Nature Reviews Clinical Oncology | Published online 31 Jan 2018; doi:10.1038/nrclinonc.2018.16

IMMUNOTHERAPY

Desmoplasia is no barrier to PD-1 blockade in melanoma

A rare melanoma subtype, accounting for <4% of cases, is characterized by a highly desmoplastic stroma and a lack of targetable mutations, and thus insensitivity to chemotherapy and BRAF/MEK kinase inhibitors. One might also expect the dense fibrous stroma of these desmoplastic melanomas (DMs) to be a barrier to effective immunotherapy. However, these tumours are associated with UV light-induced DNA damage and have a high mutational burden, leading to the antithetical hypothesis that DMs, like other melanomas, will be sensitive to immune-checkpoint inhibitors.

To test this theory, 60 patients with DMs were identified retrospectively from a cohort of 1,058 patients treated with PD-1-blockade immunotherapy, and their tumour specimens and clinical outcomes were evalutated. In this small subgroup, the complete response (CR) rate was 32% and the overall objective response rate was 70%. "This represents the highest response rate to anti-PD-1 therapy," which is perhaps unsurprising considering that this "tumour type has among the highest mutational burden of all cancers and has evidence of an active adaptive immune response at baseline," explains Siwen Hu-Lieskovan, who supervised the project.

Indeed, analysis of pretreatment biopsy samples of 19 DMs and 13 non-DMs revealed that the DM subtype had a higher percentage of PD-L1-positive cells in the tumour parenchyma ($P = 0.04$) and invasive margins ($P = 0.16$) than the non-DM subtype. This difference might reflect a greater degree of reactive immune resistance because $CD8^+$ T cell densities were also higher in DMs than in non-DMs (although the differences were not statistically significant). Importantly, the baseline density of $CD8^+$ T cells at the invasive tumour margin seemed to be associated with responsiveness to PD-1 blockade, but this association was only significant for non-DMs ($P = 0.002$). By contrast, mutational burden was not associated with treatment response.

> "For a disease with limited treatment options, these outcomes are very promising"

At a median follow up of 22 months, disease progression had occurred in 9 of 23 patients with a partial response, but in 0 of 19 patients with a CR. Moreover, the median progression-free and overall survival have not been reached. Estimated 2-year overall survival was 74%, and at least two patients have survived for >5 years. For a disease with limited treatment options, these outcomes are very promising.

"The dense stroma surrounding the DMs does not appear to be a barrier to the response to immunotherapy," summarizes Antoni Ribas, who also supervised the project. "The findings of this study have prompted the opening of a new clinical trial involving >100 centres across the USA, sponsored by the National Cancer Institute, to offer the anti-PD-1 antibody pembrolizumab to patients with desmoplastic melanoma," he concludes.

David Killock

ORIGINAL ARTICLE Eroglu, Z. *et al.* High response rate to PD-1 blockade in desmoplastic melanomas. *Nature* **553**, 347–350 (2018)