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Should a Patient With a BRAF-Mutated Tumor Receive Targeted vs ICI Neoadjuvant Therapy?

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, "Should a patient with a BRAF-mutated tumor receive targeted vs Immune Checkpoint Inhibitor neoadjuvant therapy?"

So, the question is, what kind of data do we have to help us? Because frankly, there aren't trials that directly compare neoadjuvant therapy with targeted versus immunotherapy. However, we have a lot of indirect data. What about BRAF + MEK vs Immune Checkpoint Inhibitor Adjuvant Therapy? Well, interestingly, the stage three relapse-free survival data from COMBI-A/D at five years, look just about as good as Checkmate-238 or Keynote-054, which respectively assessed the adjuvant efficacy of Nivolumab for a year or Pembrolizumab for a year. However, if you look at all the metastatic data, it suggests that immuno-oncology drugs, meaning Immune Checkpoint Inhibitors, should be the preferred first treatment, followed by targeted therapy if there's then progression. My personal opinion is, I favor the use of targeted therapy for the borderline stage IIIA patients, with a relatively good, expected outcome, since there are few irreversible toxicities. And even though based on most of the information I know, I generally will go with immunotherapy first. I think targeted therapy and adjuvant therapy has a lot of virtue. And, it has fewer long-term side effects, so in the cost-benefit analysis, with a low risk of relapse, I will tend to go with the targeted therapy. And again, if you do a back-of-the-napkin calculation, there's probably a slight advantage, if you take out from COMBI-A/D, the IIIAs, and you take out the stage fours from Checkmate-238. You now have a comparable group of IIIB, IIICs. There's probably a little bit of an advantage in relapse-free survival, to immuno-oncology drug Nivo versus the BRAF MEK intervention. but again, that's a back of the napkin calculation and again it's not, there's never been any appropriate comparison of those two treatments.

Now, what about neoadjuvant Dabrafenib and Trametinib in stage IIIB IIIC resected melanoma? Well, this was extensively analyzed by Georgina Long in a very nice manuscript that was published. It's now four years ago, and she had something like 35 patients enrolled and there was a very good pathologic complete response rate of about 50%. Interestingly, just about the same RECIST response rate. And if you look at metabolic response with a PET scan all the same, so it sounds like you get about a half and half pathologic complete response rate.

The problem is if you look at the relapse-free survival for all of the patients and remember it's a single-arm study, you're not doing a comparison here. If you look at the relapse-free survival and look at two years, so go to 24 months for all the patients we're looking at less than a 50% relapse-free survival. I have a bit of a problem with that because if you look at just adjuvant nevo or pembro you had a 50% relapse-free survival at five years. So I'm a little troubled by the fact that with the targeted therapy as neoadjuvant therapy you don't do as well as with adjuvant immuno-oncology drugs. And again, if you look at the PAT CR or the fate of the patients who get a PAT CR, as I've shown you in the past with IPI nivo or nivo rela or pembro alone almost all those patients have not relapsed by two

years. You go look at the relapse re survival curve here for the PAT CR patients, it does not look as good. And if you look at the non-PAT CR patients about a third to a half of them will have not relapsed by two years with IO agents. But if you look at the bottom curve almost all of them relapsed by two years. So, I have the gut feeling that neoadjuvant targeted therapy will not work as well. And if you look at the compilation from Alex Menses, again he's presented this in nature medicine as a publication last year, and this was from a ASCO presentation of a couple of years back. Very nice curve. I think it gives you a really good comparison even though the follow-ups are shorter for the immunotherapy neoadjuvant treatment on the left compared to the targeted neoadjuvant treatment on the right. Look how well the patients who get a PAT CR do in terms of relapse re-survival with IO therapy on the left. They do great. You don't do as well with even a PAT CR with targeted therapy. And in his compilation almost all the non-PAT CR patients were relapsed by two years. That is not the case with IPI nivo or pembro or NEVO alone on the left with the IO neoadjuvant therapy compilation.

Again, if you look at the pooled analysis of the patients who get IO therapy when they get any pathologic response more than 50% those are the three curves at the top. They do great. And admittedly, if you don't get a path partial response if you have less than 50% regression at the time of surgery, you don't do so well. But everybody else does very well. And again, if you look at the same data from Alex Menses from last year in his Nature Medicine article I think you'll agree the yellow curve doesn't look as good as the IO curve of path CRS. And look what happens if you get a path partial response or no response most all those patients would relapse. It is very different in the curve I just showed you before of the patients who got immuno-oncology neoadjuvant therapy. So, I think the data although these are of course not randomized studies they're retrospective comparisons, I think make it clear that IO neoadjuvant therapy looks better than targeted neoadjuvant therapy.

And again, if you look at the study of the neo trio study that was done in Australia, presented by Georgina Long at ASCO this year, again, small numbers, 20 patients per group but she looked at pembro neoadjuvant therapy for two doses followed by adjuvant pembro versus dabrafenib trametinib for a couple of weeks. Then you get pembro or concurrent dabrafenib trametinib pembro in this relapse-free survival curve. Admittedly, with not even 24 months of follow-up, there's no difference. The implication being that targeted therapy doesn't add anything to immuno-oncology neoadjuvant therapy which says you're probably better off going just with the immuno-oncology drugs. And this is just pembrolizumab in this particular study.
Again, the most definitive therapeutic data in my mind come from the DREAMSeq trial. And again, we're not in neoadjuvant treatment here we're in metastatic therapy. So, this is not an adjuvant comparison it's not a neoadjuvant comparison. It's data that indirectly is useful for the neoadjuvant mode and DREAMSeq was Mike Atkins' study, intergroup study. You either got IPI nivo induction therapy for metastatic disease. If you progressed, you got targeted therapy with DAP trim that's at the top in black or you got DAP trim first for your metastatic your first metastatic therapy. And if you progressed you then got IPI nivo and that's in red. And I think it's pretty obvious that there's a 20% difference there. The hazard ratio is very favorable. The P-value is real. I think it's pretty obvious that in the DREAMSeq trial IO therapy is your preferred first treatment, not targeted therapy. So, when it comes to neoadjuvant therapy I would have to conclude based on the direct and indirect data that I have, that you're better off getting IO therapy.

So again, what do I conclude? Again, there are several studies of BRAF MEK neoadjuvant therapy in stage III resectable disease, which shows that the relapse re-survival is inferior to IO therapy for each category of patient. Whether you get a path cr, neuro path cr, which means 90% plus necrosis, or pathologic partial response from 50 to 90 or no response, which is less than 50% in every category you're better off if you give just neoadjuvant therapy with no adjuvant therapy you're better off getting IO therapy first. In my opinion, targeted neoadjuvant therapy would only be indicated if a patient could not be treated with immune checkpoint inhibitor therapy. If they had had allograph transplant in the past a significant history of autoimmune disease like lupus, rheumatoid arthritis, scleroderma that was active, or if they had really fast-growing bulky disease that needed treatment to render somewhat operable, I think then it's perfectly appropriate to use targeted therapy. Again, at this time, the preponderance of evidence is that IO therapy should be preferred when neoadjuvant-off protocol or investigation treatment is used. I thank you for your attention.

Announcer:
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