Relative Roles of Targeted Therapies and Immunotherapies in Melanoma

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In this interview, Dr. Mario Sznol shares unique insights into two treatment approaches for melanoma--targeted therapies and a drug that targets the Programmed Death 1 pathway--including how they compare and how they might be combined.

Dr. Mario Sznol is Professor of Medicine at the Yale School of Medicine and the clinical Research Program Leader of the Yale Cancer Center’s Melanoma Program. Dr. Sznol has been involved in cutting-edge research into both targeted therapies for melanoma (he was an investigator on the melanoma DNA sequencing study recently published in Nature Genetics[1]) and immunotherapies for this deadly skin cancer—most recently, a drug that targets the Programmed Death 1 pathway. In this interview, Dr. Sznol shares unique insights into these two treatment approaches, including how they compare and how they might be combined.

Oncology:
In the recent Nature Genetics melanoma DNA sequencing study, new mutations (eg, the RAC1 mutation) were identified that appear to be implicated in melanoma tumorigenesis. What do you think will be the clinical significance of these discoveries?

Dr. Sznol: This is work led by Dr. Ruth Halaban. The study gives us more information about the mutational landscape of melanoma. It’s clear that multiple mutations will be involved in the pathogenesis of melanoma, and we may have to target multiple pathways in order to get optimal effects. We also have a better understanding of other possible pathways that are involved in the malignant behavior of melanomas that have BRAF mutations, and aberrant pathway activation in melanomas that don’t have any of the previously known mutations, for example in BRAF or NRAS. But we don’t immediately have a clear path to clinical translation—for example, a drug therapy—just yet. There will be a great deal of biology that needs to be explored and understood before we can decide what drugs or what combinations of drugs can be effective in the clinic for each of these different subtypes of melanomas that are being defined by the molecular mutations. Although the major findings were directed to RAC1 and phosphatase mutations, multiple genes were mutated, and multiple mutations were found upstream and downstream of RAC. There were also multiple copy number alterations and deletions of tumor suppressor genes. The sequencing information is telling us the complexity of the pathogenesis of melanoma.

Oncology: How does the immunotherapy approach to melanoma treatment compare with the targeted therapy approach, in terms of both efficacy and toxicity?

Dr. Sznol: Right at the moment, when we’re targeting just a single mutation, or even a single pathway, we see very, very good clinical antitumor results, but as far as I can tell, we don’t yet cure anybody. We certainly observe very good tumor responses, improved time to progression, and improved overall survival. It is possible over time, as we understand more and more of these pathways and can target multiple pathways at the same time, that we may get close to a cure with targeted agents. But it’s
also important to understand that when you target multiple pathways, you will likely observe more and more toxicity in most cases. This may not be true in all cases, for example, BRAF and MEK. The BRAF and MEK combination may be better tolerated than agents that just target BRAF mutations or MEK mutations alone.

Overall, the small molecule–targeted drugs are generally fairly well tolerated. Patients can develop chronic tolerable toxicities. But it appears that patients have to keep taking the drugs continuously. So in our treatment unit, we tend to use the targeted therapies as the second or subsequent approach for treatment of patients with melanoma, because the immunotherapies clearly produce durable responses in a subset of patients—and in fact, some patients have durable responses long enough that we begin to start thinking that they might not ever relapse from their melanoma. So we approach most of our patients, even those who have molecular mutations targeted by those small molecules, with immunotherapies first, and if the immunotherapy doesn’t work, then we offer the targeted agents, which we know can still prolong their life, although without actually curing their disease.

The immunotherapies will have very different toxicities. They will induce mostly inflammatory events or autoimmune-type events, including colitis, hepatitis, rashes, endocrinopathies—but generally we’ve learned to manage most of these toxicities. Although patients can get very ill with these drugs, we can get them through the adverse events, and then at some point the adverse events resolve and the patients will no longer be requiring or receiving treatment. Most toxicities are generally completely reversible, with the exception of the endocrinopathies, which require simple hormone replacement. I would guess the quality of life overall will probably be better over time because patients are not requiring chronic therapy to control the melanoma. So at the end of the day, my own bias is that the risk/benefit ratio for the immunotherapies is probably superior to that of the targeted agents. But we shouldn’t view them as one versus the other, because they’re both important modalities to treat patients with melanoma. There are patients who won’t respond to immunotherapy and will need targeted agents. And there will be patients in whom combining the two modalities or using them in sequence will be ideal. I’m very glad we have both of these types of treatments available to patients today. I’m convinced that we’re prolonging the lives of many patients very significantly because we can offer both types of treatment.

Dr. sznol: Do you see the two classes of melanoma therapy—immunotherapy and targeted therapy—as best used in sequence, or do you think they could be synergistic if used together?

Oncology: Almost certainly there will be a combination regimen of a targeted agent and an immunotherapy that’s going to better than either one alone—for a couple of reasons. For example, there are patients who come to see us who have very high tumor volumes and rapid disease progression. And in those patients, there is almost no way that we can give them immunotherapy because it takes too long for the immunotherapy to demonstrate its effect. Those patients will need an agent that will reduce their tumor bulk substantially, to allow time for the immunotherapy to work. So you can see situations where, for example, we might give vemurafenib first or in combination with an immunotherapy. The other reason for combinations is that the targeted agents tend not to cure most patients. They cause great responses; but most patients progress. There are recent data suggesting that targeted agents produce an immune infiltrate inside the tumor. If we can activate those immune cells inside the tumor that arrive there as a result of the targeted agent, we may begin to see synergistic antitumor effects, and we may perhaps increase the cure rate in patients with melanoma. And finally, very interesting preclinical studies have shown that targeted molecular approaches work best in the context of an active immune system and work less well in an immunocompromised mouse. That means the immune system is playing some role in the anti-tumor effects of agents that target tumor cell mutations or signaling pathways directly, and suggests that immune therapies could be timed correctly to work synergistically with molecularly-targeted agents. I still don’t know whether sequencing or combining the approaches will produce the best effects, and we have to be wary of unanticipated antagonistic interactions.

Oncology: What was learned from the Nature Genetics melanoma DNA sequencing study with regard to the origins and development of non–sun-exposed melanomas?

Oncology: For non–sun-exposed melanomas, as you know, they have many fewer mutations than sun-exposed melanomas. Non–sun-exposed melanomas can have driving mutations—c-kit, for example, in acral/lentiginous and mucosal melanomas, which has been known for some time. But what Dr. Halaban found is that in certain non–sun-exposed melanomas, there are more gene copy number alterations and more deletions, suggesting that overexpression of a certain subset of genes—mechanisms that we don’t completely understand—and loss of tumor suppressors drive that malignancy. You can imagine that the tumor may be driven by a combination of genetic changes,
including copy number alteration of certain genes, hyper- or hypomethylation of genes that turn off or turn on certain genes, and maybe loss of other genes that are tumor suppressors. I don’t believe we know much more than that at this point. We need to wait patiently for the biologic studies in order to take those observations and translate them into the clinic.

**References:**

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