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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Prosecution: Argument for BRAF/MEK-Targeted Adjuvant Treatment of Stage III Melanoma

Announcer:
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Dr. Weber:
We have before the court today an important question, what is the optimal treatment for a patient with completely resected stage III BRAF-mutant melanoma? Is it single-agent immune checkpoint inhibition, or is it BRAF/MEK targeted therapy? We will now hear the evidentiary phase of the trial beginning with the prosecution's case. Dr. Sullivan, you may call your first witness.

Dr. Sullivan:
Thank you, Your Honor. The prosecution calls Dr. Sapna Patel from MD Anderson Cancer Center to the stage. Dr. Patel, we contend that single-agent immune checkpoint inhibitor therapy is not the preferred approach for treating this patient. What is your expert opinion?

Dr. Patel:
I think we have to step back and consider the range of potential treatment options after surgery. That is to say, adjuvant anti PD-1 therapy, nivolumab or pembrolizumab, or adjuvant dabrafenib plus trametinib, or even observation. We do not have combination immune checkpoint inhibitor in this setting, and we've moved past the use of interferon or ipilimumab in the adjuvant setting.

I think we can agree that immune checkpoint inhibitor may be more optimal than targeted therapy in a few settings; the neoadjuvant space and the frontline metastatic setting, maybe even the treatment of brain metastasis, but single-agent immune checkpoint inhibitor may not be optimal in the adjuvant setting.

Dr. Sullivan:
And what evidence do you have to support this assertion?

Dr. Patel:
Well, treatment with dabrafenib plus trametinib in the adjuvant setting does not merely delay relapse, but it also increases the percentage of patients who are likely to remain melanoma-free in the long term. And this can be estimated using this statistical cure model.

Real-world data series point to the median time from adjuvant anti-PD-1 administration to melanoma recurrence being short, less than 6 months. While the median time to recurrence from adjuvant targeted therapy is long, nearly 18 months.

Dr. Sullivan:
And the implication of this is what?

Dr. Patel:
It means that the majority of melanoma recurrences in patients treated with adjuvant anti-PD-1 therapy occur on treatment. And this

means while taking the prescribed year of treatment. In contrast, most recurrences in patients treated with adjuvant targeted therapy occur off treatment after the prescribed treatment is completed. So let me restate that. Recurrences after BRAF/MEK adjuvant therapy occur after the drugs are stopped. And it should be noted that they're stopped mainly for completion of therapy, not for toxicity, in comparison to adjuvant PD-1 recurrences that more commonly occur while still on treatment. And based on this real-world data regarding timing and patterns of recurrence, we can say that adjuvant BRAF/MEK targeted therapy is superior to single-agent anti-PD-1 therapy, since recurrence while targeted therapy is being administered is exceedingly rare.

Dr. Sullivan:
Thank you for that, Dr. Patel. I'd like to briefly revisit your comment about immune checkpoint inhibitors being superior in other treatment settings. It seems to me that most, if not all, of the preferred regimens in the frontline metastatic setting incorporate immune checkpoint inhibitor therapy in some form.

Dr. Patel:
Yes, that's an important point. The effectiveness of immune checkpoint inhibitor after the use and potential failure of adjuvant anti-PD-1 in melanoma is actually unknown and it could lead to decreased efficacy of future immunotherapy due to resistance. But since we know that the use of BRAF/MEK in the frontline setting for metastatic melanoma is suboptimal compared to immune checkpoint inhibitor, using immune checkpoint inhibitor here in the adjuvant setting potentially reduces options for frontline treatment for those who go on to develop metastatic disease on adjuvant anti-PD-1 therapy.

In those real-world series of recurrences after adjuvant therapy, these poor response rates to further immune checkpoint inhibitor are also shown. Response rates to combination immunotherapy treatment after adjuvant anti-PD-1 are low, ranging from 11% to 26%. And the response rate to single agent anti-PD-1 after progression on adjuvant anti-PD-1 is 0%, and 40% and a small reporting of 5 patients who occurred after stopping the adjuvant anti-PD-1, at least in that real-world series. On the other hand, responses to combination immunotherapy after adjuvant BRAF/MEK-targeted therapy remain high, 62 to 63%

Dr. Sullivan:
Great, thank you very much for taking us through that. Now, certainly efficacy is important, but we also have to take into account the safety profile of the available options. Yes?

Dr. Patel:
Of course. And I would just point out that the toxicities incurred from adjuvant BRAF/MEK subside quickly after cessation of treatment. But by comparison, there's a portion of patients treated with adjuvant anti-PD-1 who will incur long-term immune-related toxicities. As you know, we have no way of picking out these patients who develop long-term immune checkpoint inhibitor toxicity before it happens.

Dr. Sullivan:
And can you explain to the jury why that is relevant for them to consider?

Dr. Patel:
Well, I would say that the benefits-to-risk ratio in the adjuvant setting where a patient is melanoma free, it's an important consideration for many patients. A portion, up to 30 to 50% of these patients, may already be cured from their melanoma. And so it asks the question, what are we doing incurring toxicity in this group of patients?

Dr. Sullivan:
Got it. So Dr. Patel, in your expert opinion is single-agent immune checkpoint inhibitor the preferred treatment for a patient with completely resected stage III BRAF-mutant melanoma?

Dr. Patel:
I'm sorry, is this microphone on? Did I mince my words here? Allow me to say it one more time. The use of adjuvant BRAF/MEK is the preferred treatment due to longer time to recurrence, resolution of side effects upon cessation of treatment, and preservation of high response rates to combination immunotherapy in the unresectable or advanced melanoma setting. It reserves the use of immune checkpoint inhibitor for those patients whose melanoma recurs, who are not cured by surgery and by adjuvant BRAF/MEK.

Dr. Sullivan:
Right. Thank you, Dr. Patel. No more questions.

Dr. Weber:
Does the defense wish to cross examine the witness?

Dr. Hamid:
Yes. Judge Weber. Thank you. Dr. Patel, you note that BRAF-targeted therapy is the appropriate option due to the lack of selective

pressure to develop immune

Resistance. Answer me this. Are you aware that there are data of BRAF-targeted therapy causing immune insensitivity? The IPRES situation presented by Dr. Ribas and Lo of UCLA.

Dr. Patel:
I'm aware of the data you present as it relates to metastatic melanoma. But in the curative adjuvant setting where we are trying to avoid development of metastasis, not certain this hypothesis is relevant, and have not seen evidence to support the supposition that the use of adjuvant targeted therapy causes immunotherapy resistance in the metastatic setting.

Dr. Hamid:
What did the DREAMSeq trial show in relation to response rate of immunotherapy post BRAF therapy?

Dr. Patel:
Well, it's another metastatic example. DREAMSeq is the frontline metastatic setting in patients who did not receive adjuvant targeted therapy or adjuvant immunotherapy. It is not the situation we are litigating, which is the optimal regimen in the adjuvant setting. You seem to be perseverating around this idea of preserving a future option. In the adjuvant setting is where we are trying to cure a patient and avoid the need for a future option.

Dr. Hamid:
You showed some data with PD-1 therapy after BRAF therapy. Have you seen the recent data showing response rate of combination immunotherapy of 60% post PD-1 therapy failure?

Dr. Patel:
Okay, it seems like you want to stay on this topic. So the data that you're referencing is limited to 13 patients. It's generally not considered best practice to make decisions regarding how to treat the broader melanoma population in the adjuvant setting based on results from 13 patients with metastatic melanoma. Your

point may be well made that this data informs how to treat a metastatic patient who has received adjuvant anti-PD-1, but not the other way around; it does not inform choice of adjuvant therapy. Furthermore, as I noted with prosecutor Sullivan, the real-world evidence response rate in over 150 patients to combination immunotherapy in the metastatic setting after adjuvant PD-1 using currently available medicines, not clinical trial, unavailable in the current light of day agents, that's low, 18 to 26% after adjuvant anti-PD-1 therapy. But response rates to combination immunotherapy after adjuvant BRAF/MEK-targeted therapy is high, 62%, suggesting there is no immune resistance that you are raising. Response rates to combination immunotherapy in the metastatic setting are higher after adjuvant targeted therapy than after adjuvant anti-PD-1.

Dr. Hamid:
No further questions, Your Honor.

Dr. Weber:
Dr Sullivan, any further witnesses?

Dr. Sullivan:
Not at this time, Your Honor.

Dr. Weber:
Very well. Let's move on to the defense.

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