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Prosecution: Argument for Anti-CTLA-4-based Frontline Combination ICI Treatment of Stage IV Melanoma

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Dr. Weber:
Thank you. Today we have before the court a very pressing question regarding the optimal first-line treatment for a patient with stage IV BRAF wild-type melanoma: Which is preferred, anti-CTLA- anti-PD-1, or anti-LAG3 anti-PD-1? We will now begin the evidentiary phase of the trial. Dr. Patel, you may call your first witness.

Dr. Patel:
The prosecution calls Dr. Beverly Hills, Dr. Omid Hamid of the Angeles Clinic and Research Institute to the stand. Dr. Hamid, we contend that NIVO/RELA is not the preferred approach for treating a patient with stage IV BRAF wild-type melanoma. What is your expert opinion?

Dr. Hamid:
Dr. Patel, in the setting of all-comer metastatic melanoma, advanced melanoma patients, we need to discuss the need to first do no harm. This is not related to toxicities, but related to long-term survival benefit. We do have these data with CTLA-4 PD-1 combination therapy when used in patients with stage IV BRAF wild-type melanoma. There are long-term survival data with CTLA-4 PD-1 at 78 months. There are data showing that 3-year progression-free survival is associated with lack of progression and long-term survival. Complete response and partial response at 3 years are durable, and correlate with survival. We have not yet met these endpoints in relation to RELA/NIVO. In fact, there are major issues with discussing anti-LAG3 anti-PD-1 in the same breath as anti-CTLA-4 anti-PD-1, and legitimizing this conversation on an equal footing for both regimens. We can't do this, not now, not in the face of recent data that brings into question the validity of the current dose and schedule of the combination with anti-LAG3.

Dr. Patel:
That's quite concerning to hear. Could you please tell the jury what concerns you most about comparing the two approaches at this time?

Dr. Hamid:
Well, recent data have brought to question the optimal dosing of anti-LAG3 with anti-PD-1. We have not yet made the decision that this is the best we have to offer in the LAG3 setting. I would refer you to phase 1 data I presented at ASCO on the combination of fianlimab, an anti-LAG3 antibody, and cemiplimab, an anti-PD-1 antibody in patients with advanced melanoma. At a fianlimab dose of 1,600 mg plus cemiplimab 350 mg every 3 weeks, we saw significant durable responses and a safety profile that was similar to anti-PD-1 therapy

with the exception of some adrenal insufficiency.

Dr. Patel:
Those new data are quite eye-opening. However, the defense would have us believe that a valid comparison could be made on the strength of available efficacy data.

Dr. Hamid:
And I would strongly disagree. There is no evidence of the benefits of this combination in relation to patients with hepatic metastases, but there is with anti-CTLA-4 anti-PD-1.

Now let's talk about brain metastases, which develop insidiously and are difficult to treat. Brain metastases exist even when we don't see them on scans. Ultimately, we need to prevent or treat them. With RELA/NIVO, we have yet to see anything similar IPI/NIVO's record of treating brain metastases. Simply put, we have no CNS metastases data with RELA/NIVO, and we do with IPI/NIVO. Hazard ratios are not enough; they remove the importance of long-term follow-up data. Finally, response rates are higher with the IPI/NIVO combination. The trials are randomized phase 3 trials. You can't dispute that a response rate of 58%, which we see with IPI/NIVO, is not better than 43%, which we see with RELA/NIVO. I feel that both sides should agree that one should always put your best foot forward in the first line with combination checkpoint inhibitors upfront, and the best option is anti-CTLA-4 anti-PD-1.

Dr. Patel:
Well, what's left then with the NIVO/RELA argument? Is it just an advantage based on less toxicity? We heard an opening statement that the safety profile of NIVO/RELA combination is highly advantageous. Are you swayed by this argument?

Dr. Hamid:
No, not in the least. Our discussion cannot be manipulated through the distraction of toxicity. This so-called advantage is obviated through the ability to use flipped dose with IPI1 and NIVO3. As we saw The CheckMate 511 study, IPI1/NIVO3 had a markedly improved safety profile versus standard dose IPI/NIVO dosing. And as the distinguished Judge Dr. Weber pointed out himself in his opening statement, the efficacy of the two dosing regimens is essentially equivalent with regard to progression-free and overall survival. So, no, our colleagues are looking to argue on toxicity concerns that are easily ameliorated.

Dr. Patel:
Thank you, Dr. Hamid, for your expert opinion. Please lay it on the line for us. Is there any doubt in your mind that IPI/NIVO remains the preferred approach for the first-line treatment of patients with stage IV BRAF wild-type melanoma?

Dr. Hamid:
I have absolutely no doubt that CTLA-4 PD-1 is the preferred approach. We cannot lose the gains that we have made based on a new challenger. And we should not desert a true champion just because of perceived toxicity issues. We have data showing IPI/NIVO benefit in the adjuvant stage IV setting through IMMUNED. In the most difficult situations such as brain metastases, CheckMate 204. And hepatic metastases in BRAF-mutant melanoma. We have years and years of data.

Meanwhile, the anti-LAG, anti-PD-1 data include just one trial, and it was not a head-to-head trial that compared to IPI/NIVO to RELA/NIVO.

Dr. Patel:
Thank you, Dr. Hamid. No more questions.

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

Dr. Luke:
Yes, Judge Weber. Thank you. Dr. Hamid, I would put it on you that the response rate to relatlimab plus nivolumab is approximately the same as ipilimumab plus nivolumab when the latter is evaluated by blinded independent central review. And furthermore, when looking at RELA-047 clinical trial, the absolute improvement in progression-free survival and the overall response rate is similar and slightly greater than that of ipilimumab plus nivolumab.

Dr. Hamid:
That does not in any way take away from the fact that the CheckMate 67 trial confirmed the benefit of anti-CTLA-4 anti-PD-1 in objective response rate progression-free survival and overall survival, as well as treatment-free interval over ipilimumab alone, with over 7.5 years of follow-up.

The treatment-free interval of anti-CTLA-4 anti-PD-1 combination is also improved compared to nivolumab monotherapy. This benefit in

overall survival is maintained across all subgroups; age, geography, LDH, and BRAF status, and tumor burden. We don't have anything of the sort with anti-LAG3 anti-PD-1 combinations, not to mention brain metastases, hepatic metastases, or BRAF-mutant disease. You want the truth? You can't handle the truth. I don't make decisions based on approximate. If you believe so, then you're out of order, you're out of order, the whole trial is out of order, they're out of order.

Dr. Luke:
Still neither therapy has shown to definitively improve overall survival as compared with nivolumab alone. However, both appear to do so in a non-statistically significant but clearly clinically meaningful way.

Dr. Hamid:
Clearly meaningful is long-term benefit. That is lacking here with the RELA/NIVO combination.

Dr. Luke:
Dr. Hamid, are you using long-term benefit to distract the jury from the meaningful and immediate issues at hand? We have clear data on toxicity. And the frequency of serious toxicity with nivolumab plus relatlimab is two to three times less than that of nivolumab plus ipilimumab.

Dr. Hamid:
Dr. Luke, we are not here to speak on toxicity. We're past the point where toxicities are an issue. It only clouds the main point that anti-CTLA-4 anti-PD-1 is the best option. In cases where there is a need to avoid toxicity, there are clear data from CheckMate 511 that we can decrease toxicity to the level observed with anti-LAG3 anti-PD-1. If we look at these studies side by side, you can see that the rates of treatment-related adverse events are roughly similar, as are the rates of treatment-related adverse events leading to discontinuation.

Dr. Luke:
Dr. Hamid, am I understanding you right that the jury should view these adverse event rates as similar? It's been a long time since I've handled a math textbook, but tell me, is 33% still greater than 22%? Or did they change that? And while I'm at it, is 24% still greater than 10%?

Dr. Hamid:
Correct. I said roughly similar; a small price to pay given the advantageous survival benefit that IPI/NIVO provides.

Dr. Luke:
No further questions, Your Honor.

Dr. Weber:
Dr. Patel, any further witnesses?

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

Dr. Weber:
Then let's move on to the defense.

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