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Which Resected Stage II Melanoma Patients Benefit from Adjuvant ICI Therapy?

Announcer:
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Dr. Khushalani:
So hello, my name is Nikhil Khushalani. I'm a Medical Oncologist in the Department of Cutaneous Oncology at the Moffitt Cancer Center in Tampa, Florida. Today I'd like to talk to you about high-risk stage II melanoma that has been resected, and what are the options for consideration of adjuvant therapy and how do we actually try to utilize the emerging data in some of the treatment decisions that we make?

Let's start off with a simple case. This is a 51-year-old lady who notices a change in the mole on her right shoulder. This has now started becoming protuberant, becoming nodular, has been itching, and occasional bleeding. A biopsy demonstrates nodular melanoma. This is thick with a Breslow depth of 4.3 mm. It is ulcerated, so this is a T4b tumor and there is no evidence of perineural invasion. An ultrasonography reveals normal-appearing nodes in the axilla and the neck, and she undergoes a wide excision with lymph nodes scintigraphy. Two lymph nodes are retrieved from the right axilla, and both of these are identified without any evidence of metastatic spread. The primary site resection does reveal residual melanoma but of lesser depth. Staging CTs, as well as brain MRI were negative. And she also underwent next generation sequencing of her tumor that demonstrated an actionable mutation in BRAF.

So the key question that we see in a patient like this is what are the options that are currently appropriate for consideration? How would we counsel this patient on risk strategies? What is the risk of her melanoma recurring? And how does this impact some of the decisions that she would need to make?

In order to understand this a little bit better, it's worthwhile taking a quick look on the left-hand side here at the AJCC version 8 melanoma-specific survival for stage II patients which are the bottom two graphs, bottom two curves, as you can see, for stage IIB and IIC melanoma that included accumulative of approximately 2,400 patients. And you can clearly see that even from year 5 to year 10, relapses do occur and that compromises melanoma-specific survival for these patients. So much so that the 10-year melanoma-specific survival for high-risk stage IIC patients is 75%.

On the right-hand side, I've put up similar graphs that were derived from the German Central Melanoma Registry, which is a prospectively maintained database of the first diagnosis of melanoma. And what this specifically highlights is stage for stage, and I've specifically highlighted IIB and IIC here as the topics of discussion stage for stage, it appears that in the German registry, the outcome or the prognosis for these patients may actually be slightly worse, where the 10-year melanoma-specific survival for stage IIC on the German registry, this is specifically for the 10,000 patients who are included in the confirmation cohort, was approximately 65%.

So I think these are important points that we have to take into account as medical oncologists while counseling our patients. If one had to put this same information in very simplistic or different perspectives, one would say that the probability of dying from melanoma is approximately 20% for stage IIB patients and about 35% for stage IIC patients, if one looks at the CMMR data on the right-hand side, and again, this is important information to take into account.

Adjuvant therapy, i.e. treatment that is offered after resection of high-risk disease, is primarily an opportunity to reduce the risk of relapse and hopefully, to eventually improve overall survivorship in these patients.

This is a busy slide. It primarily highlights the current state of adjuvant therapy of contemporary clinical trials in 2023, across from when ipilimumab was approved based on results of the EORTC 18071 trial, all the way down to the dabrafenib and trametinib in patients who have resected stage III melanoma that expresses an actionable mutation in BRAF. The bottom two rows are primarily high-risk stage IIB and IIC disease that we'll discuss in a little more detail in the subsequent slides. But what I've really tried to highlight and summarize here is the relapse-free survival as well as the distant metastases-free survival across these trials.

The KEYNOTE-716 study was a prospective randomized trial, specifically for high +-risk stage IIB and IIC melanoma, a negative sentinel note that was required with pathology confirmation, and this was open to patients who were 12 or older. And thus, a pediatric age group population was also included. And this was included as part of the risk stratification as well. This trial enrolled almost 1,000 patients over 2 years. And the randomization was 1 is to 1 between pembrolizumab being administered for up to 1 year, versus placebo being administered for up to 1 year. And the primary endpoints were relapse-free survival with the secondary endpoints listed here.

When first presented at plenary sessions, and then subsequently published in *The Lancet*, what you can clearly see on the top graphs A and B are the interim, the first and the second interim analyses that demonstrated a statistically significant improvement in the relapse-free survival for the pembrolizumab arm with a significant hazard ratio of 0.65. At the second interim analysis, a formal statistical analysis was not required, because this trial had already met its endpoint at the first analysis itself. At the bottom were the same curves as part of sensitivity analysis, where they also included new primary melanomas as an event within that setting. So what you can see at the secondary analysis 15% of patients in the pembrolizumab arm and 24% in the placebo arm, had either recurred or died at that time. At the third interim analysis, which now also looked at a secondary endpoint DMFS, or distant metastases-free survival, this was noted to be significant for pembrolizumab relative to placebo as well.

So while there's no doubt about efficacy, the key question is, is this for everyone? Or are there groups of patients that we have to be more concerned about because of toxicity? It should be noted as an immune checkpoint inhibitor, this drug does have toxicity. These are the most common grade 3 and 4 adverse events which occurred in up to 17% of patients, and pembrolizumab had to be discontinued in 16% of patients related to an adverse event. I'd like to highlight the adverse events of interest, particularly those that require long-term endocrine replacement therapy that clearly can impact quality of life for our patients, hypothyroidism, steroid requirements, and adrenal insufficiency, they're rare but devastating complication of type 1 diabetes, where patients will require lifelong insulin supplementation. And therefore, we as oncologists, it's incumbent on us to have these discussions very honestly with our patients and help them make a shared decision as to how they wish to proceed.

Similarly, nivolumab was also tested in a virtually identical population of resected stage IIB and IIC patients. The only difference in CheckMate-76K being the randomization was a 2's to 1 randomization in favor of nivolumab. And at the 1-year mark, the recurrence-free survival was statistically significant, with an impressive hazard ratio favoring nivolumab of 0.42, suggesting a 58% improvement in the risk for relapse for these patients with high-risk disease. Similarly, the distant metastases-free survival was also highly statistically significant, with a hazard ratio of 0.47. These were presented at the Society for Melanoma Research meeting in 2022. As of now, pembrolizumab does have FDA regulatory approval in this high-risk setting. Nivolumab does not as yet have this approval. But the anticipation is these are very, very similar results, almost mirror images of each other. Toxicity, just as I mentioned earlier, again, mirrors what we saw with pembrolizumab, with a 17% discontinuation rate for an adverse event.

So I think taking into context the patient that I presented earlier in this segment, stage IIC disease, young individual, no major medical comorbidities, I think it is very reasonable to consider adjuvant immunotherapy for that individual. While that patient does have an actionable BRAF mutation, adjuvant BRAF and MEK inhibitors are not approved at this point in time for patients with resected stage II melanoma, certainly the stage III setting is different. So I think adjuvant anti-PD1 therapy with either pembrolizumab or nivolumab for 1 year does improve relapse-free survival as well as distant metastases-free survival for these high-risk patients with stage IIB and IIC disease. And we have to balance the both short-term acute as well as chronic long-term toxicities that may impact quality of life with the efficacy that may be obtained by treating these patients in the adjuvant setting. In other words, communication, education, and a shared decision-making is absolutely paramount. Thank you for your attention.

Announcer:
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