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Optimizing Adjuvant Treatment for Stage IV Melanoma Patients Rendered NED After Surgery

Announcer:
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Dr. Khushalani:
Hello, my name is Nikhil Khushalani. I'm a Medical Oncologist in Cutaneous Oncology at the Moffitt Cancer Center in Tampa, Florida. What I'd like to discuss today is high-risk stage IV resected patients with melanoma, and aiming to optimize adjuvant therapy in these patients that have been rendered without evidence of disease following curative attempt at surgery.

So let's try to highlight this topic with a case presentation. We have a 51-year-old, white female, who originally presented with a stage IIC melanoma the right shoulder. At that time, she underwent a wide excision and nodal scintigraphy, which essentially confirmed the absence of nodal metastases. At that time, contrast-enhanced imaging of the torso and the brain were negative. Next generation sequencing demonstrated an actionable BRAF mutation, and after an informed decision or discussion with that patient, she elected to undergo observation, rather than receiving adjuvant immune checkpoint inhibitor therapy, and she was followed with cross-sectional imaging every 6 months. At year 4 in her follow-up, we now notice a 1.8-cm right lower lobe lung nodule without any other abnormality. Brain imaging repeated again was negative. And she undergoes a minimally invasive thoracotomy, given that this was a solitary site of likely metastases, and a long disease-free interval or relapse-free interval. Final pathology confirms metastatic melanoma 1.6 cm, negative margins were obtained.

So the key question on the table now is with this patient now with resected metastatic disease, or I will use the term loosely, resected stage IV disease, that has now been rendered without evidence of disease, is there data to tell us or help us make decisions on postoperative therapy? Or should we pursue expectant observation?

So I think to try and answer this question, one has to first understand how to patients with resected stage IV melanoma fair. And this was an older trial SWOG 9430, which essentially looked at initially 77 patients, but the ones who are included in final analysis based on eligibility and being rendered disease free by complete surgical resection of their all oligometastatic disease, were 64 patients. And these patients essentially formed the primary analysis. And as you can see here, on the top left graph, the 6-month estimate of relapse-free survival was 45%. And the 1-year estimate of overall survivorship, at the bottom right, was 75%, telling us that a quarter of patients unfortunately had already succumbed likely either to recurrent disease, or due to additional medical comorbidities. When one looks at median relapse-free survival on this trial, it was about 5 months. But importantly, as you look at the survival curves, the overall survivorship anticipated in this study at 4 years was about 31%. So this tells you that surgery can actually cure a small percentage, but the risk for relapse remains extraordinarily high.

Despite this very high risk of recurrence, most of these patients have never been included in previous adjuvant trials of melanoma, though some of the more contemporary trials have now recognized this and routinely will include and potentially stratify these patients within modern day trials for immunotherapy. The first among these was CheckMate 238, which examined the role of adjuvant nivolumab in patients with resected stage IIIB, IIIC, or resected, stage IV disease. And this was based on AJCC version 7 classification,

randomizing them to a year of nivolumab administered every 2 weeks, versus ipilimumab administered every 3 weeks for 4 doses, followed by maintenance therapy for up to 1 year. And the primary endpoint for this trial was relapse-free survival with secondary endpoints of overall survivorship as well.

And in multiple iterations of this trial that have either been presented at various meetings, or in publications, starting with *The New England Journal of Medicine*, this trial clearly showed an improvement in relapse-free survival with adjuvant nivolumab compared to adjuvant ipilimumab. At the 5-year mark, as can be highlighted on this study. The 5-year relapse-free survival with nivolumab was 49% which was numerically better than that with ipilimumab, though, did not reach statistical superiority at that point in time. And part of it was that an adequate number of events had not occurred, and therefore only 73% power at that point in time, as opposed to the potential 88% power for significance. So ongoing analysis from the study, the secondary treatments that these patients received in terms of crossover and additional biomarkers are being actively investigated and reported out, but essentially highlights that nivolumab would be an appropriate option for these high-risk patients as well.

What about trying to escalate therapy in terms of checkpoint inhibition? This was the IMMUNED trial which is a placebo-controlled, randomized, phase 2 study that essentially randomized patients with resected oligometastatic disease to 1 of 3 arms. One arm was combination ipilimumab plus nivolumab administered at standard doses for 4 cycles, followed by up to 1 year of maintenance nivolumab that was 56 patients. Second arm was standard nivolumab alone for up to 1 year. And the third arm was placebo, because at that point in time when the trial was designed, there was no standard-of-care option for patients with resected stage IV disease. The primary endpoint here was relapse-free survival, and then secondary endpoints of overall survival as well.

These results were subsequently updated after – at the time of final analysis. At the initial analysis, there was clear improvement in relapse-free survival when the combination of nivolumab plus ipilimumab was compared to placebo. At the final analysis that is highlighted here on the left-hand side, the hazard ratio for that comparison was 0.25. Similarly, nivolumab was superior to placebo in the same setting. On the right-hand side, you see the same curves for overall survivorship, where again, a very significant hazard ratio of 0.41 for the combination relative to placebo, and you see the 4-year relapse-free survivals at the bottom there.

What is really important to take away here is high rate of grade 3 and grade 4 adverse events with that combination arm as one would expect, and 62% of patients discontinued combination therapy secondary to toxicity. So it really becomes important to risk balance this toxicity relative to what the risk of recurrence would be, and what the patient could potentially tolerate since both options would be very reasonable.

At our center, in conjunction with the New York University, we did a trial that looked at alternate dosing of ipilimumab plus nivolumab, utilizing a lower dose as can be seen here in cohort 5, though only 20 patients in those two cohorts 4 and 5, and then separate cohort of cohort 6 also utilizing a lower dose of ipilimumab with standard dosing of nivolumab as induction therapy, followed by maintenance treatment for up to 1 or 2 years of therapy. In the modified arm, 35% of patients required discontinuation in our study. And the 5-year relapse-free survival across the entire cohort was 71%. Again, the caveat here is a small study limited to two institutions; and therefore, whether or not this would be an appropriate dosing regimen remains to be investigated further in a more prospective manner at this point in time.

So going back to the case, clearly a high-risk case, an individual that has relapsed after 4 years of therapy, and one needs to make a decision whether consideration to adjuvant nivolumab based on CheckMate 238 or combination IPI plus NIVO based on IMMUNED are appropriate options for these patients to reduce their risk of relapse. Toxicity with combination therapies can certainly be prohibited and therefore shared decision-making with the patient is really important. Now, one could consider adjuvant BRAF targeted therapy if this - given that this patient was BRAF mutant. I think the caveat is that all of the contemporary trials published so far did not include resected stage IV disease within their treatment cohorts. So one would have to be very cautious about utilizing that in the setting, though the anticipation and extrapolation would be that this would also be a reasonable approach in a patient who has a known contraindication to immunotherapy.

I thank you for your attention.

Announcer:
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