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

Preventing Disease Recurrence with Adjuvant Therapy in Stage IIB/IIC Melanoma

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[CHAPTER 1]

Dr Luke:
The emergence of immunotherapy for the adjuvant treatment of stage IIB and IIC melanoma has transformed the way we treat our patients. Are you as excited as we are to see how adjuvant treatment can help our patients?

This is CME on ReachMD, and I'm Dr. Jason Luke. Here with me is Dr. Tara Mitchell.

Dr. Mitchell:
Hello, thanks for having me.

Dr. Luke:
Dr. Mitchell, let's begin by discussing the coordination of care in early-stage melanoma. What's the importance of early referral for possible adjuvant therapy?

Dr. Mitchell:
At our center, we are actually seeing all patients with stage IIB and IIC in medical oncology now, and we have been for a few years. Our dermatologists and our surgical oncology referring doctors, including our Mohs surgeons, our head and neck surgeons, and our surgical oncologists, are all aware of the importance of referring patients with stage IIB and IIC disease to medical oncology as soon as that clinical diagnosis has been made, either pre- or postoperatively.

The importance of the early referral is because these patients with stage IIB and IIC melanoma have a reasonably high risk of recurrence, in the rate of 30% or more for stage IIB, and 40, as high as 50% for patients with stage IIC disease, which is higher than some patients even with stage IIIA disease. And so the reason for early referral is because they really need someone who is very skilled at understanding patterns of melanoma recurrence to be monitoring these patients with routine checkups, history and physical, and also with cross-sectional imaging. At our center, we offer cross-sectional imaging every 6 months for these patients with stage IIB and stage IIC high-risk disease in line with NCCN guidelines for patients with a high risk of recurrence for up to 5 years.

So we want to see these patients so that we can ensure close and vigilant and proactive follow-up, but also so that we can have an opportunity to discuss with them the option of adjuvant therapy and whether it's reasonable or appropriate. And that's a very individualized discussion with each patient based on their individual risk, risk tolerance for recurrence, and for treatment-related side effects, and one that we have in great depth with the patient and the family members as a shared decision-making about whether to proceed with close follow-up and observation alone or to consider adjuvant therapy with PD-1 blockade in these patients with a high risk of recurrence.

Dr. Luke:
Absolutely. And so I'd second that, that these patients are at high risk of recurrence. And getting them referred early is important so that they can be aware of all of their options and have an optimized treatment plan pursued.

In chapter 2, we'll be discussing clinical evidence and recommendations for the role of immunotherapy in stage IIB and IIC melanoma. Stay tuned.

[CHAPTER 2]

Dr Luke:
Welcome back. We're diving into clinical evidence and recommendations for the role of immunotherapy in stage IIB and IIC melanoma. I'm going to start by outlining some of the key data that supports this approach.

At the current time, the NCCN guidelines suggest that it's reasonable and appropriate to discuss the use of adjuvant therapy for patients with resected stage IV, stage III, and now more recently, stage IIB and IIC melanoma. And that approach is supported by data from the KEYNOTE-716 clinical trial of pembrolizumab that compared pembrolizumab versus a placebo in that high-risk stage IIB and IIC setting. So in that clinical trial, approximately 1,000 patients were randomized 1-to-1 to either receive pembrolizumab or placebo, and they were followed over time.

At the first interim analysis of the clinical trial that was prespecified at 1 year, the statistically significant result was already achieved to show a difference in terms of recurrence-free survival that had an advantage to pembrolizumab relative to placebo. And there, we saw a hazard ratio of 0.65, so a 35% reduction in the risk of recurrence. And that's been stable over several subsequent updates. Importantly, that improvement in recurrence-free survival has also translated to an improvement in distant metastasis-free survival as well. So certainly, we'll need to follow those patients out over a longer period of time to know about the impact on overall survival, but this is an indication that's supported with an FDA label and certainly is reasonable to discuss with patients.

Now it's important to note as well, that a clinical trial has now read out for nivolumab in high-risk stage IIB and IIC melanoma as well. And this was the CheckMate 76K study. And this study randomized patients 2-to-1 to receive nivolumab as compared with the placebo. But similar to the KEYNOTE-716 study, on the first interim analysis, it was observed that nivolumab improved recurrence-free survival as compared with the placebo. And in that study, the initial hazard ratio readout was 0.42, which suggested a 58% reduction in recurrence risk.

And the toxicity profiles of both pembrolizumab and nivolumab look to be very similar and are consistent with how we use anti-PD-1 antibodies in other settings. So certainly, one must be cognizant of the incidence for immune-related adverse events, particularly thyroid events, which are the most common, but there are a smattering of very serious immune-related adverse events that cannot be rectified, such as pancreatitis leading to type 1 diabetes and other severe autoimmune events. And so for that reason then, consideration of whether or not adjuvant therapy is appropriate for every patient is a personalized discussion.

Now I'd really emphasize that while the exact numbers between the two clinical trials, KEYNOTE-716 and CheckMate 76K, are slightly different, in reality, if you compare them side by side, the activity of anti-PD-1 looks to be just about exactly the same.

So pembrolizumab is currently the standard of care when considering the NCCN guidelines. We think it's very soon, however, that nivolumab will also be listed there, given that nivolumab and pembrolizumab are functionally interchangeable in every other setting where we use them in melanoma.

So, Dr. Mitchell, anything further you'd like to add about that data?

Dr. Mitchell:
I think that was a great summary. I think that when I speak to patients in the clinic, it's more useful to them rather than the, you know, hearing numbers about the risk reduction, to hear what are the actual chances that my cancer is going to come back, and how will this help? And so approximately, both studies showed very similarly that there was about a 10% to 15% reduction in the chance of melanoma recurrence. So I tell patients, if there is an 80% chance that you're going to be cancer free, now it's going to be a 90% chance. So that's, I think, very practical in terms of patient understanding. And I think that gives them a perspective too that many patients have a very good risk, and some of these patients will be cancer free regardless of therapy, and that they're taking on additional risks to consider therapy. And so really, they have to be motivated to commit to the therapy and to accept the side effects.

And then I remind them that close observation is an equally reasonable option, considering that there hasn't been long-term evidence of efficacy in terms of survival data that we have, and that these drugs are highly effective in stage IV disease.

And so either the observation or the adjuvant therapy are equally reasonable. The decision is highly personalized and really depends on

how the patient perceives their risk and the risk of toxicity.

Dr. Luke:
That's tremendously insightful and, I think, a very patient-centric way to think about engaging in these complicated discussions.

So this has been great. Next up, we'll discuss a case scenario and treatment options for a patient with early-stage melanoma.

[CHAPTER 3]

Dr. Luke:
For those just listening in, you're listening to CME on ReachMD. I'm Dr. Jason Luke, and here with me today is Dr. Tara Mitchell. We're discussing the prevention of disease recurrence with adjuvant therapy in stage IIB and IIC melanoma.

Welcome back. Now that we've got an understanding of the clinical data on adjuvant immunotherapy and the treatment of stage IIB and IIC melanoma, let's put it into some context.

So Dr. Mitchell, let's go through a case scenario and get some recommendations for treating this hypothetical patient. So a 72-year-old man with significant sun exposure from working as a farmer has a bleeding mass on his upper back that's found by his wife. After having an appointment to see his primary care physician, he's referred to a dermatologist. A biopsy of the lesion demonstrates a 4.3-mm Breslow depth melanoma with ulceration. He undergoes sentinel node evaluation and wide local excision, and no involvement of the sentinel node is noted, and no further melanoma is excised from the primary site. Thus, he's diagnosed as stage IIC melanoma. Given his diagnosis, his surgeon and medical oncologist note that he has approximately an 82% likelihood of survival over 5 years. As he's an active person, he wants to pursue options that would reduce his risk of recurrence.

So, Dr. Mitchell, how would you treat this patient?

Dr. Mitchell:
And this is such a frequent instance that we see patients like this in the clinic every week. And so we really have to start by educating the patient, talking to them about their personal risk of recurrence for their stage that's specific to the stage IIC disease that he has. And so I discuss with these patients the plan of close follow-up that I highly recommend to all patients.

I discuss with them, also, the pattern of recurrence and remind them that while there may be a 20% to 30% chance of recurrence in high-risk stage II, that half of those recurrences may be localized to the side of the primary melanoma or the regional lymph nodes and may be amenable to curative-intent surgical intervention at the time of recurrence, but that half of those recurrences, roughly 12% or so, will be metastatic at the time of the first recurrence.

And so, I think that one of the very important values to point out when considering adjuvant therapy and whether it's of meaning to a patient is their reduction in distant metastasis-free survival, which I thought was a very meaningful endpoint in the studies. And so to talk to this patient and to tell him that treatment may lower his risk of metastatic disease from 12% down to 6% – clearly a statistically very significant, meaningful reduction in risk – but what that means to the patient is very subjective. One patient may say, “Well, I'm happy to know that I don't have to do anything and these drugs are highly effective if it were to come back in stage IV, I would be, you know, more than willing to undergo therapy.” Others may say, “I will sleep better at night knowing that I can do anything possible to lower my chance of recurrence.” And it's those patients that I feel very comfortable offering adjuvant therapy to, whether they have stage II disease or whether they have stage III disease. If the patient is looking for an aggressive option to lower their risk of recurrence, they don't have any obvious contraindications to immune therapy, and that they understand the risks, then I think this is an aggressive, reasonable option for this patient to consider adjuvant PD-1 blockade for up to a year.

I'm very quick to point out to patients that I see them before every dose, we get labs before every dose, and we decide at every visit whether it's appropriate to continue or to stop based on any setbacks in quality of life, well-being, independence, or severe toxicities for which I would consider that the patient would have to stop for safety concerns.

So when we consider all of that at each visit, we go dose by dose for up to 1 year, is how I put it to patients, but that we can stop sooner for any risk of severe toxicity.

I think that having this conversation takes time and energy, but it's a worthwhile, detailed discussion that is individual to each patient. It helps to have family engagement and involvement when having these conversations, too, to see which patient feels very comfortable with the risk of toxicity and the goal of reducing the risk of recurrence in the absence of long-term survival data and which patients feel more comfortable with an observation plan. And then to reassure them that we'll take good care of them and be vigilant about follow-up in any of these patients, including imaging.

Dr. Luke:

Absolutely. So I think that consideration about the risk of side effects versus the risk of recurrence, I think, is really at the heart of this. And I think you described that really, really well.

Well, this has certainly been a fascinating conversation. So to summarize, I think, in a few key points, it's important to be aware that stage IIB and IIC melanoma is at high risk of recurrence; in fact, similar to that of stage IIIA and IIIB. And there are immunotherapy adjuvant options, with the form of anti-PD-1 antibodies, that are available for patients. So in your clinical practice, please be aware of that because offering that to patients, I think, is important, albeit in the context of that safety versus efficacy consideration.

Unfortunately, that's all the time we have today. So I want to thank our audience for listening in and thank Dr. Tara Mitchell for joining me and for sharing all of her valuable insights. It was great speaking with you today.

Dr. Mitchell:
Goodbye, thanks for having me.

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