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What is the Future of Adjuvant Therapy for Resectable Melanoma?

Announcer:
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Dr. Mitchell:
Hello, I'm Dr. Tara Mitchell from the University of Pennsylvania's Abramson Cancer Center, and I'm here today with Dr. Nikhil Khushalani, discussing adjuvant therapy in melanoma.

Dr. Khushalani:
Hi there, Dr. Mitchell. Nikhil Khushalani here. I'm the Vice Chair and Senior Member in Cutaneous Oncology at the Moffitt Cancer Center in Tampa.

Dr. Mitchell:
Dr. Khushalani, tell me what you think is the future of adjuvant therapy for resectable melanoma? What comes to mind first for you?

Dr. Khushalani:
That's a great question. I think one of the first things that now we are almost obligated to think of for the future is the sequencing of our treatments. Traditionally, we've always believed that adjuvant therapy is surgery to no evidence of disease. And based on stratifying patients relative to their risk, we then offer them systemic therapy to hopefully eliminate any micrometastatic disease that they may have, and therefore try to prevent relapses, delay relapses, and ultimately the goal being overall survivorship. And traditionally, we sort of lumped everyone together starting in the stage IIIs from IIIA, IIIB, IIIC, and IIID now as part of the melanoma staging, but as you know very well our risk of relapse can vary from 25 to 30%, for the stage IIIA's to almost as high as 70% in stage IIID, so this is a very heterogeneous group. And now we also take into account the resectable stage IV patients, which have been included in some of the contemporary adjuvant trials as well.

So I think the first stratification that I now make is, is the patient presenting with a macroscopic relapse, i.e. are there palpable, clinically evident nodes? Which therefore begs the question is, should we consider systemic therapy first, i.e. neoadjuvant therapy with a plan to resect after a finite period of time, and then risk stratify and give them additional systemic therapy based on their pathologic response? So that is certainly one stratification that we consider.

And this really came to light recently with the publication of SWOG 1801, where a simple question was asked is, does the transposition of pembrolizumab which traditionally is given in the postoperative setting for resectable high-risk disease, should we give 3 cycles upfront for patients with macroscopic or clinically evident disease? Do exactly the same operation, and then give them the balance of the 8 to 9 months of pembrolizumab in the postoperative setting? And what that trial clearly showed us was that the neoadjuvant/adjuvant arm improved the event-free survival significantly, relative to the adjuvant-only arm, which was traditionally our standard of care. So I think we have to take that into account in the design of future trials. I personally would find it very hard to have all of these patients go directly to a total lymph node dissection, and give them all of their postoperative treatment later, when we now have prospective results suggesting that the efficacy of that treatment is likely higher when we give it up front.

Dr. Mitchell:
That's absolutely right. And in fact, there was a 23% absolute reduction in the rate of recurrence. So what I mean by that is at 2 years, there were, in the group of patients who received neoadjuvant therapy with pembrolizumab followed by surgery, 72% of patients remained cancer free; whereas at 2 years, those who received cancer therapy, adjuvant therapy only after, it was 49%. So from 72 to 49%, a huge difference in the number of patients who remained cancer free despite having the exact same total number of treatments with adjuvant pembrolizumab and surgery. And so I think that that has to be the future of melanoma therapy in patients who are amenable to adjuvant and neoadjuvant therapy, compared to adjuvant therapy alone. It may be related to the presence of tumor being immunogenic and getting a better response out of immunotherapy when used in that setting than in adjuvant therapy after the removal of surgery and maybe only the presence of microscopic disease. So I think that neoadjuvant therapy absolutely is one future direction.

I think there's also maybe room for individualizing therapy. What are your thoughts about that?

Dr. Khushalani:
So that's, I think, an area of active investigation. So I guess one way to look at it is individualizing therapy based on biomarkers that a patient may have up front on their tumor itself, including looking at, for example, a gene expression score, or a high interferon gamma score, and that may allow us to potentially de-escalate therapy. Personally, I don't think that has reached primetime yet. I'd like to see prospective validation of some of those approaches.

Certainly, another way of individualizing therapy, one could ask the same question if a tumor – a patient's tumor has an actionable BRAF mutation and macroscopic disease, should we consider immunotherapy? Should we consider targeted therapy? Personally, I still think the jury's out on that. And that's an entirely, in my opinion in terms of a bias, where I don't think we have adequate data to conclusively say one is better than the other or the other is inferior to one. Because there's so much variability between the designs of our neoadjuvant trials, particularly in terms of, number one, drugs used, number two, the duration of therapy. And I think one could make the argument is should we actually give neoadjuvant therapy even for a slightly longer duration of time, will we see better responses? So I think in my mind, the jury's still out on that.

And we should certainly design some of our prospective trials to highlight that there is the International Neoadjuvant Melanoma Consortium that is aiming to do just that, where we are trying to unite investigators globally, to try and answer these questions in a very formalized fashion. So I think that those are really parts of the future from that standpoint.

Dr. Mitchell:
That's right, and we, as you mentioned, the INMC has been, you know, integral in, you know, unifying sites. And one of the clinical trials we eagerly await the outcomes from is the NADINA trial. So one of the approaches has been to individualize adjuvant therapy based on their response to neoadjuvant therapy. And so some of the questions being looked at in some of these trials are, can we change the adjuvant therapy to BRAF targeted therapy in a patient who has a suboptimal response to neoadjuvant therapy? Or can we reduce the amount of surgery in patients who have a near-complete or a complete pathological response to neoadjuvant therapy? And so some of those ways of individualizing adjuvant therapy based on neoadjuvant therapy response are being studied and asked in large randomized clinical trials, as are questions have come novel combinations of neoadjuvant therapy such as nivolumab, relatlimab, and other investigational approaches. In fact, the neoadjuvant platform is, I think, a very valuable one in studying novel combinations in terms of studying mechanisms of response and resistance in the tumor at the time of pretreatment and at the time of surgical resection. So I think that's going to be the future of adjuvant therapy too is personalizing immunotherapy adjuvant therapy.

And lastly, what do you think about vaccine therapy approaches. Or the mRNA vaccine data has been very recently, a stage 2 study we have of course we await you know, stage 3 results for that.

Dr. Khushalani:
No, absolutely. I think there's a lot of promise, there was a lot of hype. This was presented at the American Association of Cancer Research meeting recently, with some additional updates provided at ASCO 2023. I think this approach is, as you point out, very personalized. That is utilizing the tumor to develop a vaccine construct, which is being administered in combination with an immune checkpoint inhibitor. Certainly the original trial, which was a phase 2 randomized study, had very provocative and intriguing results, benefits showing clear benefit for the combination arm relative to pembrolizumab, I think this clearly requires validation in a prospective trial. And if validated, that certainly would be the first vaccine-associated adjuvant study to demonstrate benefit for high-risk resected melanoma. And it's sort of we are bringing the treatment to the patient, utilizing clues that we can get from the tumors and trying to sort of manipulate that immune system, utilizing that signature that we can develop.

I think the previous point that you mentioned in terms of possible de-escalation of therapy, I think that's a very, very appropriate goal for our patients. Patients who achieve a pathologic complete response to neoadjuvant immunotherapy, the vast majority of them greater than 92 to 93% of them, do not have a relapse. And so we can safely de-escalate that therapy in those patients as well. Certainly, a lot

of this requires prospective validation. And the phase 3 NADINA trial, which is an international study that you mentioned, is looking at exactly that approach is 2 cycles of upfront low-dose ipilimumab plus nivolumab, followed by planned surgery at 6 weeks, and then subsequent adapting of the postoperative therapy versus all of this treatment being administered in the postoperative setting with adjuvant nivolumab. And I think that will give us some answers, hopefully when it reads out sometime next year.

Dr. Mitchell:
Absolutely. So there's a lot of momentum and a lot of potential and we eagerly await the results of many of these clinical trials to inform the future of adjuvant and neoadjuvant therapy for melanoma.

Dr. Khushalani:
Certainly. And we look forward to those results. Thank you.

Announcer:
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