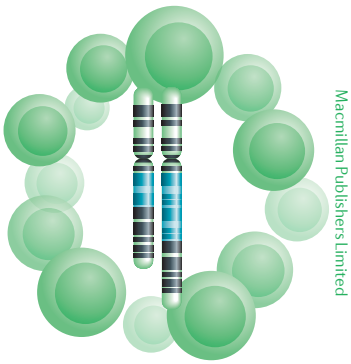
Nature Reviews Clinical Oncology | Published online 21 Mar 2017; doi:10.1038/nrclinonc.2017.41

IMMUNOTHERAPY

Genomic and immunological features predict a response

Despite enabling durable remissions in some patients with advanced-stage cancer most patients fail to respond to immune-checkpoint inhibition. Now, research in a cohort of patients with advanced-stage melanoma receiving anti-CTLA-4, followed by anti-PD-1 antibodies upon tumour progression reveals several genomic and immune-related features associated with a response to these agents, which might enable more-targeted selection of patients to receive such treatments.



Highlighting the rationale for this approach, senior author Jennifer Wargo explains: "numerous studies have investigated biomarkers of sensitivity to immune-checkpoint blockade. However, little is known about the interactions between genomic and immune factors." Furthermore, "no studies have looked into the effects of sequential CTLA-4 and PD-1 blockade in patients".

Investigators collected serial pretreatment, on-treatment, and post-treatment biopsy samples from 56 patients with metastatic melanoma who received sequential CTLA-4 and PD-1 drug inhibitorsion. Biopsy samples were then investigated using a variety of genetic analyses to explore the effects of mutation load, neoantigens, intratumour heterogeneity, copy-number alterations, and T-cell receptor (TCR) clonality on responsiveness to treatment.

A significant correlation was found between a lack of response to both CTLA-4 and PD-1 inhibition and an increased pretreatment burden of copy-number-loss (CNL) mutations. Furthemore, localized, recurrent CNL mutations were observed in regions containing tumour-suppressor genes located on several chromosomes, including 6q, 10q and 11q23.3.

The longitudinal approach used also revealed a potential mechanism of acquired sensitivity to PD-1 inhibition. All three patients with matched pretreatment samples available who responded to PD-1 inhibition developed an increased level of TCR clonality following CTLA-4 inhibition, compared with one of five non-responders (of note, the 'non-responder' with increased TCR clonality remained on treatment, and had no evidence of disease at the latest follow-up assessment). Both observations were independent of alterations in mutation load or predicted neoantigen load, which failed to predict responses to CTLA-4 or PD-1 inhibition, a finding that might be explained by the low number of patients included in this study.

These latest findings highlight the existence of a complex interplay between specific genomic and immunological features of both the tumour itself, and the microenvironment, which probably all contribute to the ability of each patient to respond to immune-checkpoint inhibition. Wargo summarizes: "our findings suggest that CTLA-4 blockade might prime T cells for subsequent PD-1 blockade in certain patients. Therefore, sequential CTLA-4 and PD-1 blockade might provide additive clinical benefit in some patients, compared with monotherapy". When asked about future directions, Wargo adds: "the machine-learning approach of building a predictive model using mutation load, CNL burden, and TCR clonality in a larger validation cohort will reveal the importance of these markers in the clinical setting".

Peter Sidaway

ORIGINAL ARTICLE Roh, W. *et al.* Integrated molecular analysis of tumor biopsies on sequential CTLA-4 and PD-1 blockade reveals markers of response and resistance. *Sci. Transl Med.* http://dx.doi.org/10.1126/scitranslmed.aah3560 (2017)