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FC-SILENT ANTI-TIGIT ANTIBODIES POTENTIATE ANTI-TUMOR IMMUNITY WITHOUT DEPLETING REGULATORY T CELLS

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**Background** TIGIT is an inhibitory receptor expressed on T and NK cell subsets that outcompetes an activating receptor, CD226, for shared ligands. The TIGIT checkpoint blockade field has focused on evaluating efficacy and elucidating mechanisms of action related to Fc-enabled antibody formats. Here, we report efficacy and pharmacology associated with clinical and mouse tool Fc-silent anti-TIGIT antibodies relative to Fc-enabled counterparts.

**Methods** Human NSCLC tumor (pre-treatment stages I-IV) and mouse MC38 tumor and tumor-draining lymph node (tdLN) cell suspensions were interrogated for expression of TIGIT and associated receptors by flow cytometry. Anti-tumor efficacy and pharmacodynamic changes were assessed using tool Fc-silent or Fc-enabled anti-mouse TIGIT antibodies in the MC38 tumor model. The ability of human TIGIT-specific clinical antibodies that are Fc-silent (domvanalimab) or Fc-enabled (AB308) to promote NK-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) was evaluated using an *in vitro* co-culture system and by measuring absolute T cell counts in longitudinal peripheral blood patient samples from Phase 1 dose escalation clinical trials NCT03628677 and NCT04772989. Anecdotal clinical outcomes in two patients from NCT03628677 receiving domvanalimab in combination with an anti-PD-1 antibody, zimberelimab, are also reported.

**Results** Human and mouse tumor-infiltrating lymphocytes express TIGIT and CD226 on regulatory T cells (Treg), CD4+ non-Treg, and on CD8+ T cells with tumor-reactive or exhausted/dysfunctional phenotypes. In mice, combining Fc-silent or Fc-enabled anti-TIGIT, with anti-PD-1 antibodies resulted in enhanced tumor control, but by mechanisms that differentially shape the tumor microenvironment. Fc-silent anti-TIGIT did not deplete Treg yet promoted activation of tumor-specific precursor-exhausted CD8+ populations in the tdLN. In contrast, Fc-enabled anti-TIGIT depleted Treg in mice. Consistent with the murine system, Fc-enabled human TIGIT-specific antibody AB308 induced ADCC against TIGIT-expressing human Treg *in vitro*, with preferential depletion of a Helios+ Treg subset with an activated/effector phenotype. In humans, significant and stable decreases in Treg were measured in the peripheral blood of cancer patients treated with AB308. In contrast, domvanalimab did not deplete Treg *in vitro*, and patients treated with domvanalimab in combination with anti-PD-1 antibody zimberelimab experienced partial responses while maintaining stable peripheral Treg frequencies on treatment.

**Conclusions** We demonstrate that Fc-silent anti-TIGIT antibodies potentiate activation of tumor-specific T cells and anti-tumor efficacy without depleting Treg (figure 1). These data provide critical insights related to activity of anti-TIGIT antibodies lacking Fc functionality, such as domvanalimab.

**Ethics Approval** Animal studies were performed at Arcus Biosciences in accordance with federal, state, and institutional guidelines and were approved by Arcus Biosciences’ Institutional Animal Care and Use Committee. Dissociated tumor biopsies were obtained from Discovery Life Sciences with informed written consent and according to Institutional Review Board approved guidelines in accordance with the Declaration of Helsinki. Clinical studies were performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Protocols and amendments were approved by institutional review boards for each study site. All patients provided written informed consent.