MELANOMA

What's new under the Sun for ICIs?

Two recently published clinical studies provide new insights into the use of immune-checkpoint inhibitors (ICIs) in patients with melanoma, regarding the intracranial activity of these antibodies and the optimal monitoring of response to treatment.

Around 30% of patients with melanoma have brain metastases at diagnosis, which usually confer a dismal prognosis. Intracranial activity has been demonstrated for several ICIs when used as monotherapy in patients with melanoma with untreated brain metastases, but limited evidence on combinations is available.

In the phase II CheckMate 204 study, 94 patients with melanoma and untreated brain metastases received the anti-programmed cell death 1 (PD-1) antibody nivolumab combined with the anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) antibody ipilimumab before maintenance nivolumab. At a median follow-up duration of 14 months, the intracranial partial response (PR) and complete response (CR) rates were 30% and 26%, respectively; 90% of all responses were ongoing at the time of analysis. The rate of intracranial clinical benefit (defined

as patients with a CR, PR, or stable disease (SD) for ≥ 6 months) was 57%. These rates are consistent with those observed in the subgroup analyses of a phase II randomized trial, in which 27 treatment-naïve patients with brain metastatic melanoma received nivolumab plus ipilimumab and 19 treatment-naïve patients received nivolumab alone. At a median of 17 months of follow up, 56% and 21% of patients receiving the combination and nivolumab monotherapy, respectively, had intracranial responses (CR or PR); the intracranial CR rates were 19% and 11%, respectively.

In CheckMate 204, the 6-month and 9-month overall survival (OS) were 92.3% and 82.8%, respectively; the estimated 12-month OS was 81.5%. Grade 3–4 adverse events (AEs) were reported in 55% of patients and led to treatment discontinuation in 20% of patients. The incidence of AEs of any grade affecting the central nervous system was 36%, of which ~20% were of grade 3–4 (and brain oedema <5%).

“Our results confirm that combination immunotherapy is safe and as efficacious for melanoma metastatic to the brain as it is for tumours outside of the brain,” comments Hussein Tawbi. “We hope that combinations will herald a new era for all patients with metastatic melanoma to the brain, although several challenges remain, including the optimal timing and sequence of immunotherapy with stereotactic radiation therapy,” he adds.

Assessments of responses to ICIs are currently performed using CT, but can be challenging because the response criteria were originally developed to assess responses to cytotoxic therapies. “The small group of patients (~20%) with melanoma with a CR on standard CT have

excellent long-term outcomes; however, many more patients have a PR or SD and yet can also have good long-term outcomes,” explains Alexander Menzies.

Menzies and colleagues compared therapeutic response assessment using ^{18}F -FDG-PET and CT in 104 patients with unresectable or metastatic melanoma without disease progression after 1 year of treatment with anti-PD-1 antibodies alone or combined with ipilimumab. Responses were coded conventionally (CR, PR, SD, or progressive disease (PD)) or as metabolic responses (CMR, PMR, SMD, or PMD), depending on whether they were assessed using CT or PET, respectively. At 1 year, 66% of patients had a PR, whereas 75% of patients had a CMR (68% of whom had only a PR on CT). All patients with a CMR who had a PET evaluation at 2 years ($n=27$) remained in CMR — 13, 13, and 1 of these patients had a CR, PR, and SD, respectively.

“Our data confirm the hypothesis that a substantial proportion of patients have residual lesions on CT that likely do not represent viable tumour,” summarizes Menzies. “These patients can have long-term disease control and potentially cease treatment earlier (before 2 years). For those with viable disease, a change in therapy might be required before overt disease progression on CT,” he concludes.

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ORIGINAL ARTICLES Tawbi, H. A. et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N. Engl. J. Med.* <https://doi.org/10.1056/NEJMoa1805453> (2018) | Tan, A. C. et al. FDG-PET response and outcome from anti-PD-1 therapy in metastatic melanoma. *Ann. Oncol.* <https://doi.org/10.1093/annonc/mdy330> (2018)

FURTHER READING Long, G. V. et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol.* **19**, 672–681 (2018)

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