TPS 9148

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-[L]1) 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-[L]1 drugs, such as pembrolizumab, are the currently approved first-line treatment for patients with metastatic NSCLC harboring a PD-[L]1 TPS of ≥50%[4]
- Treatment with PD-[L]1 inhibitors is associated with improved objective response rate (ORR), progression-free survival (PFS), and overall survival in patients with metastatic NSCLC[5-7]
  - High PD-[L]1 expression is a known biomarker of response to anti–PD-[L]1 therapies in metastatic NSCLC
  - Novel treatment regimens combining anti-PD-[L]1 therapy with additional immune checkpoint inhibitors may provide increased clinical benefit over PD-[L]1 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[9,10] (**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-[L]1-mediated immunosuppressive effects and resulting in enhanced tumor cell death[11,12]
- 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[13]

Figure 1. Checkpoint Inhibition and the TIGIT Pathway

PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; NK, natural killer; TIGIT, T cell immunoglobulin and ITIM domain.

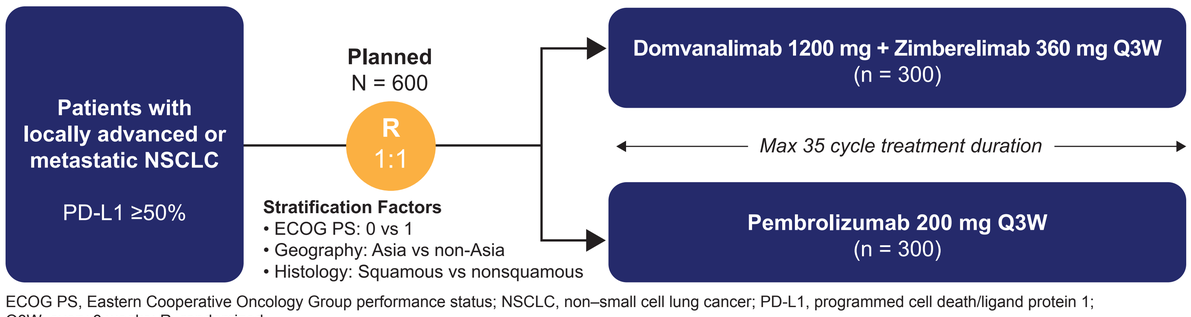
Study Objective

- ARC-10 will investigate the efficacy and safety of combination therapy with domvanalimab (anti-TIGIT) and zimberelimab (anti-PD-1) compared with pembrolizumab (anti-PD-1) monotherapy in front-line patients with PD-L1 high metastatic NSCLC

Study Design

- ARC-10 (NCT04736173) is a global, multicenter, randomized, open-label, phase 3 study (**Figure 2**)
- Approximately 600 patients will be randomly assigned 1:1 to receive either:
  - Combination therapy with domvanalimab 1200 mg and zimberelimab 360 mg, administered intravenously every 3 weeks
  - Pembrolizumab monotherapy 200 mg, administered intravenously every 3 weeks
- Patients will receive treatment on day 1 of each 21-day cycle until disease progression, intolerance, or a maximum of 35 cycles
- Randomization will be stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1), geographical region (Asia vs non-Asia), and histology (squamous vs nonsquamous)

Figure 2. ARC-10 Study Design



ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer; PD-L1, programmed cell death/ligand protein 1; Q3W, every 3 weeks; R, randomized.

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

Key Inclusion Criteria	Key Exclusion Criteria
• Histologically confirmed, locally advanced or metastatic NSCLC • ≥1 measurable lesion(s) per RECIST v1.1 • High PD-L1 (SP263) expression (TC ≥50%), confirmed by central laboratory • ECOG performance status of 0-1 • Patients must be treatment-naive with respect to locally advanced or metastatic disease; patients who received prior treatment for early stage disease must have completed treatment ≥6 months prior to first study treatment	• Genomic tumor aberrations for which targeted therapies are approved and available (eg, *EGFR, ALK, ROS, BRAF, NTRK*) • Prior treatment with any anti-PD-[L]1 therapy or any other therapeutic antibody targeting an immune checkpoint

ECOG, Eastern Cooperative Oncology Group; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cell.

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

Primary End Point	Secondary End Points	Safety End Points
• Overall survival	• Progression-free survival, assessed via BICR • Confirmed objective response rate, assessed via BICR • Health-related quality of life, assessed by measuring the time to first symptom deterioration in the NSCLC-Symptom Assessment Questionnaire total score	• Incidence and severity of treatment-emergent adverse events • Changes in clinical laboratory parameters and vital signs

BICR, blinded independent central review; non–small cell lung cancer.

Statistical Considerations

- 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
- Safety analyses will be performed in the safety population, defined as all randomized participants who received ≥1 dose of study treatment

Status

- The study is currently open for enrollment in Asia, North and South America, Africa, and Europe

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