



## Patient Education for Melanoma Skin Cancer

### BRAF Mutated Melanoma

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#### TRANSCRIPT

So, what if a melanoma has a BRAF mutation? Many of us will hear this or know of someone that had a BRAF type melanoma. What does that really mean? And we hear the term “genetics” for BRAF. What's all this about? The first thing I'll say is if a BRAF mutation is present in a melanoma, it's not a genetically inherited problem that someone has. It just means that the genes of the melanoma tumor itself went awry in such a way to produce an abnormal BRAF protein.

So, most melanomas are not genetically inherited in the way that we typically think about genetically inherited syndromes and such. Most melanomas happen because of what's called a sporadic change, where the DNA in the tumor itself undergoes changes and produces a melanoma. And in the context of a BRAF mutation, that's exactly the case. Genetically, within the melanoma tumor itself, an abnormal protein is produced. That's BRAF here, and what happens is BRAF, when it's abnormal, shown in green here, triggers a cascade of other proteins to be abnormal as well, and that results in excess growth and proliferation of the melanoma cells.

If you remember, at the beginning of the talk, I talked about the ways that the cells become abnormal and cancer cells continue to divide and grow, even when they shouldn't. BRAF is one of the reasons that the melanomas may divide and grow when they shouldn't. And if you have a BRAF in the melanoma, again, it's not an inherited thing that you got from one of your parents, it's something that just happened in the melanoma itself.

If you do have the BRAF, you may be a candidate for drugs that block the BRAF pathway. And when you block the BRAF pathway, typically that's what the drug that blocks BRAF itself and its partner protein called MEK. So, your doctor will probably talk to you about a BRAF inhibitor and a MEK inhibitor that are usually given in combination to treat BRAF melanoma.

There's a lot of debate about which patients should get the BRAF drugs first or immunotherapy drugs first. And I won't go into all those details today other than to talk to your doctor about it. But in the unresectable Stage Three setting or in the Stage Four setting of melanoma, typically, immunotherapy is given first and then the BRAF drugs are given subsequently, and only given to people with the BRAF kind of melanoma.



And one might say, “Well, I don't have the BRAF, maybe I should try this anyways.” But if you don't have the BRAF mutation and you try this, it's not a good idea because this can actually make the melanomas grow more. So, it's better to only give these drugs to people with the BRAF mutation.

In addition to that, it's important that you do genetic sequencing such that patients that don't have a BRAF mutation could have something called an NRAS mutation. An NRAS mutation is a different kind of mutation that's present in 20% of patients with melanoma, and it's the second most common type of mutation in melanoma. NRAS is not something that can be targeted now with our existing drugs. But it's important that we continue to look for different trials and ways that we can target NRAS in the future. So, that can be a successful strategy for patients with NRAS melanoma.

Some drugs that target MEK have been associated with benefits for NRAS melanoma, but not all of them have been shown to be effective in all contexts, and it's important to talk to your doctor if you have an NRAS mutation with melanoma.

As an example of ways that BRAF can be successfully targeted, this is a kind of patient that had a BRAF mutation in a PET scan at baseline and day 15 on treatment with a BRAF inhibitor. And one can see on the left, there are a lot of different cells that are lighting up in this patient's PET scan with BRAF melanoma. And on the right, after just two weeks of treatment with the BRAF inhibitor, you have a really impressive decrease in lymph node activity with this BRAF inhibitor. And then a lot of the lymph nodes have improved and have gone away in this particular patient, and that's to show that the BRAF strategy can be very, very effective in patients with the BRAF mutant melanoma. So, although it's not necessarily better than immune therapy in those contexts, it is something that you should think about and discuss with your doctor if you do have a BRAF mutation