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

Defense: Argument for Single Agent ICI Adjuvant Treatment of Stage III Melanoma

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Dr. Weber:
We have before us the compelling case of whether single-agent immune checkpoint inhibition, or BRAF/MEK-targeted therapy should be considered the preferred treatment for completely resected stage III BRAF-mutant melanoma. We have heard the prosecution's evidence. Now we will hear the defense's arguments in support of single-agent immune checkpoint inhibition.

Dr. Hamid, you may call your witness.

Dr. Hamid:
Thank you, Judge. The defense calls Dr. Jason Luke from UPMC Hillman Cancer Center. Dr. Luke, thank you for testifying. It's the defense's position that single-agent immune checkpoint inhibitors should be the preferred option for completely resected stage III BRAF-mutant melanoma. Do you agree? And if so, why?

Dr. Luke:
Yes, I do agree. Treatment with an anti-PD-1 monotherapy, such as nivolumab or pembrolizumab, is the optimal treatment choice for patients with high-risk melanoma, due to convenience for the patient and physician, as well as the underlying biology and the treatment kinetics of immunotherapy.

Dr. Hamid:
Okay, but could you explain what you mean by convenient?

Dr. Luke:
Well, sure. Simply put, anti-PD-1 is the easy option for patients with dosing regimens only requiring treatment every 3 to 6 weeks.

Dr. Hamid:
Fair enough. But I think the jury may need further explanation regarding the underlying biology and treatment kinetics.

Dr. Luke:
Well, anti-PD-1 treatment does not require molecular testing, and therefore, can be initiated rapidly after surgery. And translational data suggests that even single doses of anti-PD-1 therapy drive efficacy in neoadjuvant and metastatic clinical trials, such that only should toxicity arise, it is reasonable to stop treatment and only to monitor.

Dr. Hamid:
I see your point. However, the opposing counsel has gone through great efforts to portray BRAF/MEK as being the optimal choice in this setting. How would you address this?

Dr. Luke:

I'd say the treatment with BRAF/MEK is certainly not optimal. In general, it causes more toxicity for the average patient. And the long-term impact of its treatment benefit is unclear in the current era of melanoma therapeutics.

Dr. Hamid:
I'd like you to unpack that statement regarding toxicity. Aren't most of the toxicities low grade?

Dr. Luke:
Well, absolutely they're low grade, but they're also chronic and clinically significant. We're talking about pyrexia, skin issues, and gastrointestinal discomfort. All of these are expected with the dabrafenib and trametinib in the adjuvant setting. I'd also like to point out that dabrafenib and trametinib require that patients modify daily activities to facilitate twice-per-day dosing, as well as the refrigeration of the medications.

Dr. Hamid:
So these toxicities are significant and meaningful to the patient. But can we just withhold treatment or dose reduce?

Dr. Luke:
Well, of course we could. But it's well established that stopping or dose reduction of BRAF inhibitors attenuates their benefit in similar settings. Thus, should toxicity arise, it may be the case that a patient would derive less benefit from BRAF inhibition if stopped early.

Dr. Hamid:
Wow. This is a very compelling testimony. I'll ask you one last time, Dr. Luke, based on the available data, should single-agent immune checkpoint inhibitor be considered the optimal treatment choice for patients with BRAF-mutated completely resected stage III melanoma?

Dr. Luke:
Absolutely. Anti-PD-1 immunotherapy is the optimal approach, as it's the easiest and least toxic for patients. And the biology of response is most consistent with an early treatment effect.

Dr. Hamid:
Thank you for your expert opinions on this important topic. No further questions, Your Honor.

Dr. Weber:
Prosecution, your cross examination.

Dr. Sullivan:
Thank you, Judge Weber. I do have some questions for the witness. Dr. Luke, do you believe that single-agent anti-PD-1 therapy is the optimal therapy option for patients with BRAF-mutant melanoma?

Dr. Luke:
Well, of course. Individual patients circumstances and preferences are essential to take into account. I do believe that anti-PD-1 is the preferred strategy over BRAF plus MEK inhibitors in patients with BRAF-mutant melanoma.

Dr. Sullivan:
Thank you, Dr. Luke. I'd like to take on something that you said a little bit earlier about convenience. Is patient convenience a reason to not treat patients with a superior therapy?

Dr. Luke:
Well, again, presuming that an individual patient does not have a strong preference, generally, we would choose therapy based on efficacy. In the case of adjuvant therapy, outcomes are roughly similar are in terms of the primary endpoints used in clinical trials being relapse-free survival. In other contexts, other aspects of the therapy's delivery and side effect profile are then appropriate to take into account.

Dr. Sullivan:
Got it. And so it seems like there's a higher rate of chronic side effects with adjuvant anti-PD-1 antibody therapy. So, Dr. Luke, do you feel that a higher rate of chronic toxicity is more convenient for patients?

Dr. Luke:
Well, I would suggest the framing of the question as to whether chronic toxicity is more convenient for patients, certainly lacks nuance or clarity. Certainly, there are some patients who experienced long-term low-grade or chronic toxicities with immunotherapy, such as fatigue and others. However, nearly all patients who are treated with the dabrafenib plus trametinib will have noticeable toxicity while on therapy. Therefore, the question is poorly framed as if either/or considerations are in play. The almost certainty of day-to-day life-

relevant toxicities and inconvenience of BRAF plus MEK inhibitors must be discussed with the patient, as compared with the potential for chronic toxicity. But the much more convenient administration of immunotherapy.

Dr. Sullivan:
Great. I have no other questions, Your Honor.

Dr. Weber:
Dr. Sullivan, do you wish to call any other witnesses?

Dr. Sullivan:
No, Your Honor. The prosecution rests.

Dr. Weber:
Dr. Hamid?

Dr. Hamid:
The defense rests.

Dr. Weber:
This concludes the evidentiary portion of the trial. The court is in recess until we hear the closing arguments.

Announcer:
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