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

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**Introduction**

- Lung cancer is the second most common cancer and the leading cause of cancer death in the United States.
- Although immune checkpoint inhibitors have improved clinical outcomes in patients with metastatic non-small cell lung cancer (mNSCLC), only a small proportion of patients respond to single-agent treatment, an urgent need for more effective treatments or treatment combinations.
- Domvanalimab (AB156) 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.
- As domvanalimab is Fc-silent, it does not stimulate antibody-dependent cellular cytotoxicity (ADCC)-mediated destruction of tumor cells.
- 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.
- Studies have shown that dual blockade of TIGIT and PD-1 increases antitumor activity relative to PD-1 inhibition.
- 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.

**Figure 1. Checkpoint inhibition and the TIGIT pathway.**

**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 alterations 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 non-squamous), and geographic region (East Asia vs non-East Asia).

**Table 1. Primary, secondary, and exploratory endpoints**

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**Key Eligibility Criteria**

**Inclusion**

- Patients aged ≥ 18 years with histologically confirmed stage IV NSCLC.
- Measurable disease per RECIST v1.1 criteria.
- No prior systemic treatment for metastatic NSCLC.
- ECOG PS 0 or 1.
- Known genomic alterations in active autoimmune disease that required systemic treatment.

**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, MET, 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/LD that required systemic 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.

**Study Sites/Enrollment**

- 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.

**Study Endpoints**

- Safety, and quality of life

**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](https://clinicaltrials.gov/ct2/show/NCT05502237)

**References**

9. Li JY. Presented at ASCO; Sep 9-14, 2021; Hong Kong, China.

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