STAR-121: A Phase 3, Randomized Study of Domvanalimab (DOM) and Zimberelimab (ZIM) in Combination With Chemotherapy vs Pembrolizumab (PEMBRO) and Chemotherapy in Patients With Untreated Metastatic Non-Small Cell Lung Cancer (mNSCLC) With No Actionable Gene Alterations

Poster TPS9141

STAR-121

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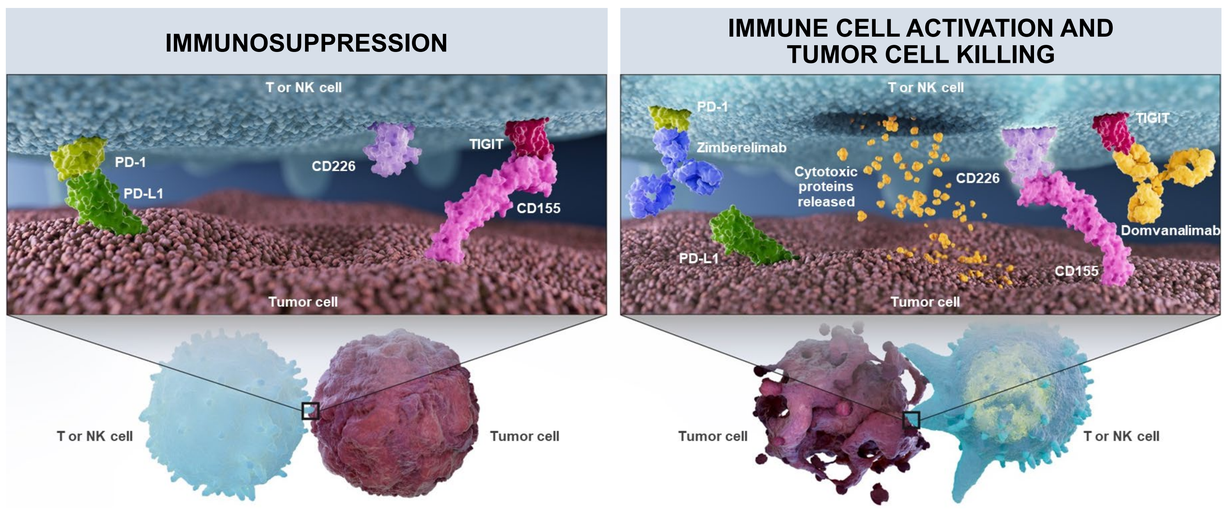
Introduction

- Lung cancer is the second most common cancer and the leading cause of cancer death in the United States[1]
- Although immune checkpoint inhibitors have improved clinical outcomes in patients with metastatic non-small cell lung cancer (mNSCLC),[2,3] only a small proportion of patients respond to single-agent treatment, emphasizing an urgent need for more effective treatments or treatment combinations[4]
- Domvanalimab (AB154) is an Fc-silent humanized immunoglobulin (Ig) G1 monoclonal antibody that blocks interaction between T cell Ig and ITIM domain (TIGIT) and its ligand CD155, thus reducing immunosuppression of T cells and natural killer cells and promoting antitumor activity[5]
  - As domvanalimab is Fc-silent, it does not stimulate antibody-dependent cellular cytotoxicity (ADCC)–mediated destruction of TIGIT-bearing leukocytes[6]
- Zimberelimab (AB122) is an anti–programmed death-1 (PD-1) humanized IgG4 monoclonal antibody that demonstrated antitumor activity in vivo and preliminary clinical activity in multiple tumor types[7]; it is approved in China to treat relapsed or refractory classical Hodgkin's lymphoma[8]
- Studies have shown that dual blockade of TIGIT and PD-1 increases antitumor activity relative to PD-1 inhibition[9]
- In the ARC-7 randomized phase 2 study in PD-L1–high, first-line mNSCLC, domvanalimab and zimberelimab combination therapy demonstrated a higher objective response rate and longer median progression-free survival than zimberelimab monotherapy and was generally well tolerated[5]

Figure 1. Checkpoint inhibition and the TIGIT pathway[10]



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

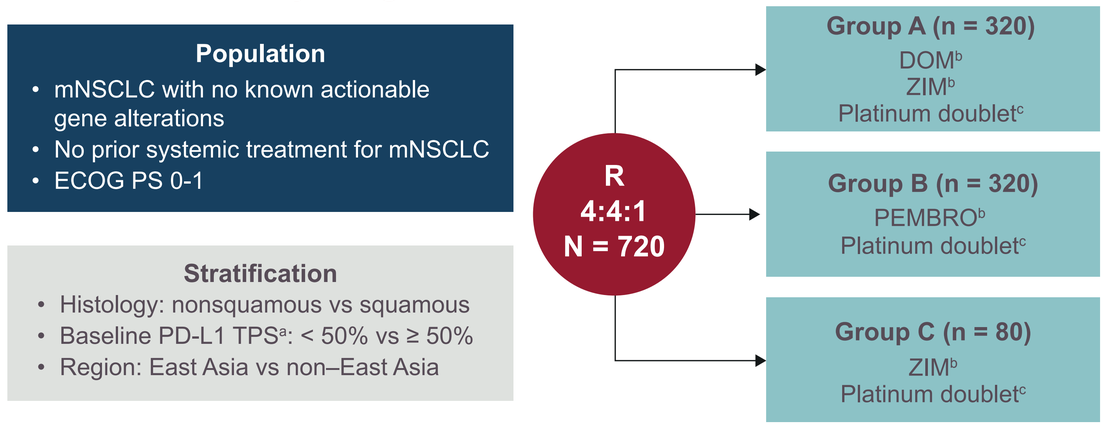
Study Objectives

- The primary objective is to compare the effect of domvanalimab and zimberelimab in combination with chemotherapy relative to pembrolizumab in combination with chemotherapy (Group A vs Group B) on progression-free survival by blinded independent central review (BICR) and overall survival
- The secondary objective is to compare the effect of domvanalimab and zimberelimab in combination with chemotherapy relative to pembrolizumab in combination with chemotherapy (Group A vs Group B) on objective response rate and duration of response by BICR, safety, and quality of life

Study Design

- STAR-121 is a phase 3, global, open-label randomized study evaluating the safety and efficacy of domvanalimab and zimberelimab plus chemotherapy versus pembrolizumab as first-line therapy for patients with mNSCLC with no *EGFR* or *ALK* aberrations or other known actionable gene alterations
- Approximately 720 patients will be randomized into 3 groups (A, B, or C) in a 4:4:1 ratio and stratified by baseline PD-L1 tumor proportion score (< 50% vs ≥ 50%), histology (squamous vs nonsquamous), and geographic region (East Asia vs non–East Asia)

Figure 2. STAR-121 study design



DOM, domvanalimab; ECOG PS, Eastern Cooperative Oncology Group performance status; mNSCLC, metastatic non-small cell lung cancer; PD-L1, programmed cell death ligand 1; PEMBRO, pembrolizumab; R, randomized; TPS, tumor proportion score; ZIM, zimberelimab.

[a]PD-L1 TPS will be tested by the sponsor's central laboratory at screening, for stratification at randomization. Testing will be performed using Ventana PD-L1 (SP263) assay. [b]Domvanalimab 1200 mg, zimberelimab 360 mg, and pembrolizumab 200 mg are given every 3 weeks (Q3W) for a maximum of 35 doses. [c]Choice of chemotherapy is dependent on histology and will be administered for 4 cycles. Patients with nonsquamous histology will receive cisplatin 75 mg/m^2 or carboplatin area under the curve (AUC) 5 with pemetrexed 500 mg/m^2 Q3W. Those with squamous histology will receive carboplatin AUC 6 Q3W with paclitaxel 200 mg/m^2 Q3W or Nab-paclitaxel 100 mg/m^2 weekly. After the completion of the first 4 cycles, maintenance pemetrexed of 500 mg/m^2 Q3W will be continued only in patients with nonsquamous histology until progressive disease or intolerable toxicities.

The first external data monitoring committee review is planned after a safety run-in period, defined as approximately 20 participants randomized in Group A completing at least 1 full study cycle.

Key Eligibility Criteria

Inclusion

- Patients aged ≥ 18 years with histologically confirmed stage IV NSCLC
- Measurable disease per RECIST v1.1 criteria
- Documented negative test results for *EGFR* and *ALK* gene alterations
- Adequate tumor tissue from locations not radiated prior to biopsy to evaluate PD-L1 status prior to randomization
- No prior systemic treatment for metastatic NSCLC[a]
- ECOG PS 0 or 1
- Adequate organ function

Exclusion

- Mixed SCLC and NSCLC histology; active second malignancy within 3 years prior to enrollment
- Prior treatment with any anti–PD-1, anti–PD-L1, or any other antibody targeting an immune checkpoint
- Known genomic alterations in *ROS1*, *NTRK*, *BRAF*, *RET*, or other actionable driver oncogenes with approved therapies
- Active autoimmune disease that required systemic treatment in past 2 years
- Known active CNS metastases and/or carcinomatous meningitis (patients with previously treated brain metastases may participate provided they have stable CNS disease for at least 4 weeks prior to enrollment)
- History of noninfectious pneumonitis/ILD that required steroid treatment
- RT within 2 weeks prior to first dose of study or RT to the lung with > 30 Gy within 6 months of the first dose of the study

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; PD-1, programmed death-1; PD-L1, programmed death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiation therapy; SCLC, small cell lung cancer.

[a]Patients who received adjuvant or neoadjuvant chemotherapy are eligible if the therapy was completed at least 12 months prior to the start of study treatment.

Study Endpoints

- The primary analysis of primary endpoints will be conducted using log-rank test stratified by randomization stratification factors between Group A and B
- A Cox regression model stratified by randomization stratification factors will be used to estimate hazard ratio and its 2-sided 95% confidence interval

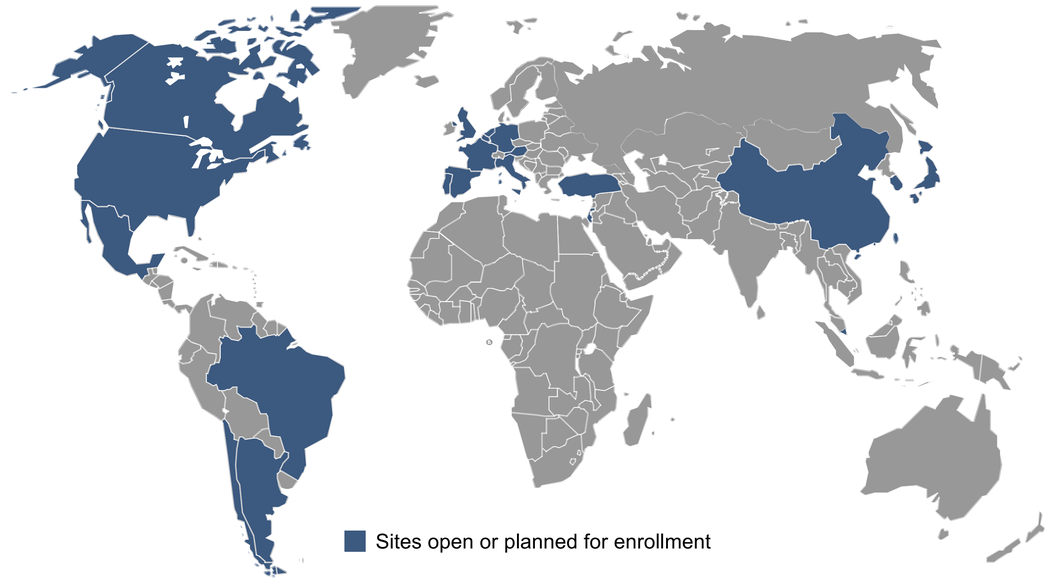
Table 1. Primary, secondary, and exploratory endpoints

Primary endpoints	Secondary endpoints	Exploratory endpoints
Progression-free survival by BICR	Objective response rate by BICR	Summary of PK concentrations
Overall survival	Duration of response by BICR	Incidence of ADA
	Safety	Correlation of response with tumor and blood biomarkers
	Quality of life	Patient-reported outcomes

ADA, antidrug antibodies; BICR, blinded independent central review; PK, pharmacokinetic.

Study Sites/Enrollment

Figure 3. STAR-121 study sites



As of April 10, 2023, the STAR-121 phase 3 study (NCT05502237) is currently enrolling participants globally in North America, South America, Europe, and Asia

For more information, please visit
https://clinicaltrials.gov/ct2/show/NCT05502237

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