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What Are the Data Supporting Adjuvant Therapy in Melanoma?

Announcer:
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Dr Weber:
Hi, I'm Dr. Jeffrey Weber. I am a medical oncologist and deputy director at Laura and Isaac Perlmutter Cancer Center here at NYU Langone Health in New York City. In this section we'll be talking about, what are the data supporting adjuvant therapy in melanoma.

And we're going to go from sort of early melanoma to late melanoma, and although the trials have been done at different times, I would like to go sort of histologically in order. And one of the more important studies in earlier-stage melanoma was the so-called Keynote-716 study. This matured about a year ago. It led to the approval of pembrolizumab early this year for patients with resected stage two B and two C melanoma. It was a nice, large randomized study of over 900 patients who either got pembrolizumab for a year at the standard dose and schedule or a placebo. And placebo was the control arm because until now we've had no approved therapy anywhere in the world for resected stage two B and two C melanoma. Relapse-free survival after a year of therapy was the endpoint. And of course, other secondary endpoints were overall survival, distant metastasis, free survival, and safety.

And the bottom line is here's your updated relapse-free survival curve with about 18 months of follow-up. And I think it's pretty clear that at about nine months the curves diverge and then at 18 months they're significantly different. The hazard ratio for the difference at 18 months which is the second analysis, is 0.61. So you have almost a 40% reduction in the risk of relapse. And you know, keep in mind the relapse rates well above 50% because many of these patients do well. But the two C's will not do well, and these data presented at Jason, by Jason Luke at SMR this past year suggest there's clear benefit in terms of relapse-free survival when stage two B two C patients are treated with pembrolizumab compared to placebo.

One of the earliest studies of checkpoint inhibitors other than the one I showed you in the last talk on ipilimumab, is the use of nivolumab as adjuvant treatment for resected stage three B, three C and four melanoma. Again, another large randomized study done mostly in the US where at that time around 2015, 2016, ipilimumab was an approved adjuvant therapy. So here the control arm was not placebo, it was ipilimumab and nivolumab was the experimental arm both given for one year. And again, relapse-free survival the primary endpoint, and again, I think you'll agree with the updated five-year relapse-free survival data, the patients getting nivolumab on the green curve clearly outperformed those on the gray curve. Getting ipilimumab, hazard ratio for relapse is 0.72, 28% reduction. The medians were very significantly different, 61 months. So, five years for NIVO, only 24 months two years for IPI. So clear superiority, for now, FDA-approved nivolumab versus ipilimumab in resected stage three B, three C, and four melanoma.

If you look at the survival data, however, there's only a minimal difference that's not statistically significantly different. You have a slight advantage at five years in the survival curve of NIVO in green versus IPI in purple or rather gray. But remember there's an inherent crossover here so that completely confuses or muddles the possibility of any change in survival because you could go from NIVO if you failed to IPI, or if you failed IPI you could go to NIVO or PEMBRO in virtually every country where this trial was done. So that makes

survival a very difficult end point.

Not to be outdone, the other excellent PD1 antibody, pembrolizumab has been tested in a slightly different randomized adjuvant study. It's resected stage three A, B, C patients and they got PEMBRO versus placebo because this was done mostly in Europe where there was no approved adjuvant therapy at the time. And again, one year of treatment relapse-free survival was the primary endpoint, and in this study, you were guaranteed if you relapsed off the placebo arm and you had metastatic disease you were guaranteed getting pembrolizumab. So, to some degree, this study addresses, should you give therapy as adjuvant now or should you wait till somebody relapses and select out those who really need the pembrolizumab and give it then?

And again, the data which have not been very recently updated but which look very impressive again for relapse-free survival on the left, a very nice almost 20% difference with a hazard ratio of 0.56 for PEMBRO in blue versus placebo and red. And if you look at distant metastasis-free survival, also excellent difference of about 16 percentage points, hazard ratio of 0.6 favoring pembrolizumab. Very impressive data. If you do the back of the calculations, they're pretty similar to what you see with nivolumab alone. So, we have now two drugs that are approved as adjuvant therapy for resected stage three melanoma.

Not to be outdone, again, targeted therapy as we know is active in metastatic disease, and the Combi-AD study was done interestingly at about the same time as the Checkmate-238 nivolumab versus IPI study. They were both presented at ESMO at the same time in 2017 literally within a half an hour of one another. And this was again a study of over 800 patients who were randomly allocated to get either dabrafenib and trametinib, the BRAF MEK drugs, or placebos again, mostly done in Europe at a time when there was no approved therapy for resected stage three melanoma. Stage three A, B, C was the were the patients who received treatment, and it was a year of therapy, as in all the other studies with relapse-free survival as the primary endpoint.

And the updated five-year survival data published in the New England Journal about a year and a half, almost two years ago, suggests that again at 60 months you're at about the median. It's actually 52%, 60 months relapse-free survival. So very similar to the 50 or 51% relapse-free survival for nivolumab, and I'm sure quite similar to pembrolizumab when those data will come out. So again, the urban legend that the targeted therapies would lead to relapse in almost all patients is not true. There's a plateau at about 50% at five years. Placebo of course is here in gray at about 36%. So clear superiority of BRAF MEK for stage three resected melanoma as adjuvant therapy compared to placebo, led to its approval also. So, we now have NIVO, PEMBRO, dabrafenib, trametinib as approved adjuvant therapies in resected high-risk melanoma.

Now a smaller study which tried to address the issue of whether IPI/NIVO would be useful adjuvant therapy was called the Immuned study which was a small study of about 160 some odd patients, who received on a random basis either IPI/NIVO at the standard doses with high dose ipilimumab at every three milligrams, kilogram every three weeks versus NIVO alone versus IPI alone. And again, relapse-free survival after a year of therapy was the endpoint, and these are updated data that are literally hot off the press.

This has been published recently in The Lancet, and again, it shows IPI/NIVO in red is clearly superior with four years of follow-up in relapse-free survival to NIVO alone in blue or placebo in green. And if you look at survival for the first time it looks like the survival is better for IPI/NIVO. Again, small numbers, this was a pilot phase two randomized study only in resected stage four melanoma. But it suggests that if you give a high enough dose of IPI and NIVO at the standard every three regression, you might benefit patients with the highest risk melanoma and you may do better than NIVO alone. Unfortunately, and I don't show the data, IPI/NIVO at a different dose was tested versus NIVO and found to have no difference in relapse-free survival. Those data were recently presented, and again it does somewhat put the damper on adjuvant studies, but we're going to be moving to neoadjuvant studies in a few minutes and I think that's where you're going to see most of the excitement. So, I thank you for your attention.

Announcer:
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