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What Are the Data Supporting Neoadjuvant Therapy in Melanoma?

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Dr. Weber:
Hi, I'm Dr. Jeffrey Weber. I am a medical oncologist and Deputy Director at the Laura and Isaac Perlmutter Cancer Center, here at NYU Langone Health in New York City. In this session, we're going to talk about what are the data supporting neoadjuvant therapy in patients with melanoma.

And there's been a long history, as you all know to neoadjuvant therapy in many cancers. And it makes sense now that we have effective and excellent therapies in metastatic melanoma that we would apply these to the neoadjuvant mode. And this is now a study that I show here which was the largest compilation up to that time, was published about a year ago in Nature of Medicine by Alex Menzies from Australia, suggesting that if you had a pathologic complete response, a pathologic complete response in high risk resected stage three melanoma which means it's resected stage 3B, 3C, 3D melanoma. In blue on the left, you did very well in terms of relapse-free survival at two years, better than any adjuvant study. Whereas if you didn't have a pathologic complete response, you didn't do quite as well. In terms of survival, similar data is shown on the right where virtually all the patients who had a pathologic CR to either targeted therapy or immunotherapy in this large compilation of almost 200 patients, they did very well. 95% survival of two years, not as good if you didn't have a pathologic CR, 83%, two years. So it sounds like as in breast cancer, lung cancer, colon cancer you get a pathologic CR, you're going to do very well. So, the question is, do we have treatments that are going to give a high rate of pathologic CR because that's what's going to be associated with doing well.

So, there's a lot of action in the neoadjuvant sphere. There are intralesional studies. We have a couple of BRAFi MEKI inhibitor studies with immunotherapy, and as I show on the right, there are a bunch of checkpoint inhibitor studies. And that one on the top just matured, just got presented with very impressive data at ESMO 2022. And we're going to talk about that in a few minutes.

One of the first studies, was a very simple straightforward pilot neoadjuvant study in a small number of patients, something like 30 patients who got a single dose of pembrolizumab. After their initial biopsy, they had to have resectable stage 3B, 3C or four disease. They then got their resection three weeks after that first dose and then they got adjuvant pembrolizumab therapy. And if you look at the disease-free survival or relapse-free survival with 18 months of follow-up, on the right, if you had 90% response or a pathologic CR or better, nobody relapsed. That's the blue curve on the right. If you had more than 10% viable tumor, two-thirds of the patients relapsed by 18 months meaning they did not do very well. Which again, reinforces the idea. If you get a near pathologic CR or a path CR, looking at that pie chart on the left that's about 30% of the patients, you're going to do very well which reinforces everything we've seen from lung, colon and breast cancer.

The next study was done by Rota Amaria published actually now four years ago that was nivolumab or ipinivo, given as neoadjuvant therapy for either three or four doses prior to surgery. And here's a real test of the idea but you're giving more treatment. And again, if

you look at the nivo alone on the left, the response rates only about pathologic CR rates, it's only 25%. And if you look at the waterfall plot, you don't get a whole heck of a lot of shrinkage. Whereas if you look at ipinivo, it sure looks like it works better. 45% path CR rate, 73% resist response rate. So, a lot of the patients respond as you would expect with ipinivo at standard doses with high dose ipi three per kilo. And that sounds like a promising possibility. The only problem is, a lot of those patients are going to get toxicity.

And again, during treatment, we had patients who progressed to metastatic disease, that's a real problem. They never came to surgery. And again, you had a significant, not a huge but a significant rate of grade three, four toxicity. So again, look at that rate of grade three, four toxicity in the combination arm, 73%, that's a real problem.

Now if you get any pathologic response with immunotherapy that is a pathologic CR, pathologic major response which is 90% or more, or even a pathologic partial response which is 50% or more, in that curve on the right, your relapse-free survival's going to be great. And again, this is from Alex Menzies compilation. We're looking at almost 200 patients here. But if you look at those who don't get 50% regression and more, they do not do well, they almost all will relapse over time because look at that orange curve on the right. It's only 24 months and already two-thirds of the patients have relapse, you know, and I know that relapse-free survival curve is going to get worse and worse. So, if we look at the targeted therapy figure on the left, the path CR patients do well, but not that well. And the pathologic partial and no responses don't do that well at all, they almost all relapse. So, it looks to a first approximation like you're going to be better off getting immunotherapy as your neoadjuvant treatment rather than targeted therapy as your neoadjuvant treatment. And this is not a trivial number of patients. I think we'd all agree that the curves on the right look a heck of a lot better than the curves on the left. And again, if you look at any pathologic response for immunotherapy that's on the right, that's enough because any pathologic response with immunotherapy gives a great relapse-free survival. And again, if you don't get a very good response pathologic no response, those patients don't do very well.

So, the newest study has been presented by Rota Amaria. This was last year at ASCO. This was relatlimab three antibody with nivolumab. In metastatic disease, it's now an approved regimen because we know relatlimabnivo is better than nivo alone. So of course, as oncologists, if we see something working metastatic disease, the next thought does it work either as adjuvant or neoadjuvant therapy? So, this was a pilot study of 30 patients where you got two doses of relatlimab and nivolumab, then you had surgery, and then you had it as adjuvant therapy for 10 doses given every four weeks. So total number of doses was 12 and you did it pretty much every four weeks. So again, very nice study, pilot study.

Look at this excellent waterfall plot. The pathologic CR near CR rate, as you'll see in a minute was something like 66% who had an excellent more than 50% resist response rate shown here. And if you look at the distribution of pathologic CR, near path cr, which is so-called major path response, it's seven plus 59 and 66%. That's a fantastic reading. And as I said, the response rate is 57%. So, this is very promising. And these are regimens that I think should be further evaluated in patients with resectable stage 3B, 3C, 3D melanoma. And if you look at the relapse-free survival probability, again, with only about 18 months of follow-up on the lower right, if you had either a 90% or more or a path CR, nobody had relapsed by 18 months in blue whereas everyone else had a significant chance of relapsing. And the toxicity to me was tolerable. If you look at the toxicities in grade three, four, 26%, but it's mostly in the adjuvant setting when you get 10 doses with the two doses, no grade three, four toxicity. So very promising regimen.

Another recently described study was the so-called PRADO study where we don't have mature data but it's a very interesting study where you give two cycles of ipinivo at the so-called flip doses. And in resectable measurable stage 3B, 3C, 3D melanoma, you put a little bead to measure where the index lymph node is and that can be injected. That's done in breast cancer all the time. And you have that index node. And all you could do is after neoadjuvant therapy, take out the index node and the investigator at Christian Blank, the PI of the study showed that if you either took out the index node or all the lymph nodes, didn't matter what happened in the index node, reflected almost 100% of what happened in all the nodes. So, it's an attempt to minimize the surgery. And here it's a little complicated, it's 99 patients. If you had a PR, path CR, near path CR, they just took out the index node and you followed the patient with no further therapy. If you had a path PR, you had all your lymph node taken out and you had no further therapy. If you had less than a 50% pathologic response, lymph node came out and then you got adjuvant nivo with or without radiotherapy. And again, the pathologic complete response rate, 50% near CR rate, 11% for a total of 66%. And again, these patients have done very well. And the question will be, in the path CR or near CR patients can you get away without adjuvant therapy? I don't know what the answer is but we're going to find out when we look at the long-term survival because we have a comparator, and we'll see in a minute what that comparator is.

The NeoTrio study, again recently presented by Georgina Long at ASCO just a few months ago. Interesting study, this time it's a pilot neoadjuvant study. We're looking at 20 or so patients each where patients either got two doses of pembro or you got dabtram for a week, then you got pembro. So you want it to be set up with the dabrafenib, trametinib, sequential therapy or you got concurrent dab, trim, pembro all the way along. And again, you did it for six weeks, you had your lymph node dissection and then you just got adjuvant pembrolizumab because that's an approved therapy. If you didn't have a pathologic response or it was less than 50%, you had the option of switching to adjuvant debrafenib, trametinib in this study.

So interesting study, but the event-free survival. And by the way, we should talk about event-free survival for a moment. Normally when you do neoadjuvant therapy, if somebody relapses before they come to surgery, you don't count them but here, these investigators did what I think was the right thing. An event counted as relapsing before surgery meaning neoadjuvant therapy didn't work. Subsequently, they also will count those who never came to adjective therapy. That is they may have had their section and they relapse before they could start adjuvant therapy. And to be fair, you should include those as an event. You should do a fair comparison. Here if you look at the event-free survival, there's no difference between the groups. I mean, I think you'll agree all of them overlap. It doesn't matter what happens, the numbers are very small. This was a pilot study of 20 patients per harm. But right now, it's not clear to me that adding dabrafenib, trametinib in any way shape or form, adds to the effect of neoadjuvant that adjuvant pembrolizumab.

If we look at the overview of neoadjuvant trials, so far, I think we would agree that looking at a pathologic CR rate, that is achieved in at least 50% of patients who get combination ipinivo as opposed to say just pembro alone. And those are very impressive numbers. And I think that sets up ipinivo at the flip doses as the least toxic but most effective regimen for neoadjuvant therapy.

Now, hot off the press, is the first randomized neoadjuvant study because all the hoopla we've heard about neoadjuvant therapy, would suggest that oh yeah, it sounds very promising. Patients do well, but these are small studies, usually 30 to 60 patients. We don't have any comparison to just surgery and adjuvant study but now to the credit of the cooperative groups and the NCI and Sapna Patel who is the principal investigator of the trial, we have a large, randomized study, over 300 patients of either surgery, followed by adjuvant standard pembrolizumab for a year versus three doses of neoadjuvant pembro, then surgery, then 15 cycles. So, everybody gets the same number of cycles, 15 cycles of adjuvant pembrolizumab therapy.

And again, event-free survival was the endpoint. This is the fairest thing. Again, an event means you can't begin adjuvant therapy within 12 weeks, usually because you relapsed already. Recurrence after surgery, means you're not going to get adjuvant therapy. Death from any cause or if you progressed on neoadjuvant therapy and you couldn't get surgery. So that's the fairest way to do this.

And again, here are the data, very impressive. Hot off the press. Neoadjuvant in terms of event-free survival beats adjuvant therapy alone. The interesting thing is, look at the adjuvant two-year relapse-free survival. With Nevo alone or pembro alone, it's more like 60 to 70%. Here it's only 49% because you count the patients who never come to adjuvant therapy. So if you count those who fail before they get treatment, there is a 23% difference in event-free survival at 24 months, very impressive. Impressive hazard ratio of 0.58, although interestingly, no difference in survival for the first 12 months, and the curves break apart, but the P value is unimpressive. And it's not obvious that we're going to see a survival difference but there certainly is an event-free survival difference. And I think it cements the idea at least using neoadjuvant therapy to render patients more surgically resectable, or even potentially to allow them to go on and not even need further surgery. Again, we're going to hear a lot more about neoadjuvant therapy in the next year, and thank you for your attention.

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