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Defense: Argument for Anti-LAG3-based Frontline Combination ICI Treatment of Stage IV Melanoma

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Dr. Weber:
We have before us the compelling case of whether anti-CTLA-4 anti-PD-1 or anti-LAG3 anti-PD-1, should be considered the preferred initial systemic treatment for stage IV BRAF wild-type melanoma. We have heard the prosecution's case against anti-LAG3 combined with anti PD-1, that is to say, relatlimab in combination with nivolumab, and in favor of the anti-CTLA-4 combination, or ipilimumab plus nivolumab. Now, we will hear the defense's arguments in favor of anti-LAG3 anti-PD-1. Dr. Luke, you may call your first witness.

Dr. Luke:
Thank you, Judge Weber. The defense calls Dr. Ryan J. Sullivan of Harvard University. Dr. Sullivan, thank you for being here today. It is our position that anti-LAG3 anti-PD-1 should be the preferred approach for initial systemic therapy in stage IV BRAF wild-type melanoma. What do you say to this?

Dr. Sullivan:
I could not agree more. The combination of anti-LAG3 anti-PD-1 is associated with a similar relative benefit as anti-CTLA-4 anti-PD-1 compared to single-agent anti-PD-1, and without the significant toxicity associated with anti-CTLA-4 anti-PD-1.

Dr. Luke:
Could you explain to the jury what you mean by similar relative benefit?

Dr. Sullivan:
Yes, of course. We see similar differences in efficacy of anti-LAG3 anti-PD-1 and single-agent anti-PD-1 than we do with combined anti-CTLA-4 anti-PD-1. We also see comparable progression-free survival and overall survival, albeit with shorter

Follow-up to anti-CTLA-4 anti-PD-1 in cross trial comparison. Yet the severe side effect rate is less than half of that of anti-CTLA-4 anti-PD-1.

Dr. Luke:
Wait. So I'm sorry. But could you repeat the last part of what you said? Less than half the toxicity?

Dr. Sullivan:
That is correct? Anti-CTLA-4 anti-PD-1 causes severe side effects in over half of patients. And that greatly dampens the efficacy signal

that has been shown in the clinical trials.

Dr. Luke:
Could you just break this down for the jury? What should we conclude from these very different toxicity profiles?

Dr. Sullivan:
My major conclusion is that anti-CTLA-4 anti-PD-1 is highly toxic therapy. It leads to high rates of severe autoinflammatory side effects which require systemic immune suppressive therapy in over half of those treated. Severe toxicity is not associated with improved benefit, and thus, a number of patients with severe toxicity progress and then have limited subsequent treatment options.

Dr. Luke:
These are very convincing arguments, Dr. Sullivan. With all of this in mind, can you say without hesitation that anti-LAG3 anti-PD-1 should be considered the optimal treatment choice for previously untreated patients with stage IV BRAF wild-type melanoma?

Dr. Sullivan:
Absolutely. Based on the comparative data from the RELATIVITY-047 trial and the CheckMate 067 study, the anti-LAG3 anti-PD-1 combination is associated with a similar degree of relative benefit compared to single-agent anti-PD-1, as anti-CTLA-

4 anti-PD-1 combination is with a severe and life-threatening adverse event rate that is less than half of that seen with the combination of anti-CTLA-4 and anti-PD-1.

Dr. Luke:
Thank you very, very much for your expert testimony on this critical matter. Your Honor, I have no further questions at this time.

Dr. Weber:
Prosecution, do you wish to cross-examine the witness?

I certainly do, Your Honor. Dr. Sullivan, words like similar, comparable, and relative benefit reek of handwaving to this intelligent and handsome judge and jury. Is this an attempt to oversimplify complex issues? What statistical evidence do you have to support the assertions that these two combination regimens have similar efficacy?

Dr. Sullivan:
It's funny, I spent the last 10 minutes of my life watching Dr. Hamid make handwaving arguments about why IPI/NIVO is the best therapy ever created. However, to answer your question, yes, there is statistical evidence to support my use of the word similar, comparative, and relative benefit in justifying why RELA/NIVO is the optimal frontline therapy for patients with newly diagnosed stage IV BRAF wild-type melanoma. It's important to note that there's no randomized trial of frontline RELA/NIVO versus frontline IPI/NIVO and patients with advanced melanoma, and it is likely there will never be.

In a scenario like this, we don't have perfect data. We have to rely on comparisons across clinical trials. The reason this is even somewhat okay statistically is that the major trials whose data justified regulatory approval of IPI/NIVO in 2015 and RELA/NIVO in 2022, include the same control arm, nivolumab plus placebo. Thus, we can use a statistical tool called the hazard ratio to compare the benefit and toxicity of IPI/NIVO versus NIVO in the CheckMate 067 trial, as well as the benefit and toxicity of RELA/NIVO versus NIVO on the RELATIVITY-047 study, and then compare the hazard ratios across trials.

So what does the data show? Let me summarize. The primary endpoint of each trial was progression-free survival. The hazard ratio of IPI/NIVO versus NIVO placebo was 0.79, comparable to the hazard ratio of RELA/NIVO versus NIVO plus placebo, which was 0.81. A key secondary endpoint of each trial was overall survival. Here, the hazard ratio of IPI/NIVO versus NIVO/placebo was 0.84. Again, comparable to the hazard ratio of RELA/NIVO versus NIVO/placebo, which is 0.82. So yes, statistically, and relatively speaking, NIVO/RELA has similar comparative benefit as IPI/NIVO.

Dr. Patel:
Thank you, Dr. Sullivan. IPI/NIVO had a sicker baseline demographic population. So these similar hazard ratios are among dissimilar patient populations. I have no further questions, Your Honor.

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

Dr. Patel:
The prosecution rests, Your Honor.

Dr. Weber:

Dr. Luke?

Dr. Luke:
The defense rests, as well.

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

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