that is deeper or thicker (more than 4 mm thick) at the primary site or involves nearby lymph nodes. Adjuvant therapy helps reduce this risk.

The approval of Novartis' dabrafenib (Tafinlar) + trametinib (Mekinist) as an adjuvant therapy for patients with BRAF-mutant melanoma represents the first FDA approval of a targeted, oral therapy to reduce the risk of BRAF-mutated melanoma returning after surgery. Similarly, the approval of Bristol-Myers Squibb's nivolumab (Opdivo) is the first PD-1 based immunotherapy in the adjuvant setting.

Both options are more effective at reducing the risk of melanoma returning with fewer side effects than the previously available options. This is important, because before deciding to take any medicine you should weigh the relative benefits versus the potential for harm due to side effects. These new, more effective and better tolerated options, make the decision to recommend adjuvant therapy for doctors — and to start it for patients — easier.

"The approval in 2018 of drugs in the adjuvant setting — nivolumab, and dabrafenib + trametinib — is an important step forward for patients after surgery because these drugs better prevent recurrences and have more manageable side effects compared to drugs available previously," noted Michael Atkins, MD, chair of MRA's Medical Advisory Panel.

Advanced Melanoma Treatment Approval. The FDA approval of the combination of encorafenib (Braftovi) and binimetinib (Mektovi) — both from Array BioPharma, Inc. — for patients with unresectable (not surgically removable) or metastatic melanoma with a BRAF mutation, as detected by an FDA-approved test, provides new treatment options for these patients. As the third targeted therapy combination to gain approval, encorafenib + binimetinib was well tolerated in clinical trials, with a potentially better side effect profile than other options.

"The approval of the combination of encorafenib + binimetinib represents the third FDA approval of a combination of drugs that target BRAF/MEK pathways," stated Atkins. "This is important for patients because it provides an effective alternative targeted therapy approach, particularly for patients who are unable to tolerate either of the other two treatment options."

Research Setbacks. Research is research, that is the study of unknown things or unanswered questions. Often science does not advance exactly as the current evidence to-date might suggest, as was the case with a new drug, an IDO inhibitor, named epacadostat. In spring 2018 a Phase 3 clinical trial was halted that was examining the addition of epacadostat to Merck's pembrolizumab (Keytruda) for treatment of patients with advanced melanoma. Preclinical evidence and smaller Phase 1 and Phase 2 clinical trials suggested the combination might prove more potent than pembrolizumab alone at improving progression-free survival and overall survival. In a planned

interim analysis, the investigators found the combination was not working as planned and the phase 3 study was halted. The 2018 story of epacadostat plus pembrolizumab is a good reminder that science remains the study of the unknown, and illustrate why well conducted clinical trials are important to prove the value of new approaches before such approaches can be approved by regulatory authorities and made generally available.

Approvals outside the US. While the US is the world leader in medical research, and the FDA usually leads the way for the approval of new drugs, or new indications of existing drugs, a few new approvals happened outside the US that are relevant to the melanoma community. In December 2018, the European Commission, the EU equivalent to the US FDA, approved pembrolizumab (Keytruda) as an adjuvant treatment for patients with resected, stage III melanoma with lymph node involvement. The regulatory agency in Japan, the Japan Pharmaceuticals and Medical Devices Agency (PMDA), also approved pembrolizumab as an adjuvant treatment for patients with melanoma in January 2019.

With these recent FDA approvals, today we have 14 approved treatments for patients with melanoma in the US, with treatments customized by stage of disease and markers identified in an individual patient's tumor. The approval of drugs globally expands the treatment options for patients in other parts of the world. Looking ahead, MRA anticipates additional Phase 3 clinical trials to report out in 2019, and remains optimistic that additional treatment options to benefit patients will come in the year ahead!

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