Characterization of AB154, a Humanized, Non-Depleting α-TIGIT Antibody Undergoing Clinical Evaluation in Subjects with Advanced Solid Tumors

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Introduction

AB154 is a humanized antibody that blocks human TIGIT (T-cell immunoreceptor with Ig and ITIM domains), an inhibitory receptor expressed on natural killer (NK) cells, $CD8^+$ T cells, $CD4^+$ T cells and regulatory T cells (T_{reg}). CD226 (or DNAX Accessory Molecule-1, DNAM-1) is an activating receptor that competes with TIGIT for shared ligands CD155 (PVR) and CD112 (Nectin-2), expressed by cancer and antigen-presenting cells. AB154 blocks TIGIT with sub-nanomolar affinity, thus prevents binding to its ligands and shifts the immune balance towards a more favorable CD226 interaction. Because AB154 is engineered without FcγR binding function, the immune suppressive TIGIT-CD155 interaction is blocked with minimal risk of depleting intra-tumoral antigen-experienced $CD8^+$ T cells. AB154 has the potential to promote sustained immune activation and tumor clearance, particularly in combination with other immunotherapies such as AB122 (anti-PD1).

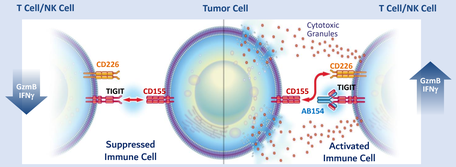


Figure 1. TIGIT binds to CD155 and results in decreased activation of the TIGIT-expressing immune cells. AB154 blockade of TIGIT allows CD155 to bind CD226, favoring T cell and NK cell activation.

Methods

Gene Expression: Expression of TIGIT, PD-1 (PDCD1), and CD226 on select tumor types were derived from RNASeq in The Cancer Genome Atlas (TCGA) database.

Immunohistochemistry (IHC): Anti-CD155 antibody (Cell Signaling Technology, D8A5G) was used to stain FFPE human tissues. Samples were deparaffinized according to standard methods and heat-induced epitope retrieval was performed using sodium citrate. Anti-rabbit HRP and DAB chromogen were used for detection.

ADCC Assay: AB154 and versions of AB154 modified to restore wild-type (WT) IgG1 effector function or to display enhanced FcγR binding via Fc mutations (EEF) were used in antibody-dependent cell cytotoxicity (ADCC) studies.

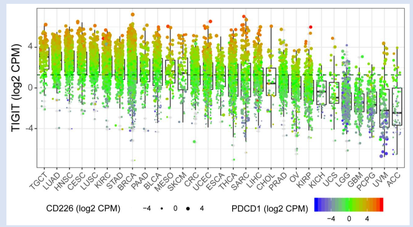
Identification of Intra-tumoral Antigen-Experienced T cells: Dissociated tumor samples from head and neck cancer patients were purchased from Discovery Life Sciences (n = 5). Cells were assessed for viability, surface and intracellular markers related to T cell lineage, exhaustion, and activation by flow cytometry.

AB154 Potency in Healthy Volunteers vs. Lung Cancer Patients: Whole blood was obtained from healthy volunteers (n = 3) and non-small cell lung carcinoma (NSCLC) patients (n = 3) and assessed by flow cytometry. TIGIT receptor occupancy was determined using saturating levels of a commercially-available human α-TIGIT antibody that binds competitively with AB154.

Clinical PK/PD: A Phase 1 dose-escalation study is underway to evaluate AB154 as a monotherapy and in combination with AB122 (anti-PD1) in subjects with advanced solid malignancies. Whole blood was assessed by flow cytometry using saturating levels of a competing anti-TIGIT antibody to determine receptor occupancy (RO) as well as changes in Ki67 expression.

Results

TIGIT, PD-1, and CD226 Are Co-Expressed on Human Tumors



TGCT: Testicular Germ Cell Tumors; **LUAD**: Lung Adenocarcinoma; **HNSC**: Head and Neck Squamous Cell Carcinoma; **CESC**: Cervical Squamous Cell Carcinoma; **LUSC**: Lung Squamous Cell Carcinoma

Figure 2. RNASeq data from TCGA reveals high levels of TIGIT and PD-1 (PDCD1) co-expression across many tumor types. CD226 is often expressed in $TIGIT^{hi}$ $PD\text{-}1^{hi}$ tumor types.

Strong CD155 Staining in Tumors of Interest

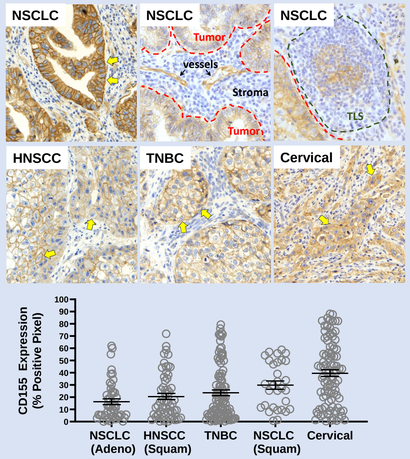
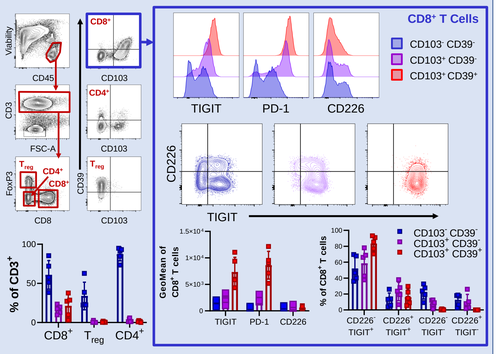


Figure 3. CD155 immunohistochemistry (IHC) shows membrane and cytoplasmic localization on cancerous cells, blood vessels, and tertiary lymphoid structures (TLS) in NSCLC and other tumors of interest. Arrows indicate positive staining. CD155 protein levels were quantified from IHC.

TIGIT and PD-1 Are Highly Expressed by Intra-tumoral Antigen-Experienced $CD8^+$ T Cells



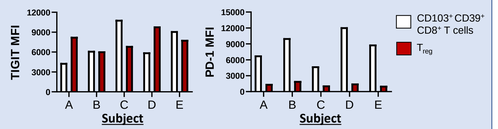


Figure 4. In T cells isolated from advanced head and neck tumor samples (n = 5), markers of antigen experience are predominantly found on the $CD8^+$ subset. $CD8^+$ antigen-experienced T cells ($CD103^+CD39^+$) express higher levels of PD-1 and TIGIT that are consistent with an "activated" or "exhausted" phenotype. CD226 is progressively lost from the inexperienced $CD103^-CD39^-$ population to the experienced $CD103^+CD39^+$ CD8 T cell population. TIGIT receptor density is often comparable or higher on antigen-experienced CD8 T cells than on T_{reg}. PD-1 is consistently highest on intra-tumoral $CD103^+CD39^+$ CD8 T cells.

Enhanced Effector Function Results in NK-Mediated Killing of Activated $TIGIT^+$ $CD8^+$ T Cells

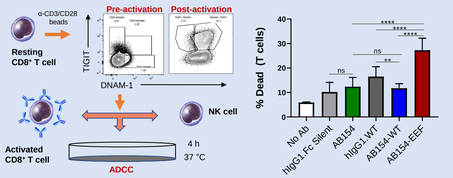


Figure 5. Activated $CD8^+$ T cells expressing high levels of TIGIT are particularly susceptible to antibody-dependent cell-mediated cytotoxicity (ADCC) when targeted by an antibody with enhanced effector function (EEF). Data from four combinations of T cell donors (n = 2) and NK cell donors (n = 2) are shown. *p ≤ 0.05. **p ≤ 0.01. ***p ≤ 0.001. ****p ≤ 0.0001.

Similar AB154 Potency on Peripheral Blood Lymphocytes Isolated from Healthy Volunteers and NSCLC Patients

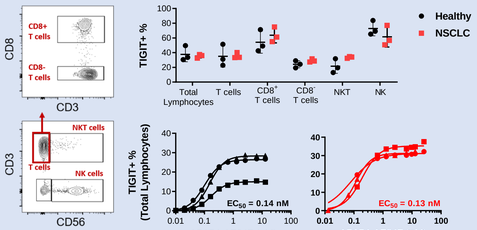
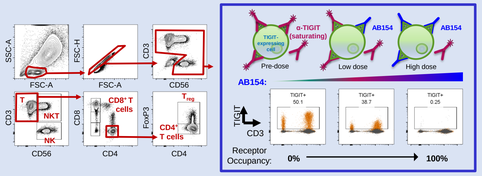


Figure 6. Patients and healthy donors had similar TIGIT expression in peripheral blood lymphocytes, including $CD8^+$ and $CD8^-$ T cells, NK cells and NKT cells, as measured using saturating levels of a commercially available α-TIGIT antibody. Fluorophore-conjugated AB154 was used to directly determine binding affinity in whole blood, with equipotency observed on lymphocytes isolated from healthy donors and cancer patients. In human whole blood, ex vivo addition of AB154 achieved complete inhibition of TIGIT.

Total Receptor Coverage Achieved in AB154 Monotherapy and Combination Cohorts



Study Arm	Cohort	AB154 Dosing (Q2W)	Receptor Occupancy (Mean+SD%) C1D15 Predose	Receptor Occupancy (Mean+SD%) C2D29 Predose
AB154 Monotherapy	1	0.5 mg/kg	99.7 ± 0.3	100 ± 0
	2	1 mg/kg	100 ± 0	100 ± 0.12
	3	3 mg/kg	100 ± 0	100 ± 0
AB154 + AB122 (240 mg) Combination	1	1 mg/kg	100 ± 0	99.6 ± 0.75
	2	3 mg/kg	100 ± 0	100 ± 0
	3	10 mg/kg	100	TBD

* Data collected as of 8-Oct-2019

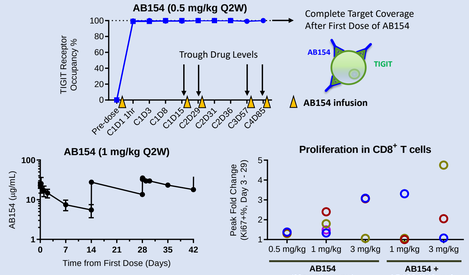


Figure 7. Complete receptor coverage has been observed in all TIGIT-expressing peripheral lymphocytes after initial dosing at every trough timepoint for all enrolled subjects. PK data for the second monotherapy cohort (AB154 at 1 mg/kg Q2W) is shown. Spikes in Ki67 expression occur between Day 3 and Day 29 in $CD8^+$ T cells for both monotherapy and combination subjects. Where present in this small number of subjects, the magnitude of this proliferative burst appears to increase in a AB154 dose-dependent manner, which may also be enhanced by combination with AB122 (anti-PD-1).

Safety and Tolerability of AB154 Demonstrated in Ongoing Phase 1 Study

1) As of the DCO of 16-Sep-2019, 10 participants have been dosed with AB154 monotherapy (0.5, 1, and 3 mg/kg) and 6 participants with AB122/AB154 combination therapy (1 and 3 mg/kg).
2) No DLTs have been observed with either regimen. DLT evaluation of the fully enrolled AB154 10 mg/kg + AB122 combination cohort is ongoing.
3) No subject has experienced any AB154-related SAEs or ≥Gr3 AEs.

Conclusions

- TIGIT, PD-1, and CD226 expression are correlated in many tumor types and are often co-expressed on tumor infiltrating lymphocytes (TILs). CD155 is also highly expressed by cancer types of interest.
- $CD8^+$ T cells make up the majority of antigen-experienced T cells in advanced head and neck tumor samples. Antigen experience occurs alongside markers of immune exhaustion and loss of CD226 expression.
- Antibodies engineered with enhanced effector function (EEF) can facilitate ADCC on intra-tumoral antigen-specific $CD8^+$ T cells.
- TIGIT receptor density is often comparable or higher on intra-tumoral antigen-experienced $CD8^+$ T cells than on T_{reg}, highlighting the danger of targeting these cells with depleting antibodies.
- AB154 potently binds TIGIT in peripheral blood from both healthy volunteers and NSCLC patients.
- AB154-dosed patients have had complete receptor coverage on all TIGIT-expressing peripheral leukocytes in this Phase 1 trial (NCT03628677). Proliferative bursts in $CD8^+$ T cells demonstrate immune engagement.
- A Phase 2 study including the combination of AB154 and AB122 is planned.