Tackling Treatment-Resistant Melanoma

15 new treatments for advanced melanoma have earned FDA approval since 2011, including targeted therapies and immunotherapy.

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The melanoma field has made incredible progress over the past decade in its ability to treat patients with advanced melanoma. This includes patients with tumors that cannot be entirely removed by surgery and patients whose tumors have spread to other parts of the body, referred to as metastatic melanoma. Since 2011, 15 new treatments have earned FDA approval, including targeted therapies directed at one of the most common genetically altered proteins in melanoma, BRAF, as well as various types of immunotherapies. However, while these pioneering advances have revolutionized the way in which melanoma is treated, not all patients yet benefit.

“Despite the progress made in the last 15 years to treat advanced melanoma, clinicians continue to struggle on a daily basis with patients who are not benefiting from all of the wonderful agents or combination of agents that have been brought forward,” said Ryan Sullivan, medical oncologist at Massachusetts General Hospital and MRA grantee. He was referring to the fact that a certain number of patients treated with targeted therapies and immunotherapies either do not respond to treatment at all (refractory to treatment), or initially respond but then at a later point progress despite treatment (resistant to treatment). In either case, it is critical to identify new treatment options for this patient population. To address this pressing topic, MRA as part of its 2022 Scientific Retreat convened a group of 40 representatives from industry, academia, and the FDA in a roundtable discussion on designing the most effective clinical trials to test novel drug combinations in patients not benefiting from approved therapies.

Designing the Best Clinical Trials to Address This Unmet Medical Need

“Patients now exposed to PD1 inhibitors that are no longer benefiting or are not benefitting right away is a very high unmet medical need and we have to make sure that we treat these patients with the right therapy once they become resistant,” offered Nageatte Ibrahim, Vice President of Oncology, Global Clinical Development at Merck and member of MRA’s Scientific Advisory Panel. There are factors to consider in setting up trials to test the effects of new drugs and/or combinations that may improve treatment effectiveness in this patient setting. Many clinical studies focused on patients with treatment resistant melanoma use a combination approach of testing a novel drug with continued administration of the same or a different checkpoint

immunotherapy. The thought behind this approach is to determine whether the novel drug would improve the activity of the backbone therapy.

However, there are some concerns with this approach. If melanoma tumors do begin to respond to the combination, it's not clear if this response is due to the novel therapy on its own or if it was the synergistic effect of both drugs combined. This begs the question as to whether continued treatment with the backbone immunotherapy is warranted.

Therefore, larger randomized clinical trials looking at the effectiveness of the novel agent alone versus the novel agent in the presence of a backbone checkpoint immunotherapy should be performed to sort out this important concern. Michael Atkins, Deputy Director of the Georgetown-Lombardi Comprehensive Cancer Center and Chair of MRA's Medical Advisory Panel added: "As we learn more about the biology of immunotherapy-resistant tumors perhaps it would be better to combine a novel agent with something else other than a checkpoint immunotherapy."

What Are the Considerations for "Special" Patient Populations?

While all patients with advanced melanoma can be treated with checkpoint immunotherapies, patients with tumors containing the BRAF mutation can also be treated with targeted therapies. However, until recently, doctors have had little prospective data to determine which treatment approach should be started first. Data from a recent Phase 3 randomized clinical trial showed that patients with a BRAF-mutation who were treated with an immunotherapy combo first (nivolumab + ipilimumab) followed by a BRAF/MEK targeted therapy experienced a greater 2-year overall survival (72%) compared with patients receiving the reverse sequence (52%). Based on these practice-changing results, more patients with BRAF-mutant melanoma will likely receive immunotherapy as first line therapy going forward. These results helped settle an important question facing clinicians.

However, with each question answered comes another to fill its place: If a patient with BRAF-mutant melanoma progresses, despite immunotherapy in the first line setting, is a clinical trial or BRAF/MEK targeted therapy more appropriate? Several oncologists including Rodabe Amaria, medical oncologist at MD Anderson Cancer Center, said that "clinicians who have treated melanoma patients for many years will be able to distinguish BRAF patients who would benefit from being treated immediately with BRAF/MEK drugs from those who could potentially forego BRAF/MEK treatment — at least for a while — and proceed directly to a clinical study."

"And what should we do with patients who progress and develop brain metastases? Are patients who have metastatic progression to the brain different? What are the criteria to include them in clinical trials?" asked Hussein Tawbi, medical oncologist at MD Anderson Cancer Center.

"There are different populations of patients with brain metastases and maybe we shouldn't put all of them in the same category. Perhaps patients with asymptomatic brain mets can go into a clinical trial whereas patients with symptomatic mets might have to be placed immediately on additional or other treatments," said Caroline Robert, Institut Gustave Roussy. Clearly following

the characteristics of patients as they progress with brain mets and defining specific criteria to include them into clinical studies is important for the melanoma medical community to pursue.

Using Large Pooled Datasets to Further Define Clinical Trial Criteria

Designing the best criteria for randomized trials for patients with treatment resistant disease will require a more detailed understanding of the characteristics of patients who have progressed after being treated with immunotherapy. “Large datasets can come from the analysis of pooled patient-level data from Phase 3 clinical trials. Companies follow Phase 3 study participants after they progress and receive long time survival information and data on subsequent therapies each participant received. Perhaps MRA is the right third party to pull this data together, which will be critical for informing better randomized clinical trial designs,” recommended David Berman, Head of Research and Development at Immunocore.

“This clearly was a lively discussion that resulted in a number of actionable items for us to follow-up on,” said Marc Hurlbert, Chief Executive Officer of the MRA. “We must continue to push forward to identify new therapeutic options for patients with treatment resistant melanoma.”

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