1069 OX40/CD137 DUAL AGONISM POTENTIATES ANTI-TUMOUR IMMUNITY BY DRIVING FUNCTIONAL REPROGRAMMING AND INSTABILITY OF REGULATORY T (T_{REG}) CELLS

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Background Immunomodulatory therapies targeting the effector T (T_{eff}) 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 (T_{reg}) cells, dependent on the transcription factor Foxp3, powerfully suppress T_{eff} cells and prevent immune-mediated rejection of tumours.[2,3] Low T_{reg} to T_{eff} cell ratios in humans are associated with favourable survival in multiple cancer types and murine models show that ablation of T_{reg} cells results in activation of $CD4^+$ or $CD8^+$ T_{eff} cells and rejection of tumours. T_{reg} 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, T_{reg} and NK cells. Preclinically, 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 T_{reg} 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) T_{reg} lineage instability, marked by accumulation of 'ex-T_{reg}' cells from T_{reg} progenitors, which gain the ability to express IFN-γ and TNF-a, and 2) T_{reg} functional reprogramming, where Foxp3+ T_{reg} cells are induced to produce effector cytokines IFN-γ and TNF-a. The ability of FS120 surrogate to drive T_{reg} 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 T_{reg} 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.

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http://dx.doi.org/10.1136/jitc-2022-SITC2022.1069