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Closing Arguments in the Case of Targeted Versus ICI Adjuvant Treatment of Stage III Melanoma

Announcer:
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Dr. Weber:
We have heard the evidence and testimony of the witnesses. Dr. Sullivan, please make your summary statement for the prosecution.

Dr. Sullivan:
Thank you, Judge. Ladies and gentlemen of the jury, the preponderance of evidence suggests that in patients with resected stage III BRAF-mutant melanoma, single-agent anti-PD-1 antibody therapy leads to an inconvenient increase in severe, potentially life-threatening toxicities, a high rate of chronic side effects without any improvement in efficacy compared to other approved agents.

The efficacy of adjuvant BRAF-targeted therapy is clear and seemingly superior to adjuvant anti-PD-1 therapy and retrospective studies, real-world analyses, and cross trial comparisons.

The toxicities of BRAF-targeted therapy are manageable and reversible with drug holds. The toxicities of anti-PD-1 antibody therapy are associated with rare but severe side effects that do not improve with withholding therapy and often require immune suppression to reverse, and thus may be permanent.

Data from retrospective analyses, real-world datasets, cross trial comparisons of randomized trials clearly show that adjuvant BRAF-targeted therapy is the optimal adjuvant therapy for resected stage III BRAF-mutant melanoma. So no, single-agent immune checkpoint inhibitor therapy should not be the preferred approach to treating completely resected stage III BRAF-mutant melanoma. Instead, BRAF/MEK-targeted therapy should be the preferred approach.

Dr. Weber:
Dr. Hamid, your summary statement please.

Dr. Hamid:
Thank you, Judge Weber. Ladies and gentlemen of the jury, we have seen the benefits of single-agent immune checkpoint inhibitor in the adjuvant setting in relation to relapse-free survival. This therapy is easy to give without delays and also with clear indication of superiority in the neoadjuvant setting, 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 the neoadjuvant and metastatic clinical setting, such that should toxicity arise, it is reasonable to stop treatment and only monitor. Today you heard from witnesses that toxicity is an issue. And most patients on BRAF inhibitor therapy experience these toxicities, fever, myalgias, rash, visual issues, cardiac side effects. You heard that early discontinuation and dose reductions are prevalent. These reductions and discontinuations directly affect efficacy of this therapy.

On the other hand, benefit from immunotherapy can be immediate and long-lasting. In the case of adjuvant therapy, outcomes are

roughly similar in terms of the primary endpoints used in clinical trials, relapse-free survival. There are no head-to-head comparisons. In that context, other aspects of the therapy's delivery and side effect profile are appropriate to take into account.

Dr. Patel pushed the idea of lack of efficacy of immunotherapy post PD-1 adjuvant treatment, but we are aware of high response rates with CTLA4 PD-1, post PD-1 therapy 25 to 30%, and LAG3 PD-1 60%. These are therapies with long-term benefit, while patients post BRAF therapy progressed in the metastatic setting, albeit not with immunotherapy. Dr. Patel fails to note that we have strong data that initial BRAF/MEK therapy may limit immunotherapy efficacy through a mechanism referred to as IPRES, or innate anti-PD-1 resistance. They want to discount the true therapy of record PD-1 through wild correlates and huge inferences, while we have presented real data and real science. PD-1 therapy is the standard. It can be improved with combinations and is being pursued, while BRAF/MEK therapy has been moved to the secondhand pile.

Therefore, the answer is yes, single-agent immune checkpoint inhibitor should be the preferred approach to treating completely resected stage III BRAF-mutated melanoma, not BRAF/MEK-targeted therapy.

Dr. Weber:
Thank you for your summary statements. Before the jury begins deliberations, I would just like to add some further context. We have heard today from witnesses and learned counsel some compelling data supporting the use of immune checkpoint inhibition in completely resected stage III melanoma, whether BRAF-mutated or BRAF-wild type. There is a clear advantage in recurrence-free and distant metastasis-free survival compared to either no therapy or the active comparator of ipilimumab.

In contrast, benefit in terms of overall survival surprisingly is lacking. We've also heard from the learned witnesses and counsel about the benefits of adjuvant BRAF plus MEK inhibition with dabrafenib and trametinib, which yields similar recurrence-free survival for patients with resected stage III melanoma that are BRAF-mutated at 5 years of follow-up, compared to immune checkpoint inhibition. We still lack long-term survival data for adjuvant BRAF plus MEK inhibition.

However, the differences between these two therapies lie in the toxicity profiles, the frequency of administration, the likelihood of permanent side effects, and the overall risk of significant side effects. At the end of the day, it may be that it is a personal choice dictated by the dialogue between the patients and the caretaking team, and not the absolute difference in data.

I would like to thank both councils for their presentations and the witnesses for their expert testimony and insights on this matter. With this, I will turn the case over to our jury, you the learners, to determine the issue of whether a single-agent immune checkpoint inhibition, or BRAF/MEK-targeted therapy should be the preferred treatment option for completely resected stage III BRAF-mutant melanoma. Please choose your verdict by answering the question that appears at the conclusion of this video.

The court is now adjourned.

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