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What Dermatologists & Surgeons Need To Know: Adjuvant Treatment for Resectable Stage III/IV Melanoma

Announcer:
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Dr. Weber:
Hello. I'm Dr. Jeffrey Weber. I'm a Medical Oncologist at the Laura and Isaac Perlmutter Cancer Center here at NYU Langone Health in New York City. I'm talking to you about key adjuvant clinical trials in resected stage III and IV melanoma.

There have been a fair number of trials. There actually have been five different adjuvant trials that have yielded important data. And if you look at the earliest trial, this was CheckMate 238, whose initial data was presented in 2017 and I show you the updated data for recurrence-free survival on the left, which was the primary endpoint of a large, randomized trial of more than 900 patients who were randomly allocated to receive nivolumab for 1 year as adjuvant therapy for resected stage IIIB/IIIC/IV melanoma, or the then just approved ipilimumab, which was an active control arm. IPI was approved in the U.S., but not elsewhere. And over time, with more than 5 years of follow-up, I think you can see on the left that the recurrence-free survival curve breaks apart early at 3 months at the first evaluation, stays apart, and it's about an 11 absolute percentage point difference at 5 years, where it looks like it's plateauing.

If you look at overall survival on the right, interestingly, it's hardly different. There's no statistically significant difference with a hazard ratio of 0.86 for survival, which, in part, reflects the fact that patients could cross over. At the time this trial was done, if you failed IPI, you could get NIVO; if you failed NIVO, you could get IPI. So that kind of made it into a crossover study.

Not to be outdone, KEYNOTE-054 was a somewhat similar adjuvant trial, but this time done mostly in Europe, which was adjuvant pembrolizumab versus placebo, because outside the U.S., there was no approved adjuvant therapy at this time for stage III/IV resected melanoma, so placebo was the appropriate control arm. And again, started later than CheckMate 238, less follow-up. But again, I think you'll agree the recurrence-free survival curves clearly break apart at the first evaluation, look very nice with a hazard ratio of 0.57, a 43% reduction in the risk of recurrence over time. And again, I'd much rather be on the blue curve than the red curve, suggesting in more than a 1,000 patient study with a 1:1 randomization, adjuvant pembrolizumab clearly reduced the risk of recurrence or death compared to placebo.

Both of these trials led to registrations for either nivolumab or pembrolizumab, so we have two nice choices for adjuvant therapy for resected stage III melanoma.

Now, the follow-up study to CheckMate 238 was a study where now nivolumab was the control arm and the experimental arm was IPI plus NIVO. Unfortunately, that was an absolutely negative study with recurrence-free survival curves for all patients in this 1,900-patient, large, well-done, phase 3, randomized study on the left, where the curves overlap. And for those who had PD-L1 less than 1% where you figure IPI/NIVO might be really useful, adjuvant IPI/NIVO did not reduce the risk of recurrence or death compared to NIVO alone.

Now let's not forget targeted therapy, because at the same time at ESMO in 2017 that I presented CheckMate 238's nice recurrence-free survival data, Axel Hauschild presented COMBI-AD's data with dabrafenib/trametinib versus placebo in a trial mostly done in Europe. Clearly benefit in terms of recurrence-free survival. And I show on this slide the updated 5-year recurrence-free survival data, where the data show or dabrafenib/trametinib in blue, clear superiority, with a 16 absolute percentage point difference in 5 years compared to placebo, placebo is in red. And again, very nice-looking data, with a hazard ratio for recurrence-free survival or death of 0.51. So you basically cut in half your risk of recurrence or death, and it's been maintained all the way through 5 years of follow up. So very nice, impressive data now for targeted therapy.

Now IMMUNED was a small, randomized phase 2 study which looked at full-dose IPI/NIVO versus NIVO alone versus placebo in resected stage IV melanoma. So a very small niche population, and if you look at the recurrence-free survival data, looks pretty good for the combo in red, compared to NIVO in blue, or doing placebo in green. And the survival curves on the right look pretty good. Again, this is not a registration study. This is not an approved regimen but says maybe full-dose IPI/NIVO is the way to go when you have resected stage IV melanoma.

Now lastly, let's talk about the most recent study that's been a randomized phase 2 study of a neoantigen vaccine with pembro versus pembro alone in resected stage IIIB, IIIC and IV disease. Neoantigens are usually mutated proteins present only in the tumor, not in normal tissue. If you have a normal antigen, you should have no immune response. But if you look at the bottom, if you have a so-called mutation, a non-synonymous mutation in the tumor, it could give rise to a neoantigen to which your body can make an immune response. And that neoantigen vaccine was tested. It's a messenger RNA vaccine from Moderna, combined with pembrolizumab versus pembro alone in a 157-patient, randomized, phase 2 study. And it was a positive study with a hazard ratio for improvement in RFS of 0.56, and the P value two-sided was 0.52, that was at 2 years of follow-up. Recently, there was a press release showing that the recurrence-free survival at 3 years of follow-up, now has a P value 0.019 and the hazard ratio has gotten even better at 0.51. So this is the first neoantigen vaccine study showing benefit with pembrolizumab versus pembrolizumab as the appropriate control arm. And these are data that, of course, led to a randomized, phase 3 study of over 1,000 patients with a similar format.

So what do we conclude about adjuvant therapy for resected stage III/IV melanoma? Single agent PD-1 pembro or NIVO, or BRAF/MEK prolong recurrence-free survival and distant metastasis-free survival in those with stage III resected disease. And NIVO does it also for resected stage IV. No change in overall survival reflecting the essential crossover design that resulted from these studies. IPI/NIVO with every 6-week IPI at a low dose of 1/kg did not prolong recurrence-free survival or distant metastasis-free survival. Full-dose IPI/NIVO, however, with IPI at 3 and NIVO at 1 in induction did appear to benefit patients with resected stage IV disease. And again, surgeons should send any patient with resected stage IIIA, B, C, D, or IV melanoma to the medical oncologist to have a conversation about adjuvant therapy. There'll be multiple choices. And the greatest need, we agree, is to have the ability to pick out those who are going to benefit from those who are not.

And again, I thank you for your attention.

Announcer:
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