Background Immunomodulatory therapies targeting the effector T (Teff) cell inhibitory signalling pathways PD-1/PD-L1 and CTLA-4 induce striking objective clinical responses in patients with certain cancer types, but are ineffective at inducing durable responses in a majority of patients.1 CD4+ regulatory T (Treg) cells, dependent on the transcription factor Foxp3, powerfully suppress Teff cells and prevent immune-mediated rejection of tumours.2,3 Low Treg to Teff cell ratios in humans are associated with favourable survival in multiple cancer types and murine models show that ablation of Treg cells results in activation of CD4+ or CD8+ Teff cells and rejection of tumours. Treg cells therefore represent an attractive target for immunostimulatory therapy.

FS120 is a novel tetravalent bispecific antibody targeting OX40 and CD137 (4-1BB), both tumour necrosis factor (TNF) receptor superfamily members which are expressed on activated and memory T-cell subsets, Treg and NK cells. Pre-clinically, an FS120 mouse surrogate antibody has demonstrated significant anti-tumour immunity in syngeneic tumour models.4 FS120 is currently being evaluated in a Phase 1 trial (NCT04648202) which aims to identify a well-tolerated and pharmacologically active dose of FS120 for exploration as monotherapy, and in combination with anti-PD-1.5

Methods We elucidate mechanisms of action of OX40/CD137 dual agonist therapy with a mouse-specific FS120 surrogate molecule, using syngeneic tumour models, in conjunction with genetic Treg lineage tracing, high-dimensional flow cytometry, transcriptome analyses and functional studies.

Results FS120 treatment invokes profound anti-tumour immune responses resulting in substantially reduced growth of syngeneic MC38 colorectal adenocarcinoma tumours. FS120 treatment induces two distinct phenomena within tumours: 1) Treg lineage instability, marked by accumulation of ‘ex-Treg’ cells from Treg progenitors, which gain the ability to express IFN-γ and TNF-α, and 2) Treg functional reprogramming, where Foxp3+ Treg cells are induced to produce effector cytokines IFN-γ and TNF-α. The ability of FS120 surrogate to drive Treg instability and functional reprogramming are not shared by anti-PD-1 therapy, suggesting a mode of therapeutic efficacy distinct from anti-PD-1. Accordingly, FS120 treatment synergises with PD-1 checkpoint blockade therapy to induce profound anti-tumour responses.

Conclusions Treatment with FS120 surrogate causes lineage instability and functional reprogramming of Treg cells, resulting in their ability to produce effector cytokines and drive tumour regression. This mode of action is distinct from anti-PD-1 therapy. These findings support a combination therapy approach exploiting the distinct anti-tumour immune activities of FS120 and anti-PD-1 in cancer patients.

REFERENCES