ARC-10: A Phase 3 Study to Evaluate Domvanalimab + Zimberelimab Versus Pembrolizumab in Front-Line, PD-L1-High, Locally Advanced or Metastatic Non–Small Cell Lung Cancer

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BACKGROUND
- Positive programmed death ligand 1 (PD-L1) expression is observed in more than 30% of non–small cell lung cancers (NSCLC) and is associated with increased tumor proliferation, as well as shorter patient survival in NSCLC.1
- Despite recent advances in NSCLC management, survival rates for patients with metastatic NSCLC are low (5-year survival rate for patients with metastatic NSCLC and tumor proportion score [TPS] ≥50% is <21.9%) and there remains an urgent need for improved treatment options.2,3
- Anti-PD-L1 drugs, such as pembrolizumab, are the currently approved first-line treatment for patients with metastatic NSCLC harboring a PD-L1 TPS of ≥50%.4
- Treatment with PD-L1 inhibitors is associated with improved objective response rate (ORR), progression-free survival (PFS), and overall survival in patients with metastatic NSCLC.5,6
- High PD-L1 expression is a known biomarker of response to anti-PD-L1 therapies in metastatic NSCLC.7
- Novel treatment regimens combining anti-PD-L1 therapy with additional immune checkpoint inhibitors may provide increased clinical benefit over PD-L1 inhibitor monotherapy.8

Investigational Therapies
- Domvanalimab (AB154) is an Fc-silent, humanized, immunoglobulin G1 (IgG1) monoclonal antibody that is designed to block the binding of the checkpoint receptor T cell immunoglobulin and ITIM domain (TIGIT) to its ligand CD155, reducing inhibition of T cells and natural killer (NK) cells and promoting antitumor activity.9 (Figure 1)
  - As domvanalimab is Fc-silent, it does not stimulate antibody-dependent cellular cytotoxicity (ADCC)-mediated destruction of TIGIT-bearing immune cells
  - Zimberelimab (AB122) is a fully human, IgG4 monoclonal antibody that binds PD-1 on T cells and NK cells, preventing PD-L1-mediated immunosuppressive effects and resulting in enhanced tumor cell death.10
  - The ARC-7 study suggested that the combination of domvanalimab and zimberelimab may provide a clinically meaningful benefit with a manageable safety profile in patients with NSCLC, compared to zimberelimab (anti-PD-1) monotherapy.11

Figure 1. Checkpoint Inhibition and the TIGIT Pathway

IMMUNOSUPPRESSION

IMMUNE CELL ACTIVATION & TUMOR CELL KILLING

PD-L1

Tumor Cell

NK Cell

Tumor Cell

T or NK Cell

Zimberelimab

Tigilaxab

Zimberelimab + domvanalimab

T or NK Cell

Tumor Cell

T or NK Cell

Figure 2. ARC-10 Study Design

Patients with locally advanced or metastatic NSCLC

PD-L1 250%

Max 35 cycle treatment duration

Pembrolizumab 200 mg Q3W (n = 300)

Domvanalimab 1200 mg + Zimberelimab 360 mg Q3W (n = 300)

Planned N = 600

R 1:1

Stratification Factors

EGFR PD-L1 0 vs 1

Geography: Asia vs non-Asia

Histology: Squamous vs nonsquamous

METHODS
Patient Population
- Eligible patients are adults with histologically confirmed, treatment-naive, locally advanced or metastatic (stage IIIb or IV), squamous or nonsquamous NSCLC.
- Key inclusion and exclusion criteria are shown in Table 1

Table 1. Key Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
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<tbody>
<tr>
<td>Histologically confirmed, locally advanced or metastatic NSCLC</td>
<td>Genomic tumor aberrations for which targeted therapies are approved and available (e.g., EGFR, ALK, ROS, BRAF, NTRK)</td>
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<td>≥1 measurable lesion per RECIST v1.1</td>
<td>Prior treatment with any anti-PD-L11 therapy or any other therapeutic antibody targeting an immune checkpoint</td>
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<td>Progression-free survival (PFS), and overall survival in patients with metastatic NSCLC.5,6</td>
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<tr>
<td>High PD-L1 (≥50%) expression, confirmed by central laboratory</td>
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<td>ECOG performance status of 0 or 1</td>
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<td>Patients who received prior treatment for early stage disease</td>
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Outcomes and End Points
- Patients will undergo tumor assessments every 9 weeks (±7 days) from randomization until disease progression or loss of clinical benefit, study withdrawal, initiation of another anticancer therapy, or death.
- All measurable and evaluable lesions will be documented at screening and reassessed at each postbaseline visit.
- Key study end points are listed in Table 2

Table 2. Key Study End Points

<table>
<thead>
<tr>
<th>Primary End Point</th>
<th>Secondary End Points</th>
<th>Safety End Points</th>
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<tbody>
<tr>
<td>Overall survival</td>
<td>Progression-free survival, assessed via BICR</td>
<td>Incidence and severity of treatment-emergent adverse events</td>
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<tr>
<td>Statistical Considerations</td>
<td>Confirmed objective response rate, assessed via BICR</td>
<td>Changes in clinical laboratory parameters and vital signs</td>
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<td>- Efficacy analyses will be performed in the intent-to-treat population, defined as all randomized participants, regardless of whether or not they received study treatment.</td>
<td>Health-related quality of life, assessed by measuring the time to first symptom deterioration in the NSCLC-Symptom Assessment Questionnaire total score</td>
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<td>- Safety analyses will be performed in the safety population, defined as all randomized participants who received ≥1 dose of study treatment</td>
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Status
- The study is currently open for enrollment in Asia, North and South America, Africa, and Europe

REFERENCES

ACKNOWLEDGMENTS
This study is sponsored by Arcus Biosciences (Hayward, CA, USA) in collaboration with Gilead Sciences, Inc (Foster City, CA, USA). Medical writing assistance was provided by Medstrava (San Diego, CA, USA) and funded by Arcus Biosciences and Gilead Sciences.

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Presented at the Annual Meeting of the American Society of Clinical Oncology (ASCO); June 2-6, 2023; Chicago, IL, USA