Melanoma Updates 2021

Molecular Profiling and Driver Mutations in Melanoma Treatment

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Dr. Meredith McKean: Over the past decade in melanoma, we've made significant advances both in immune therapy and targeted therapy. What that means is that we've identified a number of different drivers in the DNA of these tumors that are telling these tumors to continue to grow and to continue to ignore the normal cellular signals to stop growing, stop dividing, and spreading throughout the body. One of the most important drivers that's been identified in melanoma is B RAF. Studies have shown that about 40 to 50% of melanomas stage three, stage four, have a specific activating mutation in B RAF. B RAF B 600 E and K are the most common. This was the initial you know, driver for melanoma. It's also been identified in a number of other tumors, but this is also kind of opened our eyes to identifying some of these specific molecular events in melanoma.

And trying to target those with treatments B RAF has been important for, you know, identifying patients that have that driver and then trying to pair that up with treatment opportunities for patients. So when should patients have molecular profiling performed? Well, B RAF testing is considered standard of care. So, for any patient that's been diagnosed with a stage three melanoma, these patients should have B RAF testing performed. This is part of the standard of care because both immune therapy and targeted therapy are both FDA approved for the stage three setting. So, patients have the opportunity for adjuvant therapy with immune therapy, whether that is pembrolizumab or nivolumab. Or if patients have a V600 mutation and B RAF, these patients can also undergo adjuvant therapy with dibratimib and trimatinib. Now B RAF testing for stage three at this time, we don't have information that helps us know, does this change the prognosis for these patients?

And it's not part of the staging based on the information we have; this just opens up different treatment opportunities. For patients who have stage four melanoma, not only should B RAF testing, be performed, but this is really an opportunity to do more

extensive molecular profiling. So, for any patient with a stage four melanoma, I recommend doing one of the large multigene panels because this gives us information, not only for B RAF, but other drivers of cutaneous melanoma, whether this is NRAS, KIT, and another important one is NTRK fusions. So going through these different opportunities. So, B RAF, we know similar to stage three, when we identify a B RAF mutation, this in the stage, four setting also opens up targeted therapy opportunities. So, we have B RAF and MEK inhibitors that patients can use. And then this also opened up opportunities for other clinical trials.

I'm looking at kind of next generation B RAF inhibitors or other strategies to try to target this, you know, active pathway telling these cancer cells to grow. NRAS mutation is also another defined subset of patients with melanoma. And there's a number of different clinical trials trying to determine how best to target NRAS. Other mutations that may show up on panel testing that have different treatment opportunities that we see, KIT. Now, there's no FDA approved treatments, but there's been a number of different clinical trials demonstrating different oral therapies that may be beneficial for certain KIT mutations, B RCA mutations. So, there can be a correlation both with breast cancer, other tumors and melanoma that can show up on molecular profiling. But this can be helpful because not only can we sometimes identify a B RCA mutation that with a patient's history may warrant genetic testing, but whether it is germline, meaning a patients inherited it.

Or it is in the tumor, a B RCA mutation can open up opportunities for PARP inhibitors on a clinical trial. One other important area for molecular profiling that I like to point out with patient are NTRK fusions. Now, this is rare in melanoma. This may be one to 2% of patients, and that may be an over estimate, but NTRK fusions are noted in a number of different tumors. And there's two FDA approved medications that have shown excellent responses and durable responses. Meaning that if we identify one of these fusions, that patients with melanoma can take pills that are generally well tolerated, and patients can go on to have long lasting responses. Now, NTRK fusions are more commonly assessed on the most common molecular testing, but it is something worth asking your doctor to say, hey, has this been checked? Has this been covered? So, I think the future is bright for cutaneous melanoma and even some of the other melanomas where we're better understanding the different drivers of melanoma.

And then trying to pair those specific mutations up, whether that is with standard of care with B RAF MEK inhibition or with other clinical trials. And I think this is going to help us continue to better understand melanoma and what might be better treatment options moving forward. Some questions that I get from patients in clinic is, well, should I have this testing done on my tumor? Or I've heard about getting this testing done in the blood. At this point, we don't have enough information, but I always lean towards

tissue testing first. If that tissue's available, if tissue is unavailable there's been no tumor that's still available in pathology lab. I think it can be helpful to do a liquid biopsy, to be able to get that information whether that's for just B RAF testing or more complete panel testing, if either has not been done, then that can be helpful to do a liquid biopsy or evaluating in the blood to see if you can identify any of those specific mutations.

Sometimes it can also be helpful to consider repeating this testing if it's been a number of years, we do know that melanomas can evolve. You know, patients after receiving B RAF MEK the oral therapy, there's a number of different resistance mechanisms that can develop and kind of reassessing to see has that melanoma changed. A lot of that is still under investigation and is may not necessarily be approved by insurance. So that's still an area of research that we're continuing to watch and see. Would that be helpful to do repeat testing? So overall at this point, checking the B RAF status for stage three is considered standard of care. And stage four B RAF testing is also considered standard of care, but full molecular profiling is very helpful to identify other targets that can be evaluated. Whether that's on a clinical trial or patients can be treated with standard of care in stage four. So, a lot of excitement here, and I think more to come in the molecular profiling space.