ARC-7: A Phase 2 Study to Evaluate the Safety and Efficacy of Zimberelimab Monotherapy and Domvanalimab (AB154) + Zimberelimab ± Etrumadenant (AB928) in Front-Line, PD-L1-High Expressing, Non-Small Cell Lung Cancer

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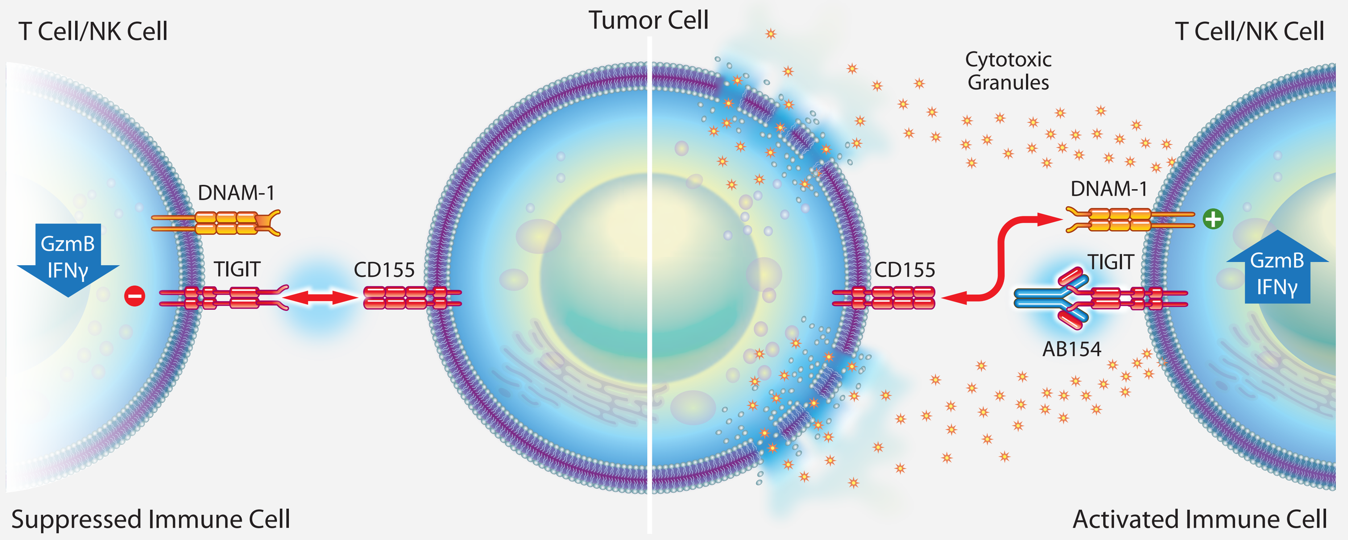
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CHECKPOINT INHIBITION AND THE TIGIT PATHWAY

- The programmed cell death protein-1 (PD-1) inhibitory pathway is a key immune checkpoint that can be exploited by tumors to enable their survival[1]
 - Zimberelimab (AB122), a monoclonal antibody (mAb) in early clinical development, potently blocks PD-1 and has an anticipated safety profile similar to other approved anti–PD-1 mAbs
- The T cell immunoreceptor with Ig and ITIM domain (TIGIT) inhibitory pathway has been previously identified as a novel immune checkpoint that influences the antitumor immune response[2] (**Figure 1**)
 - TIGIT, expressed on T cells and NK cells, binds its tumor cell-expressed ligand CD155 and as a result, immune cell effector function is abrogated[3]
 - CD155 has a greater affinity for TIGIT, but can also bind the receptor DNAX accessory molecule-1 (DNAM-1); if this occurs, the resulting signaling leads to proinflammatory cytokine production and immune cell cytotoxicity[3]
 - Thus, inhibition of TIGIT-CD155 binding promotes activation of the immune response as opposed to suppression in the tumor microenvironment (TME)

Figure 1. TIGIT-CD155 Binding Promotes Immunosuppression


T Cell/NK Cell
Tumor Cell
T Cell/NK Cell
Cytotoxic Granules
DNAM-1
TIGIT
CD155
GzmB IFNγ
CD155
DNAM-1
TIGIT
AB154
GzmB IFNγ
Suppressed Immune Cell
Activated Immune Cell

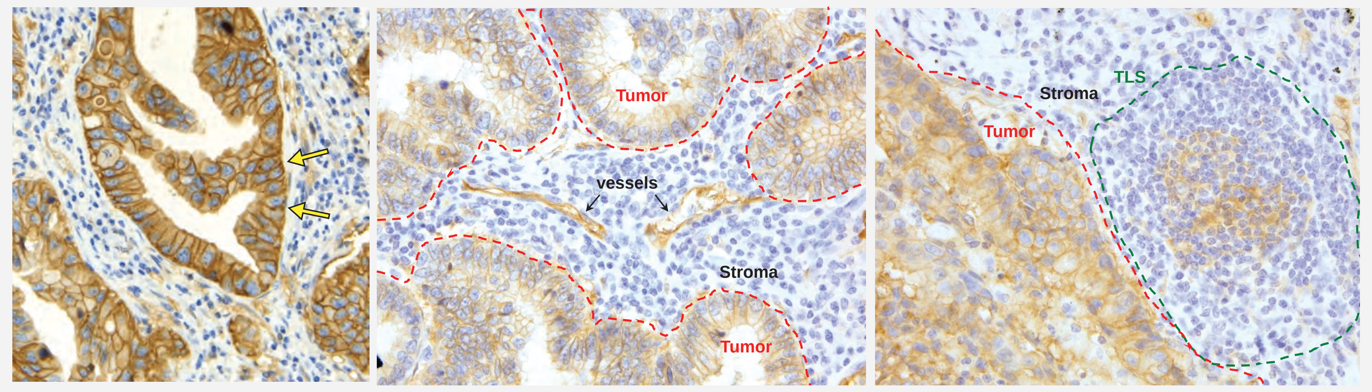
AB154, domvanalimab; DNAM-1, DNAX accessory molecule-1; GzmB, granzyme B; IFNγ, interferon gamma; NK, natural killer; TIGIT, T cell immunoreceptor with Ig and ITIM domain.

- Domvanalimab (AB154) is a humanized mAb that blocks TIGIT and is engineered to lack FcγR binding function to minimize the risk of depleting intratumoral $CD8^+$ effector T cells[4]
- Treatment with domvanalimab, particularly in combination with other checkpoint inhibitors such as zimberelimab, has the potential to promote sustained immune activation and tumor clearance

TIGIT AND PD-1 BIOLOGY IN NSCLC

- In non-small cell lung cancer (NSCLC), CD155 protein is expressed within the cytoplasm and tumor cell membranes, and on adjacent blood vessels and tertiary lymphoid structures in the TME (**Figure 2**)

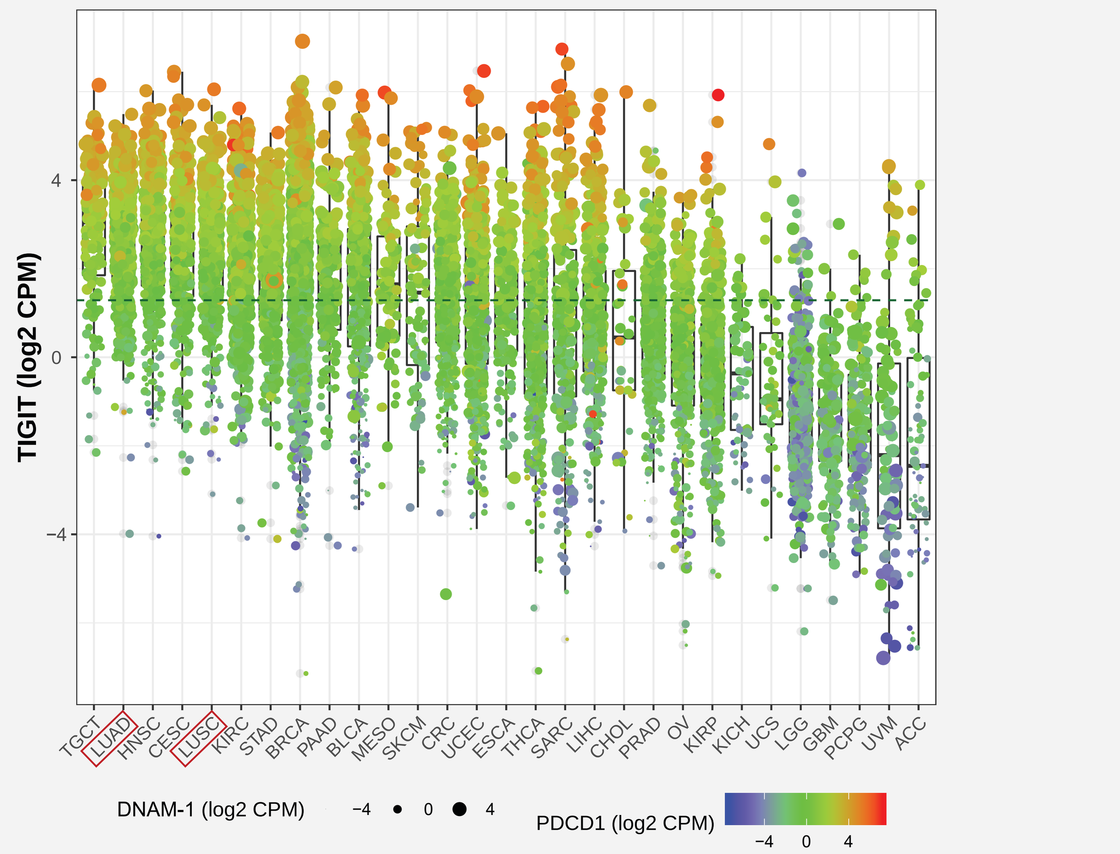
Figure 2. CD155 Protein is Found Throughout the Tumor Microenvironment[a]


Tumor
vessels
Stroma
Tumor
Stroma
TLS
Tumor

[a] Yellow arrows indicate positive CD155 staining on IHC of human NSCLC tumors. IHC, immunohistochemistry; NSCLC, non-small cell lung cancer; TLS, tertiary lymphoid structure.

- Tumors from patients with NSCLC have high expression of TIGIT, DNAM-1, and PD-1[4], suggesting that the TIGIT and PD-1 pathways may be particularly important for the growth and persistence of this tumor type (**Figure 3**)

Figure 3. TIGIT, DNAM-1, and PD-1 are Coexpressed on Human Tumors[a]

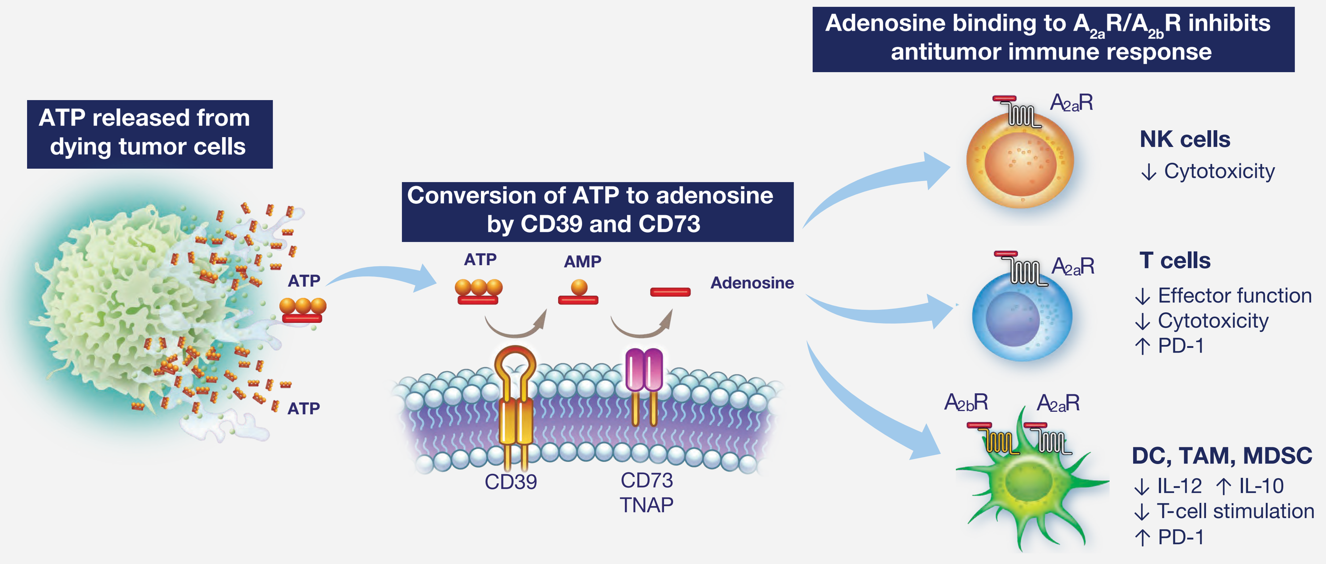

TIGIT (log2 CPM)
4
0
−4
TGCT LUAD HNSC CESC LUSC KIRC STAD BRCA PAAD BLCA MESO SKCM CRC UCEC ESCA THCA SARC LIHC CHOL PRAD OV KIRP KICH UCS LGG GBM PCPG UVM ACC
DNAM-1 (log2 CPM) −4 0 4
PDCD1 (log2 CPM) −4 0 4

[a] RNAseq data from The Cancer Genome Atlas. CPM, counts per million; DNAM-1, DNAX accessory molecule-1; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; TIGIT; T cell immunoreceptor with Ig and ITIM domain.

THE ADENOSINE AXIS IN CANCER

- Dying tumor cells release high levels of adenosine triphosphate (ATP) into the TME where CD39 and CD73 convert it to adenosine[5,6] (**Figure 4**)
- By binding adenosine receptors 2a and 2b ($A_{2a}R$ and $A_{2b}R$) expressed on immune cells, adenosine promotes immunosuppression by inhibiting critical components of the antitumor immune response and ultimately enables tumor cells to evade destruction[6]

Figure 4. Critical Role of Adenosine Pathway in Immunosuppressive Tumor Microenvironment


Adenosine binding to A2aR/A2bR inhibits antitumor immune response
ATP released from dying tumor cells
Conversion of ATP to adenosine by CD39 and CD73
ATP
AMP
Adenosine
CD39
CD73
TNAP
A2aR
NK cells
↓ Cytotoxicity
T cells
↓ Effector function
↓ Cytotoxicity
↑ PD-1
A2bR
DC, TAM, MDSC
↓ IL-12 ↑ IL-10
↓ T-cell stimulation
↑ PD-1

AMP, adenosine monophosphate; ATP, adenosine triphosphate; $A_{2a}R/A_{2b}R$, adenosine receptors 2a/2b; DC, dendritic cell; IL, interleukin; MDSC, myeloid-derived suppressor cells; NK, natural killer; TAM, tumor-associated macrophage; TNAP, tissue nonspecific alkaline phosphatase.

- Etrumadenant (AB928) is an orally bioavailable, small-molecule, selective dual antagonist of $A_{2a}R$ and $A_{2b}R$ that was specifically designed to block the immunosuppressive effects associated with high adenosine concentration within the TME; it is the only adenosine receptor antagonist in active clinical trials that potently blocks $A_{2b}R$

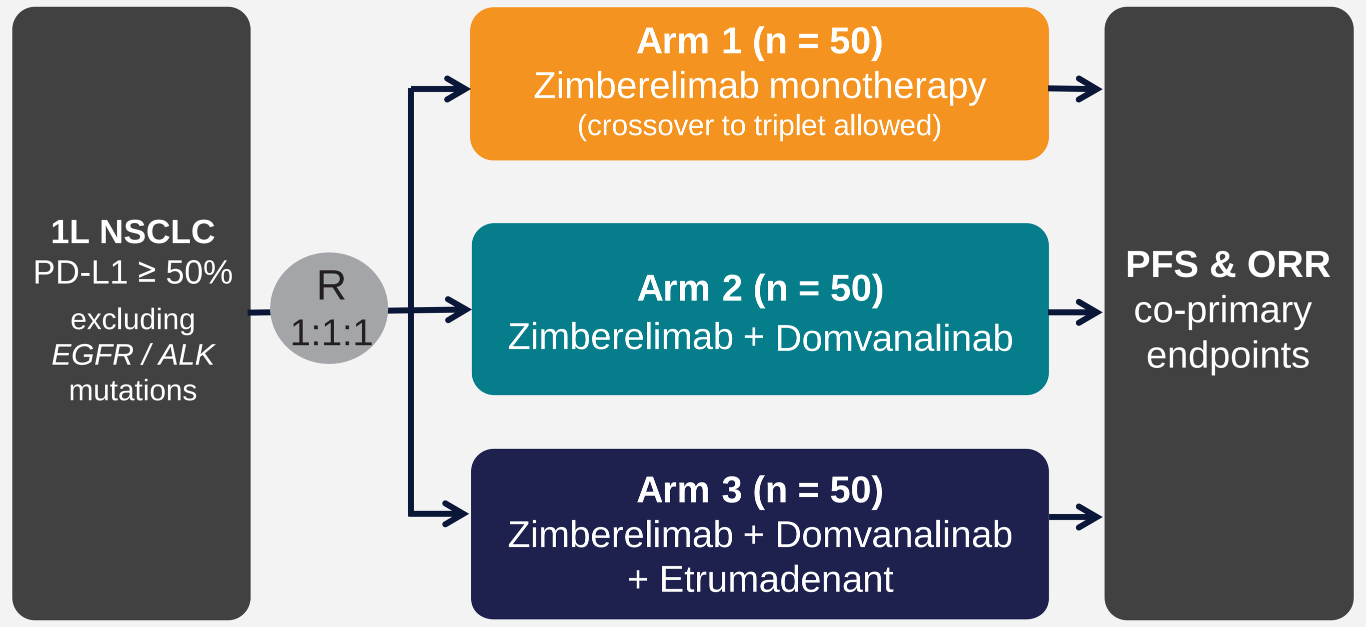
RATIONALE FOR TIGIT COMBINATIONS IN NSCLC

- For locally advanced or metastatic NSCLC, first-line treatment has historically included platinum-containing chemotherapy.[8] Median overall survival and 5-year survival rates associated with these regimens are low.[9]
- Immunotherapy agents targeting the PD-1 axis have improved outcomes for patients with NSCLC[10]; however, many patients neither initially respond to checkpoint inhibitors nor have durable responses[11], leaving an unmet need for new therapeutic approaches
- Combination therapy that includes inhibitors of the adenosine, TIGIT, and/or PD-1 pathways may hold promise for increasing efficacy without introducing significant new toxicity
 - In preclinical studies, blocking TIGIT in combination with PD-1 treatment yields greater antitumor activity and survival relative to either agent alone[11]
 - In patients with NSCLC, the adenosine pathway is a potential mechanism of resistance to anti–PD-1 therapy[12,13] and high tumor expression of CD73 is associated with poor prognosis[14], which may indicate a therapeutic advantage to combination $A_{2a}R/A_{2b}R$ and PD-1 blockade

ARC-7 Study Overview

- ARC-7 (NCT04262856) is a phase 2, multicenter, randomized, open-label, proof-of-concept study to evaluate the safety and efficacy of zimberelimab monotherapy and zimberelimab + domvanalimab ± etrumadenant in patients with PD-L1-high expressing NSCLC (**Figure 5**)

Figure 5. ARC-7 Study Design


1L NSCLC
PD-L1 ≥ 50%
excluding
EGFR / ALK
mutations
R
1:1:1
Arm 1 (n = 50)
Zimberelimab monotherapy
(crossover to triplet allowed)
Arm 2 (n = 50)
Zimberelimab + Domvanalinab
Arm 3 (n = 50)
Zimberelimab + Domvanalinab
+ Etrumadenant
PFS & ORR
co-primary
endpoints

1L, first-line; *ALK*, anaplastic lymphoma kinase; *EGFR*, epidermal growth factor receptor; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD-L1, programmed death-ligand 1; PFS, progression free survival; R, randomization.

- Key inclusion and exclusion criteria are shown in **Table 1**

Table 1. Key Eligibility Criteria for ARC-7

Key inclusion criteria	• Histologically-confirmed, treatment-naive, metastatic NSCLC • High PD-L1 expression (TPS ≥ 50%) • No *EGFR* or *ALK* genomic tumor aberrations • ≥ 1 measurable lesion per RECIST v1.1 • ECOG PS of 0 or 1
Key exclusion criteria	• Concurrent requirement for immunosuppressive medication or supraphysiologic doses of corticosteroids • Positive for hepatitis B, hepatitis C, or HIV antibody at screening

ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; *EGFR*, epithelial growth factor receptor; HIV, human immunodeficiency virus; NSCLC, non-small cell lung cancer; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TPS, tumor proportion score.

- Eligible patients (~150) will be stratified by ECOG PS (0 vs 1) and sex
- Patients randomized to Arm 1 (zimberelimab) will have the option to crossover to Arm 3 (zimberelimab + domvanalimab + etrumadenant) at the time of confirmed progressive disease (cPD); those who crossover will remain on treatment until developing cPD in Arm 3
- Primary endpoints are objective response rate and progression-free survival (RECIST v1.1); secondary endpoints include duration of response, disease control rate, overall survival, adverse events, PK, and immunogenicity
- Tumor biopsy will be performed during screening if an archival tumor sample obtained ≤ 24 months prior to screening is unavailable; an optional on-study biopsy will be performed at Day 29 if feasible
- Tumor assessments will be performed until disease progression, study withdrawal, or initiation of another anticancer treatment
- Safety and survival follow-up will continue until death, withdrawal of consent, or the end of the study, whichever occurs first
- ARC-7 is actively recruiting patients in the US, Australia, and Asia

CONCLUSIONS

- Blockade of the PD-1/PD-L1 immune checkpoint pathway has previously demonstrated clinical activity in patients with NSCLC; however, targeting additional mechanisms of immunosuppression, such as the TIGIT pathway or the adenosine axis, may be required to further improve clinical outcomes
- ARC-7 is a clinical study for patients with PD-L1–high expressing NSCLC aimed at investigating the potential clinical benefit of combination therapies targeting the PD-1, TIGIT, and adenosine pathways
- This will be the first study to investigate the triple combination of anti–PD-1, anti-TIGIT, and adenosine receptor antagonism including in patients who have progressed on PD-1 monotherapy for whom there is a high unmet need

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