MELANOMA

Early responses indicate remission

Immune-checkpoint inhibitors have dramatically improved the outcomes of a subset of patients with melanoma across several different disease settings; however, the ability to identify patients who are most likely to respond remains largely elusive. Now, data from a single-institution trial reveal several early indicators of long-term disease-free survival in patients receiving a single dose of pembrolizumab.

A total of 27 patients with stage IIIB/C or stage IV melanoma received a single neoadjuvant dose (200 mg) of pembrolizumab 3 weeks before surgery, followed by adjuvant treatment. Explaining the rationale for this approach, first author Alex Huang explains: "we knew that an immune response was detectable in the blood at 3 weeks after administration of an anti-PD-1 antibody," and therefore "we designed a clinical trial of a single dose of neoadjuvant pembrolizumab to study early immune and pathological events in the tumour."

Approximately 30% of patients (8/27) had a complete or major pathological response to pembrolizumab and remained in remission after a median follow-up duration of 25 months. Analyses of immune kinetics in the blood identified $CD8^+$ immune responses as early as 7 days after administration of pembrolizumab. Investigations of tumour material from the 20 patients with paired samples available revealed brisk lymphocyte infiltration among responders. Furthermore, tumour infiltrates from responding patients were enriched with $CD8^+$ T cells expressing PD-1, CD39 and eomesodermin, suggesting an exhausted phenotype. T cells of this phenotype were detectable before treatment, indicating that pre-existing intratumoural T cells drive the early responsiveness to pembrolizumab observed in this study. Conversely, patients with high levels of regulatory T cell proliferation were more likely to have disease recurrence. Transcriptomic analyses revealed robust associations between a neoadjuvant response signature and response to pembrolizumab.

> "Patients can have a complete tumour response after a single dose of PD-1 blockade"

Senior author Tara Mitchell summarizes: "Patients can have complete tumour responses after a single dose of PD-1 blockade. These early responses are predictive of recurrence-free survival; no patients with complete or near complete responses have developed recurrent or metastatic melanoma." These findings await further validation in a larger cohort of patients.

Peter Sidaway

ORIGINAL ARTICLE Huang, A. C. et al. A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma. *Nat. Med.* https://doi.org/10.1038/s41591-019-0357-y (2019)

BREAST CANCER

Healthier bones and less recurrence with denosumab

Adjuvant therapy with aromatase inhibitors is recommended for postmenopausal women with hormone receptor-positive (HR^+) early stage breast cancer but is associated with decreased bone mineral density and an increased risk of fractures. Adjuvant treatment with the anti-receptor activator of nuclear factor-κB ligand (RANKL) antibody denosumab was shown to significantly reduce the time to first clinical fracture in the primary analysis of the ABCSG-18 phase III trial. Now, disease-free survival (DFS) results from this trial provide additional support for denosumab in this setting.

In the ABCSG-18 trial, women with early stage HR^+ breast cancer received adjuvant denosumab ($n = 1{,}711$) or placebo ($n = 1{,}709$) together with aromatase inhibitors; 14.7% of patients in the placebo group crossed over to receive denosumab. Denosumab provided a DFS benefit over placebo: at 5 years, DFS was 89.2% (95% CI 87.6–90.8) versus 87.3% (85.7–89.0) with placebo, and at 8 years DFS was 80.6% (78.1–83.1) and 77.5% (74.8–80.2).

"The magnitude of the survival effect is comparable to that observed in trials of adjuvant bisphosphonates (which did not really show a reduction in fractures), and the monoclonal antibody has fewer adverse effects and provides better quality of life than bisphosphonates," comments Michael Gnant.

Credit: Simon Bradbrook/Springer Nature Limited

The incidence of adverse events (AEs) was similar in both treatment arms: AEs of any grade were reported by 80.0% and 79.2% of women receiving denosumab and placebo, respectively, which were grade ≥3 AEs in 30.5% in both groups.

"I believe that every postmenopausal woman with HR^+ breast cancer receiving adjuvant aromatase inhibitors should be offered this therapy that halves the risk of clinical fractures, provides a moderate but significant DFS benefit, and does not have notable adverse effects," concludes Gnant, remarking: "These injections are reasonably affordable, compared with the cost of fracture treatment or other modern anticancer therapies."

Diana Romero

ORIGINAL ARTICLE Gnant, M. et al. Adjuvant denosumab in postmenopausal patients with hormone receptor-positive breast cancer (ABCSG-18): disease-free survival results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* **20**, 339–351 (2019)