Adjuvant immunotherapy prolongs recurrence-free survival in resected stage II B/C melanoma

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The first randomised phase III clinical trial in stage II melanoma has shown a 35% reduction in the risk of recurrence with adjuvant pembrolizumab compared with placebo. The late breaking results of the KEYNOTE-716 trial are presented at the ESMO Congress 2021.

Patients with stage IIB and IIC melanoma have a deep or ulcerated primary tumour. These patients occur in similar numbers, and have the same risk of recurrence and death, as those with stage IIIA and IIIB melanoma. Despite the equivalent risk, the current standard of care is observation for stage II B/C and adjuvant therapy for stage III A/B melanoma.

Commenting on the findings, Dr. Omid Hamid, Chief of Research/Immuno-Oncology, The Angeles Clinic and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, US, chair of the congress's melanoma and other skin tumours track said: "The US Food and Drug Administration (FDA) is now examining this drug for the adjuvant treatment of stage IIB and IIC melanoma which, if approved, means we would be introducing immunotherapy earlier in the patient journey. This has the potential to spare patients recurrence and metastases. It is important to note that the trial included not just adults but also children and adolescents aged 12 years and older."

KEYNOTE-716 randomly allocated to 976 patients with complete resection of cutaneous stage IIB or IIC melanoma and no lymph node involvement to the PD-1 inhibitor pembrolizumab or placebo for up to one year. At a median follow-up of 14.4 months, pembrolizumab significantly prolonged recurrence-free survival compared to placebo, with a hazard ratio of 0.65.

"These results are set to substantially change the population of melanoma patients who get treated in the adjuvant setting," said study author Dr. Jason J. Luke, Director, Cancer Immunotherapeutics Center, UPMC Hillman Cancer Center, Pittsburgh, US. "Historically we have defined high-risk patients after surgery as those with lymph node positive disease. This trial suggests that the depth of the primary tumour and the ulceration status provide substantial information about the risk of recurrence and metastases and whether or not we might pursue adjuvant therapy. In future we will need to reconsider how we incorporate sentinel lymph node biopsy into our risk stratification."

During the 14.4-month follow-up, 54 (11.1%) patients on pembrolizumab had a recurrence compared with 82 (16.8%) on placebo, while distant recurrences were nearly halved with pembrolizumab (23 events) versus placebo (38 events). Luke pointed out: "There has been a belief that early-stage melanoma doesn't recur very fast and that these patients don't develop metastatic disease. These data clearly disprove that and show that patients with high-risk stage II melanoma recur quickly and distantly, just the same as patients with stage IIIA and IIIB. Treatment with pembrolizumab reduced that in a meaningful and statistically significant way, indicating that these stage II patients should be offered adjuvant therapy."

Luke highlighted that the potential for side-effects may have been one reason for withholding adjuvant treatment in the stage II setting: "When the only available therapies were high-dose interferon and

ipilimumab, both of which were associated with more than 50% rates of severe adverse events, that just wasn't tolerable for patients with early stage disease. But now with anti-PD-1 treatment it's a much more attractive risk/benefit scenario and given the results of this trial, I think we should be offering this to our patients."

Luke said the trial has established a benchmark for future studies: "In a world of financial constraints and personalised medicine, we'd ultimately like to know exactly who we need to treat. This trial provides a platform from which to do those molecular studies. In addition, as patients who recur in the placebo arm cross over to the pembrolizumab group, we will eventually get an answer about whether it is more effective to treat right after surgery or to wait until the melanoma comes back."

Hamid noted that the dose frequency and duration of adjuvant therapy in stage II B/C melanoma should also be evaluated: "Studies of adjuvant therapy in other stage II solid tumours have suggested that a shorter time course of therapy can provide the best risk/benefit ratio—although these were not immunotherapies. Patients in KEYNOTE-716 were treated for one year and while the incidence of grade 3 or 4 toxicity was minimal, side-effects could potentially have a significant impact on the lifestyle of these patients."

He added that longer follow-up is required to find out if there is an overall survival benefit with anti-PD-1 therapy in these patients. "We also need to determine what giving adjuvant anti-PD-1 therapy in stage II B/C means for stage III patients who recur and would currently receive this treatment," said Hamid. "I foresee that some of the regimens we now use in the metastatic setting may move up earlier in stage III disease. Ongoing clinical trials are examining novel combinations in the stage III setting – for example, VEGF targeted therapies or pegylated IL-2 or anti-LAG-3 antibody plus anti-PD-1

therapy – versus standard single agent anti-PD-1 therapy."

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