Melanoma Updates 2020

Understanding Immunotherapy Resistance Mechanisms in Melanoma

Dr. Michael Postow, M.D.

Medical Oncologist, Chief, Melanoma Services Memorial Sloan Kettering Cancer Center

Dr. Michael Postow: My name is Dr. Michael Postow, and I'm the chief of the melanoma service at Memorial Sloan Kettering Cancer Center in New York City. It's my pleasure today to talk about several important topics relevant for patients with melanoma in terms of understanding their treatment options and how we're moving forward as a field. The next topic we'll talk about is understanding immunotherapy resistance mechanisms in melanoma. And this is a really important topic because as hopeful as we all want to be for immune therapy and even BRAF MEK drugs, giving us really wonderful long-term responses, unfortunately in both approaches immune therapy approaches and BRAF MEK targeted therapy, resistance develops, and resistance may be in a couple of different varieties. Resistance essentially means the melanoma has found a way to outgrow the treatment that we're giving it or the melanoma it's really kind of outsmarted the therapies that we're delivering. In the setting of primary resistance, that means when we give a drug for whatever reason, the melanoma never really responds well to the drug and it keeps growing even despite that drug.

And the other kind of resistance that can happen is sometimes the drug works really, really well for a little while. And then eventually there's something that pops up later on that ends up being a problem that needs to be separately treated. So those are two different flavors of resistance. Resistance can be relevant for both BRAF MEK treatment, as we had been talking about previously, but also for immune therapy. To delve a little bit more deeply specifically into immunotherapy resistance mechanisms. There've been a lot of theories about what is needed for an immune therapy response. And when these things are not present, it's generally felt to be a contributing factor to melanomas resisting immune therapy. So what are those factors? The first thing I'll say is that nothing unfortunately is perfectly black and white with resistance, meaning there's no one specific factor that if your tumor has X, Y, or Z, it won't respond to immune therapy.

Or if your melanoma has A, B, or C, you're going to have a great response to immune therapy.

So, it's much more of a shade of gray kind of situation where some factors are favorable factors. Some factors are less favorable factors and likely a combination of all of these factors is going to be ultimately needed to decide who has the most likelihood of benefiting from immune therapy and who should be considered for other different types of treatment approaches. So what are some of the factors that we've been thinking about that are associated with likelihood of benefit from immune therapy? Again, it's never a black and white, yes or no type of question in terms of expectation of benefit. One factor that has been associated with responsiveness to immune therapy is how many T cells are actually in the tumor to begin with immune therapy for melanoma, whether it's blocking P1 or blocking CTLA, four of the most common immune therapy agents in melanoma, all of those drugs work by boosting T cell responses against the melanoma. So there've been a lot of studies that have looked at tumor biopsies from patients and found that the more T cells that patients have in their melanoma tumors, the greater, the likelihood that they will have to respond to immune therapy.

And there are many different studies looking at how to look at the T cells. Maybe it's certain kinds of T cells that are most important in this kind of biomarker analysis. But I think that we all generally have a consensus belief that the more T cells that you have in a tumor, the more likely you are to respond to immune therapy. But again, it's not a perfect yes or no, depending on a certain threshold of T-cells, that's one factor. The other factor that we look at a lot of times in tumor biopsies is something called tumor mutation burden. And the general belief is that the more mutations that one has in a tumor, the more likely a patient is to respond to immune therapies. And we don't believe that there's a particular threshold, meaning there's no, yes and no category that if you have a certain number of mutations, you definitely respond. And if you don't have a lot of mutations, you're not going to respond to immune therapy, but it is believed to lie along a continuum. And essentially the theory there is that the more mutations you have in a melanoma tumor, the more different it looks from normal, healthy tissue.

And the immune system has a way to zero in and focus in on the melanoma and see it as something different that shouldn't be there. And it should be something that the immune system should destroy in that context. So numbers of more mutations is better in terms of responsiveness. More T-cells is better in terms of responsiveness. I mentioned two other biomarkers in terms of understanding immune therapy, resistance and response. One of the other biomarkers that is important in understanding this is something called PD-L1. PD-L1 stands for programmed death-ligand 1, and PD-L1 is something that the tumor cells use to hide from the immune attack against the tumor. And PD-L1 high tumors mean there's a lot of this protein called PD-L1 on the surface of the melanoma tumor cells. And in those situations, it's generally believed that patients

that have high PD-L1 on their tumor cells are more likely to benefit from approaches that block PD-L1 and PD 1, which is one of the most common immune therapy strategies in melanoma.

So many times, PD-L1 is tested in tumor biopsies to see if it's high, low, or positive or negative, or sometimes it gives a percent score of how many cells are positive for this. So those are all kinds of things to talk to your doctor about. One thing I will say is it's not standard in melanoma to always have to have PD-L1 test results, to even have the T cell counts reported, or even have tumor mutation burden reported. These are still areas of ongoing research and investigation. None of these are absolutely required to have as part of routine melanoma care, but these are some of the factors that have associated with response and resistance. And the last topic I'll mention for this immune therapy resistance idea is that one of the other important mechanisms of resistance to immune therapy that has been out in the literature is the notion that melanoma cells need to show their antigens, which are parts of their proteins, that flag them for destruction by the immune response. So if a melanoma tumor cell can present its antigens to the immune system, then it is more likely to respond to immune therapy than the melanoma cells that don't present their antigens well to the immune system.

So, there are a lot of different studies looking at different steps along the ways that antigens are presented to the immune system and think about the antigen being presented to the immune system, as someone standing on a mountain and waving a flag. And if you see that flag flapping, that's the antigen being presented. And the immune response, it knows to go to target to that particular area, to destroy it. And that's what we want to do is always destroy the melanomas. But sometimes the cells find ways that they don't present those antigens or some tumors present more antigens than others. And there's a lot of different research understanding all the mechanisms into why that might be the case, but we've seen that some tumors have grown despite immune therapy or become resistant to immune therapy because of lack of antigen processing and presentation, as one additional mechanism. So immune therapy, resistance mechanisms are certainly complicated. A lot of ongoing exciting research, nothing is yet perfect to make clinical decisions based upon these results. But hopefully as we move forward in the future, we'll have more information on how to best select certain patients for certain treatments.