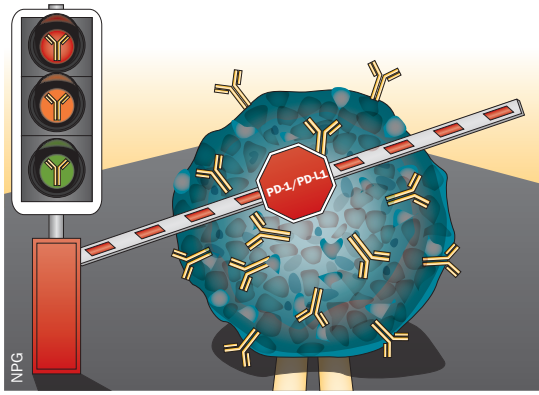
Nature Reviews Clinical Oncology **12**, 63 (2015); published online 23 December 2014; doi:10.1038/nrclinonc.2014.221

IMMUNOTHERAPY

PD-1–PD-L1 axis: efficient checkpoint blockade against cancer



Cancer immunotherapy is presently one of the areas in which major medical breakthroughs are being witnessed, with impressive results reported by several groups. Recently, three articles published in *Nature* have prodvided new insights into the type of cancers that respond to therapies that lift the breaks on antitumour immunity by blocking the programmed cell death-1 (PD-1) pathway, and characterized those patients who respond best to this checkpoint blockade.

The immune checkpoints prevent hyperactivity of the T cells, regulating the responses of our immune system. PD-1, and its ligand PD-L1 have an important role in this context. In fact, PD-L1, expressed on many cancer cells, interacts with PD-1 expressed on the surface of T-cells, inhibiting T-cells and blocking the antitumour immune response.

The first study, conducted by Paul Tumeh and co-authors, was designed to gain increased understanding of how immune cell types within the tumour microenvironment evolve in response to tumour progression. The investigators analysed tumour samples from 46 patients with metastatic melanoma obtained before and during anti-PD-1 therapy (at 20–60 days, 60–120 days, or >120 days after starting therapy), using quantitative immunohistochemistry, quantitative multiplex immunofluorescence and next-generation sequencing of T-cell antigen receptors. "We wanted to identify which immune cell types are altered during PD-1 blockade that were uniquely found in responders," explains Tumeh. With this approach, he continues, "we found that $CD8^+$ T-cells increased in numbers, were proliferating, were functionally activated, and were more clonal in responders." The investigators found that the presence of $CD8^+$ T-cells was the strongest predictor of response to anti-PD-1 therapy, suggesting that these cells drive the response to PD-1 blockade therapy.

These findings will need further validation. Nevertheless, around 70% of patients do not respond to this treatment; for these patients, Tumeh concludes, "we hope to develop a classification scheme that stratifies nonresponders and identifies groups of patients whose tumours can be reprogrammed to become responsive to PD-1 blockade."

The second study, led by Roy Herbst, was the first in-human study of the anti-PD-L1 antibody MPDL3280A; it is based on the rationale that blocking PD-L1 should increase antitumour immunity and its aim was to determine safety, activity and predictive factors for efficacy of this antibody. The study included multiple biopsies across several cancer types, such as non-small-cell lung cancer, melanoma, renal cell carcinoma, and other solid tumours. The investigators showed that responders to anti-PD-L1 therapy had tumours expressing high levels of PD-L1, and showed that the expression of PD-L1 on tumour-infiltrating immune cells is a key predictor of clinical activity. Herbst explains, "the drug is active and in unselected patients benefits approximately 20% of patients across different tumour types." This study, together with the findings from Tumeh *et al.*, demonstrates that PD-1 and PD-L1 blockade provides durable responses in a subset of patients, and that the therapy has low toxicity, with only rare high-grade adverse events. Importantly, these results expand the spectrum of malignancies in which PD-1/PD-L1 blockade has clinical activity.

In the third study, Thomas Powles *et al.* reported a new therapeutic option for patients with bladder cancer after 30 years of a steady-state phase for treatments of this disease. Bladder cancer has high levels of somatic mutations and should, therefore, be more likely to respond to immune-based therapy. On this basis, "we conducted an adaptive type clinical trial, allowing for recruitment of large numbers of patients with specific tumour types as well as biomarker positive cohorts, to assess the safety and efficacy of MPDL3280A in patients with bladder cancer," explains Powles. "The most significant findings are that metastatic bladder tumours which overexpressed the PD-L1 biomarker had a very high response rates (>50%) to MPDL3280A," he continues. These patients were deemed to have exhausted all normal treatment options, but their responses to the PD-L1 antibody are durable, and the drug was exceptionally well tolerated.

"There is an ongoing single-arm phase II study of MPDL3280A in patients with bladder cancer and a very large randomized phase III study of this drug, which is due to open soon," comments Powles. Results from the phase II study are expected next year and hopefully this therapy will be available to patients after that. These anti-PD-L1 antibody studies were awarded breakthrough status from the FDA in June 2014, highlighting the great potential of this drug.

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Original articles Powles, T. *et al.* MPDL3280A (anti-PD-L1) treatment leads to clinical activity in metastatic bladder cancer. *Nature* doi:10.1038/nature13904 | Herbst, R. S. *et al.* Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. *Nature* doi:10.1038/nature14011 | Tumeh, P. C. *et al.* PD-1 blockade induces responses by inhibiting adaptive immune resistance. *Nature* doi:10.1038/nature13954