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Adjuvant Treatment for BRAF+ Stage III Melanoma: A Case Study to Weigh ICI Versus Targeted Therapies

Announcer:
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Dr. Mitchell:
Hi, I'm Dr. Tara Mitchell, an Associate Professor of Medicine at Penn's Abramson Cancer Center, and I'll be speaking today about adjuvant treatment for BRAF positive stage III melanoma.

We'll start with a case of a 58-year-old man with stage IIIC melanoma of his right upper back and axilla. He undergoes a wide excision and therapeutic lymph node dissection for his clinically positive lymph node involvement. His tumor has a BRAF V600E mutation and he presents to medical oncology for further management and suggestions.

Adjuvant therapy options for stage III melanoma that are currently in use are adjuvant dabrafenib and trametinib for BRAF mutant melanoma, as well as adjuvant nivolumab and adjuvant pembrolizumab, both of which can be used in patients who are BRAF mutant as well as patients who are BRAF wild-type. Treatment with any of the above can be given for up to 1 year but stopped sooner for any unacceptable toxicity. And close observation alone remains a reasonable option for all patients, given the lack of any confirmed survival advantage in the era of highly effective therapies for stage IV, and due to the risk of severe permanent or life-threatening toxicity in a very rare number of patients. Adjuvant immunotherapy is now also approved for patients with stage IIB and C melanoma as well as for patients with stage III melanoma.

Here you see the clinical trials that led to the approval for adjuvant therapy of pembrolizumab the KEYNOTE-054 study, nivolumab in the CheckMate 238 study, and dabrafenib and trametinib in patients with BRAF mutant melanoma and the COMBI-AD study. You can see that all of the therapies given for up to a year have a significant improvement in recurrence-free survival on a similar order of magnitude for all of the therapies that have been studied and approved and are in clinical use today.

So how do we decide which patients need adjuvant therapy in the first place? It starts with the patient's individualized risk of cancer recurrence. I speak to each patient based on their AJCC 8 staging for melanoma about what their prognosis is, meaning what is their risk of recurrence. In addition to the pattern of recurrence, what's the risk of local, regional, and distant recurrence. In patients with a low risk of recurrence, we recommend no treatment. For example, patients with stage I and low-risk stage II patients. In patients with stage IIB and above, we consider a treatment for adjuvant therapy for up to a year. We talk about the risks of adjuvant therapy, including side effects and the time and costs spent visiting to travel to visits and at visits. And then the potential benefit of treatment, including the improved chance of staying cancer free long term.

So how do we decide which treatment to use in a patient with BRAF mutant melanoma opting for treatment? So after we've had this complex conversation about risk, side effects, potential benefit, we come to a decision about the patient preference via shared decision-making with the doctor and patient about adjuvant therapy. And once we decide that allergen therapy is appropriate for a patient and that they're willing to begin treatment, the discussion is about what treatment would be optimal for this patient with BRAF mutation

positive melanoma, knowing that either immune checkpoint blockade with PD-1 blockade or adjuvant BRAF and MEK inhibitor are approved and effective agents for reducing the risk of recurrence.

So the similar efficacy is clear, as I showed you on the prior slide and the clinical trial data. However, the side effect profiles are very different. So we discuss in detail the side effects and perhaps how they may impact a patient based on the patient's comorbidities, concurrent medications, other diagnoses, and preferences, and risk tolerance about different side effects. We cannot extrapolate data in advanced disease when choosing adjuvant therapy. So in stage IV disease, we know that there have been data to confirm that immunotherapy and that first line is superior to targeted therapy in patients with BRAF mutant melanoma. In the DREAMseq study, immunotherapy followed by targeted therapy results in increased survival in patients with BRAF mutation melanoma compared to patients who were treated with BRAF-targeted therapy first line.

Though the story is different in adjuvant therapy in which micrometastatic disease is the target of therapy, and there may not be the same outcomes, nor has there been any confirmatory trial to dictate sequence of therapy or preferred therapy. And so the decision to use therapy in which therapy to use involves a complex conversation and shared decision-making between the patient and oncologist, including a careful consideration of risks and potential benefits.

The considerations for using adjuvant therapy are we know that it reduces the risk of recurrence. However, we don't know which patients are benefiting. We have to date no ideal biomarker of treatment benefit. And we don't have long-term data to confirm any survival advantage at the 5- or 10-year time point in the current era of highly effective therapies for stage IV. So we still need to monitor patients closely for recurrence, whether they're choosing to proceed with adjuvant therapy or observation alone.

An area of momentum in adjuvant therapy for melanoma and the treatment of resectable melanoma is neoadjuvant therapy. And we've recently had for the first time a randomized clinical trial of neoadjuvant therapy for melanoma in patients with resectable clinical stage IIIB or IV melanoma, in which patients were randomly assigned to receive either neoadjuvant and adjuvant immunotherapy, or adjuvant PD-1 blockade alone for the same total duration of treatment. The outcome was that there were significantly and clinically meaningful lower recurrences in patients who received adjuvant therapy for a short course, compared to patients who leave – neoadjuvant therapy for short course, compared to patients who received adjuvant therapy alone.

So coming back to the case of the 58-year-old man with stage III BRAF mutant melanoma, he's certainly a high risk of recurrence, and I would say as high as 50 to 70% chance of recurrence, and adjuvant therapy could meaningfully reduce his risk of recurrence by 20% - on the order of 20% absolute reduction, and so he's certainly eligible and a candidate for adjuvant therapy for either dabrafenib and trametinib, or with pembrolizumab or nivolumab given for up to 1 year of therapy with close monitoring and visits with medical oncology during treatment.

In summary, adjuvant therapy can reduce recurrences in patients with high-risk melanoma, and requires a careful and individualized discussion of risks and potential benefit, and is a shared decision-making between the patient and oncologist. We certainly need longer-term data to compare adjuvant therapy versus reserving treatment for the time of recurrence. And neoadjuvant therapy represents great potential and has a lot of momentum in the field of melanoma, though it's currently considered investigational only and it's being tested in clinical trials. We've seen randomized trial data that it improves recurrences in patients compared to adjuvant therapy alone, and that pathological responses to neoadjuvant therapy or prognostic of decreased recurrence with immunotherapy. So we may finally have some biomarker of treatment efficacy in patients who are treated with neoadjuvant and adjuvant immunotherapy, and so we encourage all of our patients to consider clinical trials whenever eligible for a study of neoadjuvant therapy.

Thank you for your participation.

Announcer:
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