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

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

Announcer:
Welcome to CME on ReachMD. This episode is part of our MinuteCE curriculum.

Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives.

The views you're about to hear are not necessarily the exact viewpoints of the participating physicians. They are expressed for the purpose of presenting differing points of view in this unique medical education setting, exploring best practices in the treatment of melanoma patients.

Dr. Weber:
At this point, we have heard the evidence and testimony of the witnesses. Dr. Patel, could you please make your summary statement for the prosecution?

Dr. Patel:
Certainly, Judge Weber. Ladies and gentlemen of the jury, the regimen of NIVO/RELA is lacking in long-term data, and particularly evidence of a statistical improvement in overall survival compared to monotherapy. It also has a lower objective response rate than IPI/NIVO. And no patient with metastatic melanoma believes a response rate of 43 to 44% is comparable to 58%. One number is less than half of patients responding, and the other is more than half of patients responding. This makes it inferior to IPI/NIVO combination therapy that has demonstrated a statistically significant improvement in progression-free survival, overall survival, objective response rate, and treatment-free interval.

Today, you heard from witnesses describing lower fundamental clinical trial metrics with NIVO/RELA than with IPI/NIVO. Specifically lower and descriptive only no-nsignificant objective response rate, lower progression-free survival, and non-significant benefit in overall survival. Therefore, the long follow-up data exceeding 7.5 years with IPI/NIVO maintains this combination of superior to monotherapy checkpoint blockade in all facets for the frontline treatment of stage IV BRAF wild-type metastatic melanoma. IPI/NIVO has a track record of a long treatment-free interval, 18.1 months, and improvement in overall survival, progression-free survival, and objective response rate compared to single-agent anti-CTLA-4 checkpoint blockade.

The defense will make you believe that toxicity is more important than these efficacy and survival metrics. But I asked you, put yourself in the shoes of a melanoma patient, which of these is more important to you?

So, in summary, anti-LAG3 anti-PD-1, NIVO/RELA, should not be the first-line approach in treating stage IV BRAF wild-type melanoma in the frontline. We contend that the preferred approach should be IPI/NIVO.

Dr. Weber:
Your summary statement, Dr. Luke?

Dr. Luke:

Thank you, Judge Weber. Now, ladies and gentlemen of the jury, the anti-LAG3 anti-PD-1 approach, and that is to say relatlimab plus nivolumab, is the obvious choice as the new frontline standard of care with improved progression-free survival and overall response rate, and a clinically meaningful difference in overall survival, the data speak for themselves.

Meanwhile, on a patient level, in discussion with patients, providers can have confidence about the safety of relatlimab plus nivolumab. Whereas rates of grade 3/4 toxicities are roughly 50% for ipilimumab plus nivolumab. In this context, I basically tell my patients to expect to be admitted to the hospital if they are treated with ipilimumab plus nivolumab. While with the newer relatlimab plus nivolumab combination, this is unlikely.

Today, you heard from expert witnesses about the factors that drive treatment decisions for metastatic melanoma. You will have heard that the safety profile of relatlimab plus nivolumab is significantly better than ipilimumab plus nivolumab. While the efficacy data are roughly similar and numerically greater by an absolute calculation.

In summary, based on the evidence presented today, there can be no doubt anti-LAG3 anti-PD-1 should be the preferred frontline approach to treating stage IV BRAF wild type melanoma.

Dr. Weber:
Thank you for your summary statements. Now it's time for the jury to deliberate and reach a verdict. But before that begins, I would like to summarize what I've heard from the prosecution and from the defense.

We have heard from learned counsel and witnesses that the combination of relatlimab and nivolumab has an excellent response rate in progression-free survival, and can result in a median survival beyond 4 years. The regimen is superior in all aspects to nivolumab alone, and is well tolerated with less than a 20% rate of grade 3/4 immune-related adverse events.

We've also heard from learned counsel and witnesses that the regimen of ipilimumab and nivolumab has the longest median survival seen in a randomized phase 3 study in melanoma and is superior in all aspects to nivolumab alone or ipilimumab alone. The median overall survival of 72 months for IPI 3 mg/kg nivolumab 1 mg/kg at induction has not been surpassed by any regimen thus far. In contrast, the toxicity of that regimen is high, with a 58% rate of grade 3/4 immune-related adverse events. Even flipping the doses to IPI 1 mg/kg and NIVO 3 mg/kg at induction, results in a 34% rate of grade 3/4 immune toxicity.

The decision by patients as to which regimen to pursue will depend on the relative importance to them of overall survival at the plateau versus tolerability, and will remain an individual decision between the care team and the patient.

I would like to thank both councils for their presentations and the witnesses for their expert testimony on this pressing matter. With this, I will turn the case over to our jury, you the learners, to determine the issue of whether the anti-CTLA-4 anti-PD-1-directed approach or the anti-LAG3 anti-PD-1-directed approach should be the preferred treatment option for stage IV BRAF wild-type melanoma. Please choose your verdict by voting on the question that appears at the conclusion of this video.

The court is now adjourned.

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