



Melanoma Updates 2020

What is the Correct Choice for First Line Therapy for BRAF+ Metastatic Melanoma?

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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 first topic that we'll talk about will be understanding treatment options for patients with BRAF mutant melanoma. So the question really is, is what's the correct choice or treatment considerations for first line treatment for patients with BRAF mutant melanoma? As we may already know, BRAF mutations are present in approximately 40 to 50% of patients with melanoma. A lot of times a doctor might talk to you about having a genetic test performed for the BRAF mutation to see if it's present in the melanoma tumor to decide if treatment with BRAF directed therapy is appropriate.

And the important thing to consider is that as we talk about this, it is technically a genetic test to see if the BRAF mutation is present. But when the BRAF mutation is present in the melanoma, that does not mean that it's a genetic disorder. It does not mean that kids or siblings or other family members could be affected by having this BRAF gene. So when you have a BRAF gene in your melanoma just means the melanoma itself has the BRAF gene that is producing a protein that's abnormal and can be effectively treated with drugs that target that BRAF mutation. So when we think about the correct treatment for a patient with BRAF mutant melanoma, there's a few different considerations. And the first thing is that the treatment, when you give treatment for patients with BRAF mutations, there are two main strategies that one can think about. One strategy would be giving pills that target the BRAF mutation in the pathway, that's excited by the BRAF mutation, being [inaudible].

And that's called oral targeted therapy oral because of the pills that are taken targeted therapy, because it's targeting specifically the BRAF mutation that's abnormal in the



patient's melanoma. Again about 40 to 50% of people will have that. So it's usually a combination of two pills, a BRAF inhibitor, and something called a MEK inhibitor MEK. And the combination of those two pills has been shown to be better than taking one of the telephone by itself. And we get patients to combinations. There's three different FDA approved combinations that are available from three different drug companies. And we believe the efficacy of all three of these combinations is essentially the same. Each of these different combinations has a little bit different side effect profile. So it would be worth talking to your doctor about which combination might be right for you among these different three different combinations that are available.

But that's one strategy of combining a BRAF inhibitor and a MEK inhibitor pill, targeted therapy for patients with BRAH mutant melanoma. The other option would be immunotherapy and immunotherapy is different. You can't eat immune therapy like you take pills. You have to have immunotherapy infused by an intravenous infusion into the vein, usually in your arm or hand. And it's remains an open question of what's better for patients with melanoma. Do you take the pills that target the BRAF MEK mutations or the BRAF and MEK kinase pathway, or do you take the IV immune therapies? And what different situations should you do one versus the other? And there's a lot of disagreement on this, and there are no exact right situations to do one or the other approach because both are entirely reasonable approaches for patients with the BRAF mutant melanoma to start with in the first line setting.

One situation that one thinks about perhaps being better to start with BRAF and MEK inhibitor targeted therapy is in patients with very symptomatic melanoma, meaning if the melon almost causing pain or bleeding or causing a specific problem that you really want to make sure you get the melanoma shrunk as quickly as possible. The BRAF and MEK Pills usually are the better approach instead of immunotherapy in that situation. Some situations favor immunotherapy in patients with be BRAF mutant melanoma and the situation I think that most strongly favors immunotherapy in patients with BRAF mutant melanoma are situations where there are very similar small melanoma lesions in the brain that for which you don't need to be on steroids for. That might be a situation where actually it's better to start with a combination of immune therapy drugs, as opposed to the BRAF and MEK inhibitors as the first treatment approach. So a lot of debate on what's better between BRF and MEK inhibitors or various different immunotherapies.

And I think at the present time it's patients who need that immediate, rapid tumor shrinkage with the BRAF and MEK inhibitors, those are people that I think are really the most appropriate for BRAF MEK inhibitors upfront with BRAF mutant melanoma. The one additional piece of data that I'll mention before transitioning to some other topics is there's some new information that came out that suggested when you combine the BRAF and MEK inhibitors, vemurafenib and cobimetinib respectively, with an immune therapy drug called atezolizomab that the results look better than vemurafenib and



cobimetinib alone. Now those results are related specifically to improving the time that the BRAF and MEK inhibitors work. So if you're starting a BRAF and MEK inhibitor with your physician, it would be worth asking them to see, should I be also doing atezolizomab immunotherapy when I'm starting my BRAF and MEK inhibitor in the first line setting, or should we save immune therapy for a later time point?

And there's a lot of debate and controversy on what patients really need to start with the triple of all three drugs or is starting with the BRAF and MEK inhibitor alone sufficient? I think for now there, the jury is still out on how important it really is to add the immune therapy to BRAF MEK inhibition. So really the decision for most BRAF mutant patients is starting with the BRAF and MEK inhibitors alone, or starting with immunotherapy alone. The triplet is a little bit of an exception and more to come with more data later in 2020 on that particular topic of triplets. So with that, that concludes what we would be talking about for treatment decisions for patients with BRAF mutant metastatic melanoma