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What Is the Rationale for Neoadjuvant and 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 the Laura and Isaac Perlmutter Cancer Center here at NYU Langone Health in New York City. In this section, we'll be addressing the question as to what is the rationale for neoadjuvant and adjuvant therapy in melanoma. The rationale supporting the use of adjuvant therapy is significant. For example, the tumor can be removed with less immune suppression caused by the tumor. There's a long track record for the success of adjuvant trials in breast cancer, lung cancer, colon cancer, a variety of malignancies. After surgery, most patients recover and have a pretty good performance status. You have destruction of micro metastases, which could prevent distant disease spread, and it's a potential pathway for new drug evaluation and registration.

For neoadjuvant therapy, you would hopefully get some tumor shrinkage, which would render the tumor more resectable. You would decrease the surgical morbidity, and there's, again, time-honored record for that. You could also destroy micro metastases and prevent distant disease spread. There's also now an objective measure of a patient's response to therapy, which you don't have in adjuvant treatment, so you theoretically could personalize the subsequent adjuvant therapy if it's given. It's an opportunity to collect serial biospecimens of tumor, and serum, and peripheral blood cells, which would help our understanding of drug response and resistance. And again, it's also a potential pathway for new drug evaluation and registration.

There's a variety of preclinical data that strongly support the idea that neoadjuvant checkpoint inhibition is useful and could even be better than adjuvant checkpoint inhibition. I'll just show you a snapshot of a cancer discovery article where the 4T1 breast cancer tumor cells were injected at day zero, and then you either had neoadjuvant or no neoadjuvant therapy given at day 17, and then you would have adjuvant therapy given subsequently. And if you look at the survival curves, if you give either adjuvant PD-1 alone or adjuvant PD-1 with a different immune antibody, anti-CD137, if you look at the black squares, it's pretty obvious the survival is longer either with neoadjuvant PD-1 alone on the left or neoadjuvant PD-1 CD137 on the right. So, it sounds like in mouse models, and this is just one typical article, there's a fair amount of evidence that neoadjuvant therapy could be useful if you give the immunotherapy in the mouse model prior to surgery.

Now, there's been a lot of excitement over the use of neoadjuvant therapy in melanoma, and there's even an international consortium of investigators that's been put together, and they have had position papers where they go through, for neoadjuvant studies, how should you pathologically assess the specimen, because, as in all cancers like breast, colon, lung, the assessment of pathologic response in the specimen after neoadjuvant therapy is important. So, there are standards that were described on the left by our pathologist, and there's even been a white paper on neoadjuvant trial design by Rodabe Amaria from MD Anderson, who's a leader in that field, where agreed upon principles for who to treat, how long to treat, how to get biospecimens, and what the best endpoints were, were laid down for investigators to follow.

Some of the best data that we've seen come from a compilation of neoadjuvant studies of several hundred patients from Alex Menezes published a year ago in Nature Medicine. It's a pooled analysis of both targeted immunotherapy-treated neoadjuvant patients with melanoma. All of them had resectable stage IIIB/IIIC/IIID disease. And again, if you get a pathologic complete response, as in most other cancers, in blue you do very well in terms of relapse. If you don't, you don't do as well, shown in the yellow curve, and this is only 24 months. So, most of the patients will end up relapsing beyond two years if you don't get a pathologic CR, but if you do very well, shown in blue.

Now, that should be contrasted with the fact that adjuvant therapy does prolong survival. Here's one of the few adjuvant studies which was done, again, published back in 2016, done between 2010, 2013 of ipilimumab versus placebo in resectable stage III melanoma. Somewhat similar population to what you saw in that neoadjuvant study. And there you do prolong survival. And again, we don't have much survival data in patients getting neoadjuvant therapy, but I think we all agree, adjuvant ipi, and by extension adjuvant nivo compared to nothing, or adjuvant pembro will prolong survival, whether it be indirect or direct evidence. But again, we don't have the survival data from our neoadjuvant studies yet.

There are a number of neoadjuvant studies being carried out or have just matured. As you can see, we have intralesional trials. There's a dab, tram, pembrolizumab trial that we'll talk about briefly, vem, cobimetinib, atezolizumab. Then there's a variety of checkpoint inhibitor trials, and the one on the top we'll discuss in the next section, which has just matured literally in the last week. Was presented at the ESMO meeting. So, we'll talk about that in detail.

With respect to adjuvant studies, a little bit less action. There's a BRA-Fi MEKi ongoing study with encorafenib and binimetinib, and there's the just matured, literally today, a press release came out on nivo placebo for resected stage IIB/IIC disease. We have nivo relatlimab versus nivo for stage III/IV disease, and we have pembro TIGIT versus pembro for resected stage III/IV disease. So, some adjuvant action, but a lot of the action is in the neoadjuvant space. So, we'll hear lots more about that in the coming talks. So, thanks for your attention, and we're going to move on to the next section.

Announcer:
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