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Who Is Eligible for Neoadjuvant or Adjuvant Immunotherapy?

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Dr. Gastman:
My name is Brian Gastman. I'm the Surgical and Co-Director of the Cleveland Clinic of Melanoma and High-Risk Skin Cancer Program at the Taussig Cancer Center in Cleveland, Ohio. I will be discussing who's eligible for neoadjuvant or adjuvant immunotherapy for melanoma patients. Quick definitions for our purposes. Adjuvant therapy is systemic therapy being used after definitive surgery to make a patient render no evidence of disease. Neoadjuvant therapy is the same basic therapies but given for specific amount of time prior to the same definitive therapy. Note, this is distinct from giving someone systemic therapy and then stopping for surgical salvage. And this is rarely done without also giving patients adjuvant postoperative therapy.

The case I'm going to start with is a gentleman of my own, 61 years old, relatively healthy. Over a year ago, I had a wild excision and negative cell, no biopsy. He was followed rather carefully and found to have this large axillary mass in the upper right-hand corner. You could see on the CT scan how bulky it is, and, of course, you could see the actual picture. This was found to be his only site of disease, and instead of doing surgery, we considered other therapies. Note the patient is BRAF-negative.

Now, we know if we did surgery and adjuvant therapy alone, he would be likely at least a 40% chance of having a relapse, probably more than that as most trials, like the one on your right here, included patients with much less risky situations as this patient. So, given that, what about neoadjuvant therapy? Well, it is a very new field. If you look at the pool data, monotherapy, like anti-PD-1 therapy, has about a one in three or less chance of having a significant pathologic response, which we know is important for the efficacy of this therapeutic regimen. What about giving Ipi/nivo, or so-called combination immunotherapy? Well, that has a much better effect, but so does it have much higher adverse events and many may want to hold onto this as a backup opportunity if the patient becomes unresectable or stage four. We know in 2021 there were multiple ASCO presentations looking at rela/nivo in nivolumab versus nivolumab, both in the unresectable and neoadjuvant setting, showing a positive benefit for that combination. Much of that data has still not been peer-reviewed, at least for nivolumab versus rela/nivo in the new adjuvant setting. And there's a concern of these patients not being able to be salvaged with Ipi/nivo based on this letter to the editor in the New England Medicine this year. And the other question is this all apples and oranges? You saw how large that tumor was. The average size of all trials pulled in this very important paper was about 2.2 centimeters. That's much smaller than what we're dealing with and perhaps these data are not translatable to some of the patients that we have to deal with.

What if this patient was BRAF-positive? What is the impact of Dreamseq on the resectable patient? Dreamseq were unresectable patients, but as we all know now, although it's yet to be published, it should be soon, that the use of immunotherapy before target therapy had a much better overall survival than the opposite. We also know from the SECOMBIY trial recently published that that is still true, but you could give a patient a small course of targeted therapy to make the tumor smaller, which might be useful in a situation like this and there was no difference in outcome. How important is it for the patient's quality of life being able to use a pill versus having

every three or four week IVs placed? And does age matter? This patient being 61, probably not, but some of our older patients using targeted therapies can be very difficult on them and many times they have to stop and we have to switch them over anyway.

So, what happened to this patient? After two cycles of rela/nivo, his tumor tripled in size. We had to take the axillary vein from the patient and strip out his pleura, probably only getting an R one resection margin. He's doing well, but now what? I should note that you can see the very large tumor. We were able to get this essentially primarily closed, but, in that tumor, around 50% of it was necrotic. Was that because of fast growth? Which is what we normally would think. Or is that actually indication that, despite the growth, there was an effect of the immunotherapy. That will be need to be seen in the future, but these are big questions. Should we continue the rela/nivo, switch them over to Ipi/nivo? These are all areas of deliberation.

We're going to focus on the indications for these therapies based on melanoma-specific survival risk. However, there are other aspects such as toxicity and quality of life that have to be considered. You should note that stage IIB, IIC has almost as bad MSS, melanoma-specific survival, as stage IIIC. And stage IIIA is about as good as stage IB, yet the indications are quite similar and these all have to be considered as risk and benefit when one thinks about what to give these patients. From a new adjuvant perspective, it's a little easier because the patients have to have resectable macroscopic disease which is generally stage IIIC or oligometastatic stage four.

So, we add in the modern adjuvant therapy trials to understand patient's risk. You can see looking at CheckMate-238, Keynote-054, and Combi-AD, that nivolumab versus ipi, pembro versus placebo, dabrafenib versus placebo all had positive signals and all led to FDA approval mainly for stage three disease but also resectable stage four. Now, this is important as is stage IIB, IIC data that was recently published and led to approval for pembrolizumab where it was compared versus placebo as all the data, I'm showing you here is in contrast to the previous slide, which was melanoma specific survival before any of these modern therapies were available. On the other end of the spectrum for stage four, we do know that full-dose ipilimumab nivolumab did have a signal versus nivolumab alone in oligometastatic stage four resectable disease. Interestingly, CheckMate-915, which had low dose Ipi/nivo in a similar setting for stage three did not have a positive result. Whether using Ipi/nivo in the adjuvant setting is still a question to be answered.

So, what are we trying to achieve at adjuvant therapy? Well, we're trying to prevent recurrence in relapse and improve overall survival. The only trial that was designed to look at overall survival was SWG 1404. And you'll notice I have not discussed that trial as it was negative, and none of the other trials have read out yet in terms of overall survival signal. Regardless, there are other issues with adjuvant therapy. We see that patients could be cured with surgery alone, around 44% of them, and about a third or more will recur despite having surgery and modern adjuvant therapy with an overall benefit of the therapy being one in five. If you translate that over to comparing those type of trials to the stage IIB, IIC where patients had to be sentinel biopsy negative. In that trial, Keynote-716, the benefit was one in 14. But those same patients, if they'd been sentinel biopsy positive, would have been in Keynote-054 where the benefit, again, was one in five. So, that one in 14 versus one in five is a significant risk benefit discussion to have with the patient and, to me, makes it still very important to consider sentinel biopsy in these patients. We also know that in the trials I mentioned earlier that macromestastic disease didn't do as well, which likely makes sense as these are more difficult patients, are more high-risk, but also leads to what I'm about to discuss, and that is neoadjuvant therapy, which has to be done in the setting of gross tumor which allows for a tumor microenvironment unlike the adjuvant setting where there's likely just scattered cells in theory. And maybe we can train the immune system especially when we're talking about immunotherapy. Neoadjuvant therapies also enable to be used for predicting outcome, especially if there's pathologic response, but you need a good pathologist to identify that.

And if you look here, in the major combined analysis paper in Nature Medicine in 2021, on your right you can see the effects of having 51% or more non-viable tumor in the surgical resection bed had excellent overall responses, especially when the patients continued on adjuvant therapy. Less than that, though, they did very poorly. The kind of trends, though, that we saw with the immunotherapy were not easily seen with the targeted therapy except if they had excellent responses, meaning really a complete response. There's a lot of major research opportunities and, so far, these kind of trials have led to significant discovery. Finally, doing neoadjuvant therapy builds in the delay to surgery, which may be necessary if the patient's too sick to go to surgery right away. Maybe you want to shrink the tumor to make them more operable or maybe the schedule is just impossible to get the patients in. This was particularly useful during Covid. So, one can imagine these therapies take a few weeks to be given, and then the average time from that treatment to surgery was around seven weeks over all trials with the targeted therapy group having an average of 10 weeks. And this could be very useful for the patients, the oncologists, and the surgeons as plans in a very complex situation have to be made.

There are disadvantages to new adjuvant therapy besides the fact that's still under investigation. Tumors can grow in the interim and maybe come inoperable. We saw that in the case I presented. What do you do if there's no radiologic disease like you see in the bottom right-hand corner? Do you not operate? What about the impact of the recently published PRADO study where a specific node in the basin was marked and then resected only if they had a major pathologic response, that means there was less than 10% viable tumor. The patients did not have surgery versus the rest of the group, and they did just as well or even better, which makes sense since they

had such a great response. But whether we can translate that to modern standard of care is still something that is being discussed amongst clinicians. Unfortunately, one of the other aspects of neoadjuvant trials is that radiology was not shown to be very predictive of tumor effect and outcome. And this will be discussed in a later talk that I'll be giving.

I should note, though, hot off the press, today, at ESMO in Europe, was the fact that SWG 1801 comparing neoadjuvant and adjuvant pembrolizumab for macroscopic stage three disease versus pembrolizumab in the adjuvant setting. Clearly, as you can see here, had a major effect. This is a big deal because it's the first time, even though it's only a phase two trial, that these two paradigms were compared against each other. And this may make for significant clinical changes, especially after this is peer reviewed and various details are interrogated.

So, there are number of ramifications to the surgeon. It's important for them to really understand who and when these therapies should apply to. For me, I'm very lucky to be part of a large tumor board and multidisciplinary team that help me with those questions, and I also have a willing medical oncologist to send them to who actually advocates for these type of therapies. You may not have that in your practice and it's important to identify such a person and develop a strong relationship with them. In the end, you're going to need to convince the patient, the referring physician, and even yourself that this is the right thing to do as this is going to be a new paradigm and delay surgery amongst other aspects of new adjuvant care. Be prepared, though, for the patient who gets adverse events who may not even have surgery or have that surgery delayed. The tumor may grow through therapy as we discussed earlier, or, on the opposite side, has an amazing response and the medical oncologist may want to just continue and to not have the patient go through a major operation. And, in that setting, sometimes the surgeon and the medical oncologist might be on opposite sides of the thinking process and that has to be worked out and, again, leads to the need to have a strong relationship between the two physicians, but then adds to the importance of having a true multidisciplinary team. This, in the end, will allow you to maximize patient benefit and outcome but also add conviction to your thinking processes. And this should include a pathologist as so much of the benefit in neoadjuvant therapy is being seen in the pathology and we now have important standards of practices that are now being published and being promoted, as you see on the bottom right-hand corner here. With that, I'd like to thank you all for your time and attention, and look forward to be able to give you additional talks in this series.

Announcer:
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