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Optimizing Therapeutic Selection for a Patient With Newly Diagnosed BRAF V600e-Mutated Metastatic Melanoma

Announcer:
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Dr. Betof Warner:
Hi, I'm Allison Betof Warner. I'm Director of the Melanoma Program at Stanford, and we'll be talking today about Optimizing Therapeutic Selection for a Patient with Newly Diagnosed BRAF V600e-Mutated Metastatic Melanoma.

So let's start with a case. We have a 68-year-old man with a history of stage IIA cutaneous melanoma in 2019 that was treated with surgery and sentinel lymph node biopsy. Had an initial scan that was negative for metastatic disease and was followed by dermatology until the fall of 2022 when he presented with a large, non-painful mass on his left shoulder that was biopsied and positive for melanoma. And a PET scan showed this mass on his shoulder as well as left axillary lymphadenopathy and some new small, 1-2 cm pulmonary nodules consistent with metastatic disease. He was seen in clinic and had a performance status of 0, and LDH at that time was not elevated. That was biopsied and confirmed metastatic melanoma with a BRAF V600E mutation, and his brain MRI was negative for intracranial disease.

So what do you do next? Do you start with targeted therapy with either a BRAF inhibitor or combination of BRAF plus MEK inhibitors? Start with combination dual checkpoint inhibitor therapy or single agent PD-1?

So let's talk about dual versus single agent immunotherapy in BRAF V600E mutated melanoma from the CheckMate-067 trial. And we can see here, you can see ipilimumab plus nivolumab in the red, nivolumab alone in blue, and ipilimumab alone shown here in the teal color. And you can see, while this was not – study was not powered to show superiority between the combination immunotherapy arm and single agent, you can see, certainly separation of the curves here.

Similarly, if we look at RELATIVITY-047, which looked at nivolumab plus relatlimab versus nivolumab alone, you can see in the BRAF-mutated patients a trend towards superiority of combination nivolumab plus relatlimab versus nivolumab alone for BRAF-mutated patients. While this confidence interval crosses 1 again, a trend here that suggests that dual combination immunotherapy may be superior for our patients.

But what about choosing between targeted therapy and immunotherapy? So if we look at the DREAMseq trial, which was published in 2022, this took patients with BRAF-mutated metastatic melanoma and randomized them to starting with ipi plus nivo, then moving on to targeted therapy at the time of progression, versus starting with targeted therapy and moving on to ipi plus nivo. And you can see here, this is the overall survival curves, A+C are the combination immunotherapy patients, versus patients who started with combination targeted therapy. And you can see here that the overall survival is clearly superior for patients who start with immunotherapy. Similarly, while there's an initial superiority or an initial dip in progression-free survival for patients with immunotherapy, which looks a little better

for targeted therapy at first, clearly over time, we see clear superiority for patients who start with combination immunotherapy over combination targeted therapy, and that has thus become the standard of care for these patients.

Similarly, we saw similar trial design for the SECOMBIT trial with encorafinib and binimetinib, moving on to IPI plus NIVO, versus IPI plus NIVO, moving on to Encor/bini, versus a sandwich approach where patients got 8 weeks of targeted therapy, then immunotherapy, then back to targeted therapy at the time of progression. And again, this trial, yet again, suggests superiority for patients who started with immunotherapy, which is the arm B or shown in green here, or patients who had a sandwich approach where they got a brief period of targeted therapy for 8 weeks with a planned switch to immunotherapy. And here you can see the exploratory overall survival. Again, the arm B, here was the immunotherapy first arm with a 1-year overall survival of 81%, 2 years at 73%, and 3 years at 62%.

So in summary, we saw CheckMate-067, showing an overall survival benefit of dual immunotherapy over single agent for BRAF-mutated metastatic melanoma. Similarly, RELATIVITY-047 showed a progression-free survival benefit for combination immunotherapy. And DreamSeq and SECOMBIT support sequencing dual immunotherapy prior to targeted therapy.

Thanks so much for joining us. I hope this was really informative, and we look forward to future interactions.

Announcer:
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