For Melanoma, How Much Adjuvant Therapy—Treatment After Surgery—Is Best?

Adjuvant immunotherapy can help reduce the likelihood of the skin cancer returning, but is more better or is less more?

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When Dr. Jason Luke was a medical student at Memorial Sloan Kettering Cancer Center he had the benefit of a clinical immunology rotation. “I had a front-row seat for really field-defining work,” says Luke. “I was exposed to translational immunology in clinic, which at the time was mostly vaccine-based, but I managed to grow up at the right time when all these novel [checkpoint] immunotherapies that now inform our field were in clinical development.”

Luke, now the Director of the Immunotherapy and Drug Development Center at UPMC Hillman Cancer Center and an Associate Professor of Medicine at the University of Pittsburgh, credits these early experiences with impacting the trajectory of his work, including the recently-expanded Food & Drug Administration (FDA) approval of Keytruda (pembrolizumab) in earlier stages of disease (Stage IIB and IIC) to reduce the likelihood of melanoma returning following surgery (known as adjuvant therapy).

Jason Luke, MD, FACPCourtesy of Melanoma Research Alliance

Keytruda, the first PD-1 checkpoint immunotherapy to be FDA approved in any cancer, was approved in 2014 for the treatment of surgically inoperable (unresectable) or metastatic melanoma. This was followed by the approval Opdivo (nivolumab), another PD-1 immunotherapy, a few months later for the same indication.

Later, Opdivo and Keytruda, in 2017 and 2019 respectively, were approved for use as adjuvant therapies, to reduce the likelihood of melanoma returning after surgery for patients with Stage III

disease. This was important, because studies have shown that adjuvant therapy for melanoma can reduce the risk of your melanoma returning by up to 50%.

Determining Who Is Eligible to Receive Adjuvant Therapy

However, according to Luke, even this expanded approval still excluded too many patients who might benefit from adjuvant therapy. “Patients who have surgery to remove very deep primary melanomas on their skin, but have no lymph node involvement (Stage IIB and IIC), are at equal if not higher risk of recurrence than some Stage III patients who were eligible to receive adjuvant therapy.

The misnomer, Luke felt, was that the determination of who was eligible to receive adjuvant therapy was based on surgical paradigms, not necessarily an individual’s risk of recurrence. With the help of Nageatte Ibrahim, MD at Merck, Luke was able to secure funding to create a global, phase III clinical trial to prove the value of Keytruda adjuvant therapy for patients with Stage IIB and IIC melanoma.

“It was a slam dunk,” says Luke. “The results were exactly as we had predicted and for all the reasons we suspected.” Luke credits his patients for making this clinical trial possible. On December 3, 2021, the FDA expanded approval of Keytruda to include patients with Stage IIB and IIC melanoma—representing an incredible win for the melanoma research community as it expands therapeutic options for a greater number of patients.

Adjuvant therapy, however, is not without its side effects and risks. Mild side effects can include nausea, fever, diarrhea, and fatigue. Although less common but serious, non-reversible side effects can also include diabetes, thyroid conditions, as well as skin, gastrointestinal, and lung reactions.

The evolution of adjuvant therapy has created tectonic shifts in the field—opening a range of not only treatment options but also discussion points to which the medical, research, and advocacy community are split.

These debates include the following:

- How much surgery is necessary? With FDA approval to give immunotherapy after surgery for removing a skin tumor, it raises the question of whether lymph node surgery is necessary. This is an area of substantial disagreement in the field.

- Should immunotherapy be given after surgery? Given the potential side effects and risks, should clinicians wait to see if melanoma reoccurs before treating patients, particularly as some

patients may be cured through surgery alone? How do we balance the risk of side effects versus the risk of recurrence? Moreover, if patients have already been treated with immunotherapy and their melanoma still comes back, what is the best treatment at that point?

- What are the implications on the health care system? With twice as many people eligible for treatment with an expensive medication, what does this mean for our health care system at large?

- How do we know who needs treatment in the first place? A big unknown is identifying who is at highest risk for recurrence and who is at risk of getting harmed by treatment. These are, according to Luke, two of the highest priority research questions facing the field today.

Luke adds that most patients have Stage I melanoma and despite some gene expression profile testing and tumor DNA research, it's all too early to be used at a scale to identify which patients will progress into something more advanced. "We have people with melanomas that involve lymph nodes that never come back. Meanwhile, you've got somebody with melanoma the size of a tiny dot on their skin and they develop metastatic disease," says Luke.

"These are all questions that we need to answer as a research community."

Those questions are at the centerpiece of MRA meetings. "MRA fills a unique role in melanoma research," says Luke. "They fund very important science that leads to new discoveries, and they bring everyone together at their annual Scientific Retreat. This was where the conversations with Merck around the Keytruda clinical trial first began."

Thanks, in part, to MRA, "melanoma has been the tip of the spear in cancer, leading the way," says Luke, "but we have not fixed every problem. How do we make sure that we continue to have these conversations so everybody has access to the best treatments whenever they need them?"

Luke says that in a perfect world, we could determine who is going to have melanoma come back, offer them treatment that will almost certainly cure their melanoma, and provide a perfect therapeutic window to treat patients who really need it, thus avoiding unnecessary side effects among those who don't. As "pie in the sky" as this may sound, Luke believes this future is not far away.

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