475 ANTI-TIGIT ANTIBODY TIRAGOLUMAB LEVERAGES MYELOID CELLS AND REGULATORY T CELLS TO IMPROVE PD-L1 CHECKPOINT BLOCKADE

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Background TIGIT is a co-inhibitory receptor and immune checkpoint associated with T cell and natural killer (NK) cell dysfunction in cancer. Tiragolumab is an anti-TIGIT antibody with an active, IgG1/kappa Fc. In a randomized double-blind phase 2 clinical trial in non-small cell lung cancer (NSCLC), tiragolumab + atezolizumab (anti-PD-L1) combination treatment demonstrated significant improvement relative to atezolizumab alone. However, the mechanisms underlying efficacy of this combination are not well understood.

Results Here, we show that tiragolumab functions as both a conventional checkpoint inhibitor and, via Fc gamma receptor (FcgR) engagement, as a modulator of immunosuppressive myeloid cells and T regulatory (Treg) cells. High levels of these cell subsets, which often mediate resistance to immunotherapy, were associated with treatment benefit in the tiragolumab + atezolizumab arm but not atezolizumab arm. Patients receiving the combination treatment exhibited transient on-treatment increases in serum proteins suggestive of myeloid cell activation, and decreases in circulating Treg cells. In preclinical experiments, treatment with Fc-active anti-TIGIT led to effector T cell and NK cell activation, Treg reduction, and proinflammatory modulation of myeloid cells and neutrophils.

Conclusions These findings reveal distinct mechanisms by which tiragolumab unleashes antitumor immune responses, and inform further clinical development of anti-TIGIT therapies.

Trial Registration NCT03563716

Ethics Approval Protocol approval was obtained from independent ethics committees for each participating site for both studies and an independent data monitoring committee reviewed the safety data.

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