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Opening Statements in the Case of Targeted Versus ICI Adjuvant Treatment of Stage III 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. A number of large randomized adjuvant trials in high-risk melanoma have demonstrated that recurrence-free and distant metastasis-free survival can be prolonged compared to either placebo or ipilimumab with either a single agent PD-1 blocking antibodies in all patients, or the combination of dabrafenib and trametinib compared to placebo in BRAF mutated patients with resected stage III or IV disease. More recent data have shown the same recurrence-free and distant metastasis-free survival benefit for adjuvant PD-1 antibodies in resected stages IIB or IIC melanoma. A number of studies have also shown that for those stage III patients with palpable or clinically detected lymph nodal disease, neoadjuvant therapy with 3 doses of pembrolizumab alone, or 2 doses of the combination of ipilimumab and nivolumab resulted in outstanding recurrence-free survival, especially if there was a pathologic complete response or a near pathologic complete response in the resected specimen that was taken out.

A recent randomized phase 2 study suggested that 3 doses of neoadjuvant pembrolizumab followed by surgery, then adjuvant pembrolizumab was clearly superior in event-free survival to surgery and adjuvant therapy alone.

Important unanswered questions remain whether to use targeted or immune adjuvant therapy for resected high-risk patients, whether low-risk stage IIIA and IIB patients should receive any adjuvant therapy, and whether all patients with clinically detectable disease at the time of diagnosis with stage III disease should receive neoadjuvant therapy and what type.

The case before the court today is the question of whether the optimal adjuvant treatment for a patient with completely resected BRAF mutant stage III melanoma is single-agent immune checkpoint inhibition, or should it be BRAF/MEK targeted therapy? To present the arguments in favor of and against these approaches, today we have two distinguished attorneys, Dr. Ryan J. Sullivan of Harvard University, who will argue the prosecution's case against single-agent immune checkpoint inhibition, and in favor of BRAF/MEK targeted therapy. And Dr. Omid Hamid of the Angeles Clinic and Research Institute, who will argue the defense's case in favor of single-agent immune checkpoint inhibition as the preferred approach. Both attorneys will be calling witnesses to support their arguments.

Dr. Sullivan, you may make your opening statement.

Dr. Sullivan:

Members of the jury, and a very important issue is before you today for deliberation is single-agent immune checkpoint inhibitor therapy with an anti PD-1 antibody the optimal treatment for a patient with completely resected BRAF-mutant stage III melanoma. Based on the available data, I believe you will be convinced that the answer is a resounding no.

I concede that recent data in the unresectable stage III or stage IV widely metastatic frontline treatment setting shows that combination immunotherapy with ipilimumab and nivolumab is associated with superior outcomes compared to BRAF/MEK combination therapy. However, clinical trials of combination immunotherapy, specifically the combinations of ipilimumab plus nivolumab and nivolumab plus relatlimab, have shown improved outcomes compared to single-agent anti PD-1 antibody in subgroup analysis specifically in the BRAF-mutant patients. Furthermore, the difference was most profound with the combination of ipilimumab plus nivolumab in comparison with nivolumab when nearly all the separation of the progression-free and overall survival curves of combination versus single-agent, or from patients with BRAF-mutant melanoma. Thus, the optimal treatment of unresectable metastatic melanoma in BRAF-mutant melanoma is indeed immunotherapy but it's single-agent immune check - it's not single agent immune checkpoint inhibitor therapy, it's combination immunotherapy regimens.

In patients who had resected stage III melanoma, adjuvant therapy with single-agent anti PD-1 antibody, either with nivolumab or pembrolizumab, has been shown to be associated with an improvement in relapse-free in distant metastasis-free survival, but has not been shown to be associated with improved overall survival. And this treatment is associated with permanent toxicity, specifically permanent endocrine toxicity in 20 to 25% of patients, and persistent toxicity of a wide range of side effect types in over 40% of patients.

In comparison, BRAF/MEK inhibitor therapy with the combination of dabrafenib and trametinib is associated with at least as great, if not greater, improvements in relapse-free survival for patients with resected BRAF-mutant stage III melanoma than in patients treated with single agent anti-PD-1 antibody therapy.

Additionally, there are now retrospective data since no prospective randomized trials have been, nor probably will be run, demonstrating that adjuvant BRAF-targeted therapy may be more effective at reducing risks at the cost of less long-term toxicity. Therefore, we contend that adjuvant BRAF/MEK targeted therapy is the best treatment option for patients who have resected stage III BRAF-mutant melanoma.

Dr. Weber:
We've heard the opening remarks of the prosecutor. Dr. Hamid, your opening statement please.

Dr. Hamid:
Thank you, Your Honor. Distinguished members of the jury, I will put the question to you again, is single-agent immune checkpoint inhibitor the optimal adjuvant treatment for a patient with completely resected BRAF-mutant stage III melanoma? Contrary to what my esteemed colleague argues, the answer to this question is clearly yes. We have listened to Dr. Sullivan argue his point against single-agent PD-1 therapy in the adjuvant setting, masterfully I must add, but this is sleight of hand; look here, not there.

Let's begin with the understanding that immunotherapy in the metastatic setting has proven its excellence and its benefit over BRAF-targeted therapy. We know, as oncologists, that the best of the metastatic therapy show benefit in the adjuvant setting. In the metastatic setting, we have checkpoint combinations. Dr. Sullivan correctly notes the greatest benefit in the metastatic setting is with combination. But in the true prosecution tactics by my esteemed colleague, there is a lack of the whole truth. In truth, PD-1 is the standard throughout the world. And combinations may benefit small subsets. We're not speaking about subsets. We're speaking of all patients. Dr. Sullivan states that BRAF combinations are at least as good, at least as great, but does not have any head-to-head data. He cannot make that statement. He's just putting it out there to fester as truth, half-truth, or just hearsay.

There are data of possible benefit. These are the neoadjuvant data from Alex Menzies from the Melanoma Institute of Australia that shows in patients that neoadjuvant immunotherapy is better than BRAF therapy in relation to relapse-free survival. Dr. Sullivan notes there is a toxicity risk with immuno-oncology adjuvant therapy, but fails to discuss toxicity to vision, retinal vein occlusion that is permanent, and loss of cardiac function that may be permanent, and risks to life that may also be permanent with BRAF/MEK therapy. There are risks to all therapies, and I believe that there are per-patient issues to be dealt with. But the best is PD-1 therapy. Don't take my word for it. Look around, past Dr. Sullivan's manipulative comments, and look at the field that we both belong to, drug development. There is more being done to further the field of checkpoint inhibition in the adjuvant setting. BRAF therapy has been pushed aside and moved to the post-immune space with little to no clinical work being carried out in this setting. Therefore, we contend that PD-1 therapy is the appropriate adjuvant therapy.

Dr. Weber:
Thank you. This concludes the opening statements by the prosecution and the defense. When we reconvene, we will hear testimony from expert witnesses. Court is in recess.

Announcer:
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