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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Panel: How and When Should I Assess Response to Neoadjuvant and Adjuvant ICI Therapy?

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Dr. Gastman:
Hello, we are going to be discussing today about how and when to evaluate melanoma patients on immunotherapy. We're undergoing both adjuvant and or neoadjuvant therapy. My name is Dr. Brian Gastman, I'm with the Cleveland Clinic and I run our melanoma and high-risk skin cancer program, and I'm a surgeon.

Dr. Tetzlaff:
Hi, I'm Michael Tetzlaff, I'm a professor of dermatology and pathology at the University of California, San Francisco. I'm actively practicing dermatopathology now and spent the first 10 years of my career at MD Anderson, working with the melanoma group there.

Dr. Gastman:
Fantastic. So, just to get into the topic, let's start with adjuvant therapy. You know, we've defined it probably many times in the series, but just to remind our audience in our world in melanoma, that is really post-surgical, post definitive therapy, systemic therapy, when it comes to immunotherapy. There are multiple approvals though in melanoma, targeted therapy, at least two anti-PD-1 and one anti-CTLA-4. So, the purpose of this discussion, I think we're going to probably focus mostly on the anti-PD-1-based checkpoint inhibition. And maybe I'll start with Michael. What are your thoughts on how and why to monitor these patients for therapy response and efficacy?

Dr. Tetzlaff:
So, you know, the why is a great question, Brian, because I think the real advantage of neoadjuvant therapy is it gives us that sort of interval window into how well a patient is responding to a specific agent. It also offers the ability to interrogate the tissue for specific biomarkers that might inform risk stratification going in the future, and also the opportunity to potentially modulate therapy in that interval window and decide we either continue with this or we go with something else, depending upon the extent of response. So, I think the why is a really important advantage that neoadjuvant therapy offers patients over and above the adjuvant therapy model.

Dr. Gastman:
That brings in a very good topic of where adjuvant adds it, neoadjuvant adds adjuvant. From an adjuvant only perspective, let's take that since that's the one where we've done the most phase three randomized control trials. Any thoughts from your perspective on not having that neoadjuvant information into how and why we monitor these patients, and I should say when?

Dr. Tetzlaff:
Certainly, regular intervals after initiating therapy to determine the extent of a radiographic and clinical imaging response with the caveat obviously that early on in the therapy, we know that there's a risk immune infiltrate that might show artificial growth of the tumor but really that's just a reflection of an immune response.

Dr. Gastman:
Yeah, so from my perspective, after someone's had surgery, we generally are, certainly on clinical trials but also in standard care, doing serial imaging. In our area of the woods, we have a very hard time getting PET-CT scans approved, so we tend to use CT scans, including the head and neck if it's in head and neck. Primarily otherwise, chest, abdomen, and pelvis; we're usually doing that about every three months for two years, and then usually every six months if the patients are doing well, up to five years. We're not usually getting LVHs in our department, we are getting, depending on the risk of the patient, usually a yearly brain MRI as well because melanoma is a second leading cause of brain cancer, as you know. So, adjuvant therapy: I think it's sort of well worked out because it's been around much longer and it's less under investigation. I think the big issue now is, can we do better? The anti LAG3-PD-1 trial, Rela, is out there, Relativity 098, and there'll be many others. And then of course in the earlier stage patients especially the stage 2b and 2c, there's a multitude of trials that are going to be coming out soon. So, I think it seems that from that perspective it's a much more straightforward question. But as you alluded to with the new adjuvant side that's really where the complexity comes in and a lot of investigations. So, you being also a dermatopathologist, I'm curious. What do you think about assessing the patient response versus the original biopsy? So, you get a biopsy, you give them some courses of neoadjuvant therapy and then you get the tumor specimen. How do you compare one to the other, not just the actual response in the new adjuvant resection bed?

Dr. Tetzlaff:
Yeah, that's a great question. I think there's limited utility in the comparison per se, only to the extent that the pretreatment is usually like a core biopsy and you're just getting a small piece of the bigger picture. Whereas at the time of surgery obviously you all are removing the entire tumor and that gives us the ability to really interrogate, histopathologically and grossly, the entire treated tumor bed. So, you get a much broader view of response/resistance to therapy at the time of surgery as opposed to pretreatment specimens in which you're really just getting a snapshot. That said, I think the pretreatment and sometimes even on treatment biopsies really offer a critical window for biomarker assessment to really start to understand aspects of the tumor cells and the tumor microenvironment that may inform prognostic models going forward of biomarkers that predict response and/or resistance to the therapy in question.

Dr. Gastman:
So, in the theme of how and why to follow these patients I mean once they've had their neoadjuvant therapy, they're essentially an adjuvant patient in terms of follow-up. They've had surgery, they're going to get likely clinical interval scans and physical exams. But as you know, better than almost anybody there's obviously a huge difference between a pathological complete response and a pathologic non-response. Let's assume based on the Menzies' major paper, the main analysis of all the major neoadjuvant trials, that 50% or lower of non-viable tumor is a non-pathologic response. And let's say you have that type of patient versus someone who has literally no viable tumor at all, complete pathologic response. Would you, in your mind, feel there's any reason to change how we evaluate those patients in the adjuvant setting and, in the post, neoadjuvant postsurgical setting?

Dr. Tetzlaff:
No, I think that the only way that you got to that data was through sort of a systematic approach towards identifying the extent of a viable tumor in that treated tumor bed. Until we have an empiric number that says either we don't have to evaluate that or we can modify the manner in which we've proposed to assess the tumor bed and for a number that says, 'Oh, actually the magic number is 60% response or 70% response,' and there's certainly some early data to suggest that these kind of empirical cutoffs that we assign; 50%, is just something that's a pretty reproducible cut point to distinguish a partial response from a quote, unquote, non-response. But certainly, that's just empiric based on what's practical not necessarily data-driven yet. And until we see data that really drives that distinction, I think we sort of keep with those cutoffs. And, and I would just add that the systematic approach that we proposed, and I can sort of share my screen briefly and just sort of share that, the systematic approach that we proposed is here to sort of ensure that depending upon the nodal size, less than five centimeters, you submit all that tissue. Greater than five centimeters you submit a complete cross-section per centimeter of involved node with the advantage being that you get a really systematic topographic map of that treated tumor bed either in total or at least a systematic approach through the tumor bed. And what that I think does is, again affords us a very careful assessment that was the basis for the Menzie study in which we were able to pool those different patients because they had all been processed similarly at the pathology bay and from the perspective of our cut points of complete response, partial response, and non-response. They were all processed and analyzed similarly.

Dr. Gastman:
So, it seems to me, and I get what you're saying, you're saying that since we don't know that nobody is going to recur with a pathologic complete response and we don't know when and how bad they will with or without pathologic non-response, so maybe we don't do less imaging. But then what about the opposite? So, for example, we know, I believe it was from the Australian group, that the average recurrence for adjuvant patients mainly stage three/recyclable stage four's, is around four and a half months after adjuvant therapy starts. And right now, if you get CT scans every three months, you're literally going to be in the middle of two CT scans when your

average recurrence is going to happen, right? Cause you're getting one at three months, one at six, and the average is four and a half. I would almost argue maybe we should be getting additional scans; maybe doing it every six weeks. So maybe, the pathologic complete response is you do that every three months and then after that every six months, and after two years. But for those pathologic non-responders, does the data that you've seen maybe point to the fact that we should be getting every six weeks imaging, because their risk is higher, and the timing of that risk is different so we should intensify the follow-up imaging? What do you think, or we don't have the data for that?

Dr. Tetzlaff:
No, I think that's exactly the ideal. You can sort of delineate patients according to their risk group. A complete responder, obviously based on the data that we have, is a good category to be in. And a non-responder, somebody who has 80%, 90% viable tumor still, there's all kinds of rationale. Should you change the therapy in the adjuvant setting? Do you want to be more aggressive about imaging? All of these are again, just underscoring more about the advantage to the neoadjuvant paradigm, mainly that you have that interval window to then adjust things according to the patient's proposed risk, and Alex's study I think nicely exemplifies that. And everything that you're saying I think is just aligned perfectly with the model of why neoadjuvant therapy is such a strong model.

Dr. Gastman:
I know we're near the end of time, but all this is still under investigation. These studies are pools of phase one trials, but we are getting the ability to do a lot of off labeling of neoadjuvant therapies. And I think if you're the general clinician who's not doing these on clinical trial or not studying these on your own, I do think it's really important for them not only to understand what these therapies are but also to consider maybe tailoring the approach to each patient individually within the constraints of the that patient's insurance company, to maybe up or down-regulate the amount of intensity. But I agree with you; I probably would at least try to start with what was in the clinical trials and only add to it, not detract from it. And hopefully, we'll be seeing, especially the recent data of SWOG 1801, which compared neoadjuvant anti-PD-1 for macroscopic resectable disease plus adjuvant versus the same thing without neoadjuvant regardless of pathologic response, appears to be very positive. It's very exciting that neoadjuvant, regardless if you see in pathology or not, has some additional clinical benefit of the patients. I really look forward to the peer-reviewed paper on that. I think with that, I think we're probably out of time, and thank you for this conversation. Very good to hear from experts and I always learn a lot myself.

Dr. Tetzlaff:
Thanks. Thanks for including me as well. I really appreciate the chance to chat with you.

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