Preclinical characterization of AB154, a humanized α-TIGIT antibody, for use in combination therapies

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**AB154 Binding to Human TIGIT Blocks Interaction with CD155**

- A. $EC_{50} = 0.35 \text{ nM}$
- B. $IC_{50} = 0.69 \text{ nM}$
- C. Percent TIGIT* 0.14 nM
- D. Percent TIGIT 0.13 nM
- E. IFN-γ (pg/mL)

**Co-expression of PD-1 and TIGIT in Multiple Tumor Types**

- A. Median PD-1
- B. Median TIGIT
- C. Median CD155
- D. Median CD226

**Receptor Occupancy Assay to Measure TIGIT Engagement by AB154**

- A. Receptor Occupancy Assay
- B. Lymphocyte Populations
- C. Percent of parent population (%)

**Figure 1.** Potency of AB154 was measured as a function of its binding to CHO cell line over-expressing human TIGIT (A), and its ability to block binding of soluble CD155-Fc to TIGIT (B). MFI represents mean fluorescence intensity. Fluorophore-conjugated AB154 was used to directly measure binding in whole blood isolated from 3 healthy donors (C) and 3 cancer patients (D). Combinatorial settings were assessed using mixed lymphocyte reactions (MLRs) consisting of CD4+ T cells and monocytes DC cultures. Inhibition of TIGIT in combination with α-PD-1 antibody (AB122) resulted in increased IFN-γ production relative to monotherapy (E). *p ≤ 0.05. Predicted Human Pharmacokinetic Parameters of AB154

**Figure 2.** Median TIGIT and PD-1 expression derived from The Cancer Genome Atlas (TCGA) database is shown (A). Red indicates high CD8-to-TIGIT+ ratio and blue indicates low CD8-to-TIGIT- ratio. Axis numbers indicate log2 transformed expression of counts per million. (B) CD226 negatively correlates with CD155. TIGIT expression in each tumor type is shown as a low (blue) to high (red) gradient. Distribution of TIGIT and PD-1 in T_{reg} and CD8+ T cells isolated from lung (black), colorectal (red), and renal (blue) tumors are shown (C). TIGIT mean fluorescence intensity (MFI) in each subset is shown in (D).

**Figure 3.** Receptor occupancy was determined using saturating levels ($>EC_{50}$) of a commercially-available α-TIGIT antibody that binds competitively with AB154 (A). Therefore, the apparent IC_{50} as measured in this assay, is higher than the binding affinity of AB154 shown in Figure 1. Lymphocyte distribution (B), amount of TIGIT expressed (C) and receptor occupancy (D) were comparable between cancer patients and healthy donor blood samples.

**Conclusion**

- AB154 is a humanized α-TIGIT antagonistic antibody that blocks TIGIT/CD155 interactions at potencies < 1 nM
- Combination of AB154 with α-PD-1 (AB122) antibodies significantly increased IFN-γ secretion relative to anti-PD-1 alone
- TIGIT and PD-1 expression are correlated in many tumor types and are often co-expressed on tumor infiltrating lymphocytes (TILs).
- A robust flow cytometry based assay has been developed to monitor TIGIT receptor occupancy in clinical samples
- AB154 is currently undergoing clinical evaluation in a dose escalation study, alone and in combination with AB122