The Role of Targeted Therapy in Treating Advanced Melanoma

Targeted therapies are an important part of the melanoma treatment arsenal, but where do they fit within the standard of care?

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What is BRAF? What is BRAF-mutant melanoma?

About half of patients with melanoma have the BRAF mutation in their tumor. BRAF is a molecule that helps regulate cell growth. A BRAF mutation triggers cells to develop abnormally and divide out of control. This can lead to the development of cancer, including melanoma.

There are many different ways in which BRAF can become mutated and begin behaving abnormally. A mutation called V600E is the most common type and occurs in about 70-80% of cases. The V600K mutation occurs less frequently in about 10-20% of cases. There are also rarer BRAF mutations, often called non-V600 BRAF mutations, that account for as few as 3-14% of BRAF-mutated melanomas.[1]

What is Targeted Therapy?

Targeted therapies are a class of medication that interferes with the function of abnormal molecules within cancer cells. In melanoma, these block the activity of the mutated BRAF protein, and a related protein called MEK. The goal of targeted therapy is to shut down the mutated molecules to slow the growth of melanoma cells—without harming healthy tissue. In this way, the drugs slow or stop the growth and spread of melanoma.

Drugs that inhibit BRAF and MEK molecules can provide a significant clinical benefit for patients with BRAF-mutant melanoma. The U.S. Food and Drug Administration (FDA) approved the BRAF inhibitors vemurafenib and dabrafenib and the MEK inhibitor trametinib to treat patients in advanced stages of melanoma, defined as unresectable stage III or stage IV. Building on the success of using these drugs on their own, combinations of BRAF and MEK inhibitors were also tested and later approved. Because each drug works differently, using them in combination can fight melanoma more effectively than just one therapy alone. Three targeted therapy combinations have been approved by the FDA for patients with advanced melanoma, including:

- dabrafenib & trametinib,
- vemurafenib & cobimetinib, and
- encorafenib & binimetinib.

What treatment options are available for patients with BRAF-mutant melanoma?

Before 2011, treatment options were limited and not very effective for patients with advanced melanoma. In the last decade, over a dozen new therapeutic approaches for melanoma, including targeted therapies and checkpoint immunotherapies, have earned FDA approval. Patients with BRAF-mutant melanomas have more treatment options than ever before. While all patients with advanced melanoma can be treated with checkpoint immunotherapies, only patients with tumors containing the BRAF mutation can also be treated with BRAF and MEK therapies.

Results from the DREAMSeq clinical trial found that patients with BRAF-mutant melanoma experienced greater 2-year overall survival when they started their treatment with immunotherapy, followed by targeted therapy, compared to patients receiving the reverse treatment sequence. This study shows that immunotherapy is highly effective as a first-line treatment in patients with BRAF-mutant melanoma, and suggests the use of targeted therapy later in the course of treatment, if the disease progresses.

However, there are certain scenarios when targeted therapy may be used first. For example, if a patient has immediately life threatening BRAF-mutant metastatic disease (when the melanoma has spread to other areas of the body), treating with targeted therapy for a period of time to stabilize a patient's condition before immunotherapy is used is a possibility.

Are there other approaches for using targeted therapy to treat patients with BRAF-mutant melanoma?

In an editorial[2] in the Journal of Clinical Oncology, MRA-funded investigator Dr. Ryan Sullivan of Massachusetts General Hospital discusses the role of BRAF-targeted therapy in BRAF-mutant melanoma. Despite the DREAMSeq trial results, combination targeted therapy is still highly effective for patients with advanced melanoma. Dr. Sullivan expresses in this article that "it is critical to think about which patients we should offer BRAF-targeted therapy, when in the treatment course to do so, and how we can make BRAF-targeted therapy more effective."

BRAF-targeted therapy is often used as a last resort, when other treatment options, like immunotherapy, are no longer effective. However, studies show that BRAF-targeted therapy is most effective in patients with the least amount of disease. Therefore, one possible strategy to optimize BRAF-targeted therapy is to use it as adjuvant therapy. Adjuvant therapy is an additional

treatment given after the primary treatment for a disease. In melanoma, adjuvant therapy is sometimes used after surgery to reduce the risk of melanoma returning. Adjuvant therapy can help delay or prevent the recurrence of melanoma. In this situation, following surgery, BRAF-targeted therapy may be more effective because there are fewer melanoma tumors found throughout the body. However, clinical trials are needed to test this hypothesis.

Another possible approach suggested by Dr. Sullivan to optimize BRAF-targeted therapy is to develop three drug combinations, or even possibly in the future, four drug combinations. Triplet combinations that combine a BRAF inhibitor, MEK inhibitor, and checkpoint immunotherapy have been used in the scenario where a patient is newly diagnosed with immediately life threatening BRAF-mutant metastatic melanoma. Three clinical trials have also evaluated these so-called triplet combinations of BRAF/MEK inhibitors + checkpoint immunotherapy and found significant improvements in progression-free survival, compared to targeted therapy alone. However, these trials did not compare the effects of triplet combinations to checkpoint immunotherapy alone, or a combination of immunotherapies (such as Ipilimumab + Nivolumab). Without this direct comparison, it is difficult to determine if triplet combinations are a better treatment option than the checkpoint immunotherapy that has become standard of care for BRAF-mutant melanoma.[3] Nevertheless, these trials still demonstrate that triplet combinations are feasible treatment option that may have a role for certain patients.

The optimal use of BRAF-targeted therapy may still yet be unknown. However, Dr. Sullivan suggests that there is evidence that points towards it's use in 1) patients with earlier stage disease (adjuvant therapy for stage III patients) or 2) as a last-resort therapy in patients with immunotherapy-resistant melanoma and/or combined with checkpoint immunotherapy.

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