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Opening Statements in the Case of Anti-CTLA-4-based Versus Anti-LAG3-based Frontline Combination ICI Treatment of Stage IV Melanoma

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Dr. Reimann:
All rise. Holding Court in Melanoma is now in session. The Honorable Dr. Jeffrey S. Weber of NYU Langone Health presiding.

Dr. Weber:
Thank you, please be seated. The case before the court today is the treatment of a patient with stage IV BRAF wild-type melanoma. Which first-line treatment should be used? Should it be the anti-CTLA-4 anti-PD-1 approach; that is, to say ipilimumab plus nivolumab? Or should it be the anti-LAG3 anti-PD-1 approach, a combination of relatlimab and nivolumab?

The issue to be addressed is whether the established regimen of ipilimumab and nivolumab should be the preferred first-line regimen for BRAF wild-type metastatic unresectable melanoma? Or should it be the newer regimen of relatlimab with nivolumab? The former regimen has impressive long-term survival data but quite high toxicity, to be honest. The latter regimen has shorter follow-up but is clearly less toxic. To throw a further wrench into the mix, the regimen of so-called flipped dose checkpoint inhibitor therapy at ipilimumab at 1 mg/kg and nivolumab at 3 mg/kg has also been evaluated with moderate follow-up and shown to be equivalent in progression-free and overall survival to the standard dose of ipilimumab at 3 mg/kg and nivolumab at 1 mg/kg during the induction phase.

There are now 7-year follow-up data for ipilimumab and nivolumab. And at the last ASCO meeting, we heard the projected 4-year follow up of the relatlimab and nivolumab regimen. At the end of the day, it comes down to what price overall survival. That is to say, what level of side effects are patients willing to accept for prolong survival with metastatic unresectable melanoma?

We will now hear both sides of the story. To present arguments for and against these approaches, we have two distinguished attorneys present today. Dr. Sapna Patel from MD Anderson Cancer Center, who will argue the prosecution's case against anti-LAG3 anti-PD-1 and in favor of anti-CTLA-4 anti-PD-1. And Dr. Jason Luke from the UPMC Hillman Cancer Center, who will argue against the anti-CTLA-4 anti-PD-1approach and defend the use of anti-LAG3 anti-PD-1. Doctors Patel and Luke will be calling distinguished expert witnesses to support their arguments for and against these positions.

Dr. Patel, could you make your opening statement at this time please?

Dr. Patel:

Thank you, Your Honor. Members of the jury, today you will be called upon to deliberate a crucial issue. Is anti-LAG3 anti-PD-1, henceforward known as NIVO/RELA, the optimal first-line treatment for a patient with stage IV BRAF wild-type melanoma? Based on the evidence we have today, I intend to convince you that the answer is absolutely not. We should consider anti-CTLA-4 anti-PD-1 hereto forward known as IPI/NIVO, to be the optimal choice. NIVO/RELA has met only one metric for significance, and that is progression-free survival compared to nivolumab monotherapy. I would contend that progression-free survival is not the real-world endpoint our patients are asking for. They're asking to live longer overall, not merely to live longer without progression of their melanoma.

And that leads me to note that there remains a crucial lack of statistical benefit in overall survival with NIVO/RELA compared with NIVO monotherapy, and also a lack of that statistical benefit in response rate. The hazard ratio for overall survival benefit is modest, 0.82 and non-significant as it crosses 1. And curiously, we've never seen it presented with a P value. Due to a lack of statistical benefit in overall survival and statistical hierarchy of how the study was designed, even a discussion of objective tumor response rates is exploratory. There's a numerical, but merely descriptive improvement in response rate of only 9.8%. And we really should not even be discussing this since it was only to be tested in accordance with statistical hierarchy if overall survival was positive, which it is not.

By contrast, CheckMate 067 confirms the benefit of anti-CTLA-4 anti-PD-1, IPI/NIVO, at objective response rate, progression-free survival, and overall survival as well as treatment-free interval over at ipilimumab alone, with over 7 years of follow-up. This benefit and overall survival is maintained across all subgroups; age, geography, LDH, BRAF status, and tumor burden. The duration of treatment and treatment-free interval of this combination is also improved compared to monotherapy checkpoint, IPI or NIVO, giving patients another one of their desired outcomes, time off treatment. Therefore, we contend that the long-term follow-up of IPI/NIVO has proven this combination to be the optimal frontline treatment for stage IV BRAF wild-type melanoma.

Dr. Weber:
Dr. Luke, we've heard opening remarks from the prosecution. At this time, please provide your opening statement.

Dr. Luke:
Thank you, Your Honor. Distinguished members of the jury, the esteemed Dr. Patel would have you believe that anti-LAG3 anti-PD-1 is not the optimal first-line treatment for a patient with stage IV BRAF wild-type melanoma. However, as you will see today, there is no way that anti-CTLA-4 anti-PD-1 could be the preferred approach over this promising treatment, relatlimab with nivolumab. Although a newer treatment option without the years of experience in the clinic, is at least as efficacious in terms of progression-free survival, response rate, and likely overall survival compared with ipilimumab plus nivolumab. Additionally, the safety profile of this combination is highly advantageous compared with that of ipilimumab and nivolumab. Ipilimumab plus nivolumab is a historical control. However, with improved safety, at least similar durable response outcomes, relatlimab plus nivolumab should be the new standard of care.

Dr. Weber:
Thank you. The opening statements by the prosecution and defense are now concluded. We will take a short break after which we will entertain testimony from two expert witnesses. Court is now in recess.

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