CANCER IMMUNOTHERAPY

An RNA vaccine for advanced melanoma

Reporting in *Nature*, Ugur Sahin and colleagues describe the interim results from a first-in-human phase I trial of an RNA vaccine for melanoma. Encouragingly, the data show that melanoma FixVac can induce effector T cell responses against tumour-associated antigens (TAAs) and mediate durable objective responses in immune checkpoint blockade (ICB)-experienced patients with advanced melanoma.

There have been many attempts to develop therapeutic cancer vaccines that prime T cell immunity against common TAAs, such as cancer germline antigens or lineage-restricted markers. Most vaccine trials have reported ineffective T cell induction and this has been attributed to central T cell tolerance to TAAs, which are non-mutated self-antigens. Recent efforts have focused on targeting mutant cancer antigens that will not be compromised by central T cell tolerance, but such personalized therapies also have their limitations.

The FixVac vaccine developed by the authors is an intravenously administered nanoparticulate liposomal RNA (RNA-LPX) vaccine that is optimized to target immature dendritic cells in lymphoid tissues and to drive TAA presentation on both MHC class I and class II molecules. It contains RNA-LPX encoding four TAAs — specifically, NY-ESO-1, MAGEA3, tyrosinase and TPTE — that show restricted expression in normal tissues but high prevalence and immunogenicity in melanoma. Importantly, RNA-LPX promotes expansion of antigen-specific T cells through a TLR7-driven type I interferon pathway, which is normally induced in response to viral infection.

This exploratory interim analysis involved 89 patients with late-stage melanoma that expressed at least one of the four FixVac-encoded TAAs. They underwent a minimum of eight vaccinations with FixVac (with RNA doses ranging from 7.2 to 400 µg) and some patients continued to receive monthly boosters. Some cohorts received FixVac alone, whereas others were also treated with ICB targeting PD1.

Patients showed increased metabolic activity in the spleen following vaccination, which is indicative of TLR activation in lymphoid tissue-resident immune cells. Body temperature and plasma levels of inflammatory cytokines (IFNα, IFNγ, IL-6, CXCL10 and IL-12p70) also transiently increased with higher increases seen in line with higher RNA doses. Adverse clinical events included mild-to-moderate flu-like symptoms, but these were manageable and mainly resolved within 24 hours.

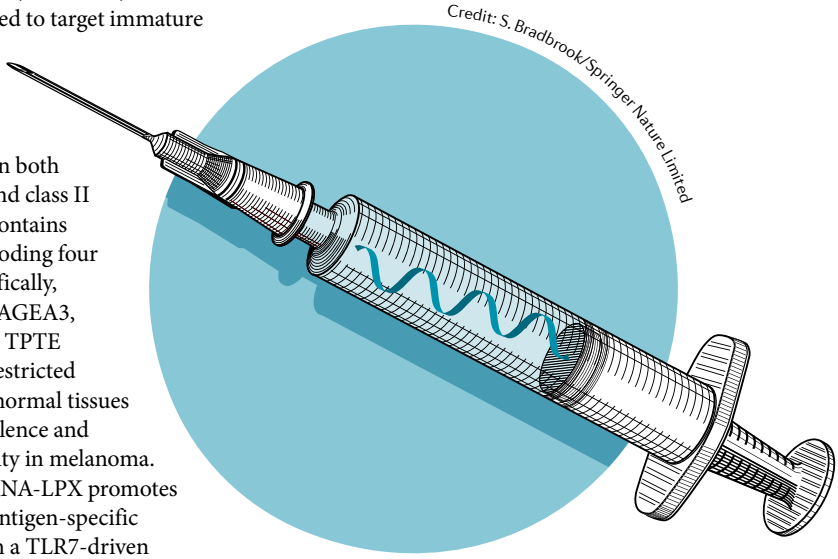
ELISpot analyses suggested that patients developed specific T cell responses against at least one TAA following vaccination, with most showing a $CD4^+$ T cell response alone or else both $CD8^+$ and $CD4^+$ T cell responses. Vaccine-induced de novo T cell responses were more common than the amplification of pre-existing T cell responses, and most high-magnitude responses involved $CD8^+$ T cells. The frequency of TAA-specific effector T cells continued to increase or remain stable in patients who had monthly FixVac boosters, but memory T cells also persisted in those who did not receive continuous vaccination.

> “melanoma FixVac can induce effector T cell responses against tumour-associated antigens”

Several patients experienced partial responses and shrinkage of metastases after vaccination and these were the individuals who developed the most prominent T cell responses. The authors identified specific $CD8^+$ T cell clones induced by FixVac and showed that these clones can mediate the killing of melanoma cells. A striking finding was that some patients who had received FixVac after anti-PD1 therapy failure showed tumour regression following vaccination, eventually progressed again but then responded to another round of anti-PD1. This is in line with the induction of $PD1^+$ effector memory T cells by FixVac. Overall, a tumour regression rate of more than 35% was seen in the ICB-experienced patients who received combined FixVac and anti-PD1 therapy, which is similar to the objective response rates seen to anti-PD1 in patients with metastatic melanoma who have not previously received ICB.

ICB has revolutionized cancer therapy but is not effective in many patients, particularly if they have lower mutational burdens in their tumours. The early findings from this trial suggest that the combined use of potent therapeutic vaccines targeting TAAs with anti-PD1 therapy could be especially effective in patients with lower mutational burdens, even if prior ICB has failed.

Yvonne Bordon



This article originally appeared in *Nat. Rev. Immunol.* (https://doi.org/10.1038/s41577-020-00417-7)

ORIGINAL ARTICLE Sahin, U. et al. An RNA vaccine drives immunity in checkpoint-inhibitor-treated melanoma. *Nature* https://doi.org/10.1038/s41586-020-2537-9 (2020)