579-B TIGIT AND PD-L1 CO-BLOCKADE PROMOTES CLONAL EXPANSION OF NON-EXHAUSTED ANTI-TUMOUR CD8+ T CELLS BY FACILITATING COSTIMULATION

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Background Blockade of the immune checkpoints PD-1 and TIGIT has demonstrated activity in mouse tumour models and human cancer patients. Although these coinhibitory receptors act at least in part by restricting costimulatory receptor signaling by CD28 and CD226 in CD8$^+$ T cells, the functional and mechanistic consequences of combination blockade of PD-1 and TIGIT remains a key unknown.

Methods We examined both single and combination therapies using the syngeneic mouse model CT26 as well as the drug FTY720, in order to dissect MOA in the periphery versus the tumor itself. Anti-PDL1/anti-TIGIT synergy was examined through *in vivo* efficacy studies as well as *ex-vivo* analysis using flow cytometry, scRNAseq, and scTCRseq.

Results Here, we show that optimal combination efficacy in mouse tumour models required leukocyte trafficking between the draining lymph nodes (dLN) and tumour. Combination blockade elicited the clonal expansion of tumor antigen-specific CD8$^+$ T cells, in a fashion that involves CD226. The expanded clones possessed properties of early effector or memory cells that emerge from a pool of stem-like memory or progenitor exhausted cells and exhibited a significant decrease in the expression of the Tox transcription factor required for the exhaustion pathway. These data suggest that in mice, PD-1 and TIGIT shape the repertoire and fate of effector and memory CD8$^+$ T cells in dLN, blood, and tumors. Interestingly, cancer patients that similarly exhibit expanded CD8$^+$ T cell clonotypes in both tumours and the periphery were associated with favorable clinical outcomes in a randomized Phase 2 trial evaluating tiragolumab (anti-TIGIT monoclonal antibody; mAb) plus atezolizumab (anti-PD-L1 mAb) in non-small cell lung cancer.

Conclusions We propose that blockade of PD-1 and TIGIT restricts entry of T cells into the exhaustion pathway by facilitating costimulatory signaling, yielding expanded clonotypes that preferentially differentiate into T effector and memory cells having greater potential for therapeutic benefit.

Ethics Approval Animal: All mice were housed and maintained at Genentech in accordance with American Association of Laboratory Animal Care guidelines. All experimental animal studies were conducted under the approval of the Institutional Animal Care and Use Committees of Genentech Lab Animal Research and were performed in an Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC)-accredited facility.

Human: Institutional review boards and ethics committees approved the protocol, and the study was done in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonization guidelines for Good Clinical Practice, and countryspecific laws and regulations. All patients provided written informed consent.

An internal monitoring committee reviewed available safety data periodically to make recommendations regarding study conduct to ensure the safety of patients enrolled in the study.

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