IMMUNOTHERAPY

Prophylactic TNF blockade reduces autoimmune toxicity

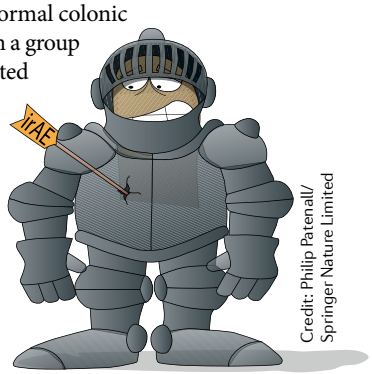
Despite the synergistic efficacy of nivolumab and ipilimumab in some advanced-stage solid tumours, serious immune-related adverse events (irAEs) are common. A new study now demonstrates that prophylactic TNF blockade reduces gastrointestinal irAEs in mice treated with dual immune-checkpoint inhibition (DCI).

The group of Ignacio Melero (University of Navarra, Spain) first demonstrated that DCI exacerbated dextran sulfate sodium (DSS)-induced autoimmune colitis in mice, which was ameliorated with prophylactic administration of an anti-TNF antibody or the TNF inhibitor etanercept. Importantly, TNF blockade before DCI did not impair antitumour efficacy in syngeneic mouse models of colon cancer and melanoma and even improved the survival and xenograft-rejection rate in DSS-treated syngeneic mouse models.

TNF blockade was found to enhance DCI-induced $CD8^+$ T cell infiltration (in the tumour and lymph nodes) and decrease activation-induced cell death in DCI-treated $CD8^+$ T cells in vitro and in vivo, providing a mechanistic rationale for these observations.

The expression of *TNF*-related transcripts and genes was found to be upregulated in normal colonic mucosal tissues from a group of four patients treated with DCI who developed colitis compared with those from four healthy individuals without bowel inflammation or cancer. In a graft-versus-host disease mouse model, prophylactic etanercept treatment reduced DCI-induced exacerbation of colitis. Similarly, in a colon cancer xenograft-induced humanized mouse model of colitis, concomitant etanercept treatment did not weaken the antitumour effects of nivolumab–ipilimumab and, importantly, diminished xenograft-induced colitis.

> prophylactic TNF inhibition could improve the safety of DCI regimens while preserving — or even enhancing — efficacy



Credit: Philip Patenall/ Springer Nature Limited

The findings have clear translational relevance, whereby prophylactic TNF inhibition could improve the safety of DCI regimens while preserving — or even enhancing — efficacy and perhaps enabling ipilimumab doses to be safely increased.

"An ongoing pilot trial in France (NCT03293784) is testing safety of the combined strategy, and a larger randomized phase II trial should soon test efficacy," adds Melero.

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ORIGINAL ARTICLE Perez-Ruiz, E. et al. Prophylactic TNF blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy. *Nature* https://doi.org/10.1038/s41586-019-1162-y (2019)

IMMUNOTHERAPY

Chemotherapy as a TONIC to invigorate PD-1 inhibition in TNBC

Disappointingly, immune-checkpoint inhibitors, such as those targeting programmed cell death 1 (PD-1), have limited single-agent activity in patients with metastatic triple-negative breast cancer (mTNBC). New findings suggest, however, that short-duration induction chemotherapy can enhance sensitivity to these agents.

In the first part of the adaptive, non-comparative, phase II TONIC trial, 67 patients with mTNBC were treated with the anti-PD-1 antibody nivolumab after 2 weeks of either hypofractionated irradiation of a single tumour site; low-dose cyclophosphamide, cisplatin or doxorubicin; or no induction therapy. Overall, the objective response rate (ORR) was 20% and, although the median progression-free survival was only 1.9 months, the median duration of response was 9 months.

> after induction treatment with doxorubicin or cisplatin, we observed trends towards increased T cell infiltration and significant upregulation of immune-related genes

ORRs with anti-PD-1 monotherapy in similar cohorts are typically 5–10%. "We observed higher than expected efficacy in the patients who received doxorubicin or cisplatin," states Marleen Kok: ORRs in the doxorubicin, cisplatin, no induction, cyclophosphamide and radiotherapy groups were 35%, 23%, 17%, 8% and 8%, respectively.

To examine the effects of each treatment on tumour immune infiltrates, biopsy sampling was performed at baseline, after induction therapy and following three cycles of nivolumab. Post-nivolumab tumour specimens were enriched for tumour-infiltrating lymphocytes (TILs), $CD8^+$ T cells and inflammatory gene signatures in responders versus non-responders. Notably, "after induction treatment with doxorubicin or cisplatin, we observed trends towards increased T cell infiltration and significant upregulation of immune-related genes, which were more pronounced after anti-PD-1 therapy," Kok explains. By contrast, T cell infiltration was not increased and the inflammatory gene signatures tended to be downregulated after induction radiotherapy. These findings suggest that certain chemotherapies, particularly doxorubicin but also cisplatin, can prime tumours for a response to PD-1 inhibitors. Hence, the doxorubicin group is currently being expanded in the second part of the trial.

"Although our cohort is small, we report several biomarkers — for example, TILs as well as $CD8^+$ T cells — that, if independently validated, could help select the right patients with mTNBC for anti-PD-1 therapy," says Kok. "Furthermore, our trial design might serve as a template for other signal-finding trials of combination immunotherapy," she concludes.

David Killock

ORIGINAL ARTICLE Voorwerk, L. et al. Immune induction strategies in metastatic triple-negative breast cancer to enhance the sensitivity to PD-1 blockade: the TONIC trial. *Nat. Med.* https://doi.org/10.1038/s41591-019-0432-4 (2019)