EDGE-Lung: A Phase 2 Open-Label Platform Study to Evaluate Immunotherapy-Based Combinations in Patients with Metastatic NSCLC

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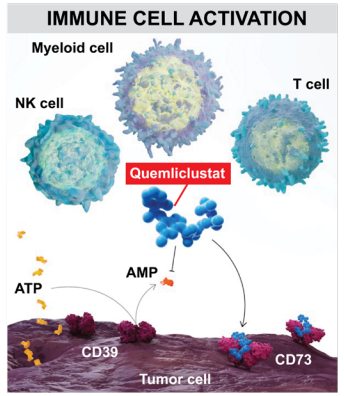
BACKGROUND

- Immunotherapy agents targeting the programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) axis have improved outcomes for patients with locally advanced or metastatic non–small cell lung cancer (NSCLC)
- Despite these advances in NSCLC management, many patients eventually progress, and long-term survival rates remain low;[1-3] thus, there is an urgent need for improved treatment options
- Novel treatment regimens combining anti–PD-[L]1 therapy with additional immune checkpoint inhibitors may provide increased clinical benefit over anti–PD-[L]1 monotherapy in patients with NSCLC[1,4,5]
  - Interim results from 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[6]
  - Preliminary results from ARC-8 demonstrated encouraging activity with quemliclustat in combination with standard of care chemotherapy and zimberelimab in patients with metastatic pancreatic adenocarcinoma[7]

Investigational Therapies

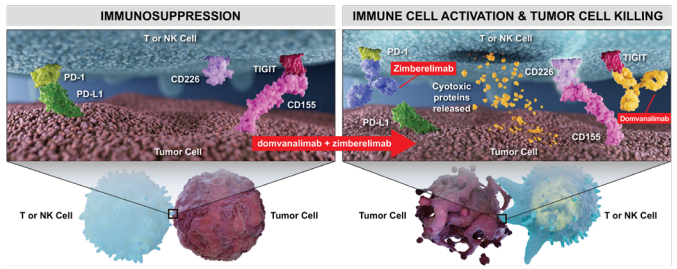
- Quemliclustat (AB680) is a potent, selective, small molecule inhibitor of CD73; by blocking production of adenosine through CD73 inhibition, quemliclustat may help reverse tumor-directed immunosuppression, activating host antitumor immunity (**Figure 1**)[8]
- Domvanalimab (AB154) is an Fc-silent, humanized, immunoglobulin G1 monoclonal antibody that blocks 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 (**Figure 2**)[9-12]
  - Blocking the CD155-TIGIT interaction allows the immunostimulatory binding of CD155 to CD226
  - As domvanalimab is Fc-silent, it does not stimulate antibody-dependent cellular cytotoxicity-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 immune-mediated tumor cell death (**Figure 2**)[13,14]

Figure 1. Targeting the Adenosine Pathway



AMP, adenosine monophosphate; ATP, adenosine triphosphate; NK, natural killer.

Figure 2. 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.

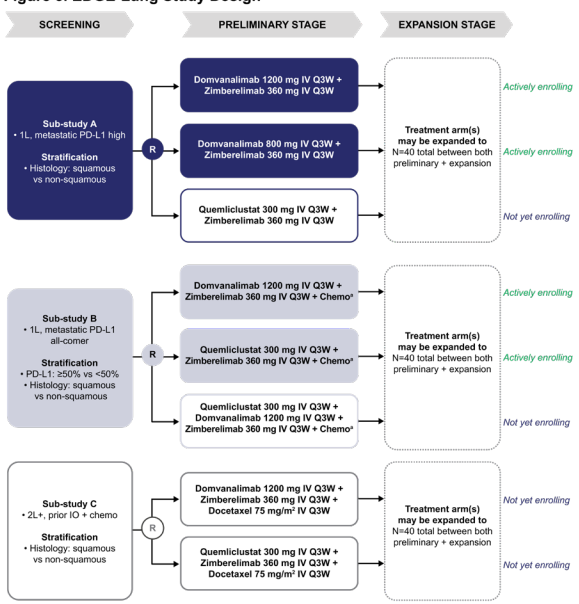
Study Objective

- The EDGE-Lung study will investigate the safety and clinical activity of novel quemliclustat- and domvanalimab-based treatment combinations in patients with metastatic NSCLC

Study Design

- EDGE-Lung (NCT05676931) is a global, multicenter, randomized, open-label, 2-stage platform, phase 2 trial (**Figure 3**)
- Different NSCLC patient populations will be treated with novel regimens via separate sub-studies. A minimum of approximately 190 patients, and up to approximately 320 patients, will be enrolled
  - Each sub-study will enroll 20 to 30 patients per treatment arm during the preliminary stage; cohorts that meet prespecified criteria may enroll further in the expansion phase, up to a total of 40 patients per treatment arm
  - Within each sub-study, patients will be randomly assigned equally between each arm open at the time of enrollment
  - If a patient is eligible for more than 1 enrolling sub-study, the investigator will determine which sub-study the patient will be enrolled into
  - Treatment arms with quemliclustat will include a dose-escalation safety run-in following a standard 3 + 3 design
- This platform study is designed with flexibility to explore additional study treatment regimens within a sub-study, stop accrual into existing treatment regimens that demonstrate minimal clinical activity or unacceptable toxicity, or explore additional NSCLC population(s) with 1 or more new sub-studies via protocol amendment

Figure 3. EDGE-Lung Study Design



1L, first line; 2L+, second or greater line; Chemo, chemotherapy; IO, immuno-oncology therapy; IV, intravenous; Q3W, every 3 weeks.
[a]Platinum doublet chemotherapy.

METHODS

Patient Population

- Eligible patients are adults with histologically confirmed metastatic squamous or non-squamous NSCLC
  - Eligible treatment-naive patients with high PD-L1 expression may be enrolled in either sub-study A or sub-study B at the discretion of the investigator
- Key inclusion and exclusion criteria are shown in **Table 1**

Table 1. Key Inclusion and Exclusion Criteria

Key Inclusion Criteria	Key Exclusion Criteria
General inclusion criteria • Age ≥18 years • Histologically-confirmed stage IV squamous or non-squamous NSCLC per AJCC version 8 • ECOG performance status of 0 or 1 • ≥1 measurable target lesion per RECIST v1.1	**General exclusion criteria** • Presence of *ALK* fusion oncogene or actionable *EGFR* mutation[a] • Known presence of any other genomic aberration or driver mutation (e.g. *ROS, BRAF, NTRK*) for which targeted therapy is locally available
Sub-study A–specific inclusion criteria • Treatment-naive for metastatic disease • Previously documented high PD-L1 expression (TPS ≥ 50% by PharmDx 22C3 or 28-8 PharmDx [Dako], or TC ≥50% by SP263 [Ventana])	**Sub-study A–specific exclusion criteria** • Prior treatment in the metastatic setting with any anti–PD-[L]1 antibody or any other therapeutic antibody targeting an immune checkpoint
Sub-study B–specific inclusion criteria • Treatment-naive for metastatic disease • Previously documented PD-L1 expression (by PharmDx 22C3 or 28-8 PharmDx [Dako], or by SP263 [Ventana]) • CrCl ≥45 mL/min (60 mL/min for patients receiving cisplatin) by Cockroft-Gault equation	**Sub-study B–specific exclusion criteria** • Prior treatment in the metastatic setting with any anti–PD-[L]1 antibody or other therapeutic antibody targeting an immune checkpoint
Sub-study C-specific inclusion criteria • PD or recurrence after platinum-based chemotherapy and anti–PD-[L]1 therapy, given concurrently or sequentially • No PD for at least 12 weeks after initiation of prior anti–PD-[L]1 therapy • Documented radiographic PD on or after the most recent regimen for metastatic NSCLC • No more than 2 prior lines of systemic therapy for metastatic disease	**Sub-study C-specific exclusion criteria** • Prior lung cancer treatment with docetaxel, anti-TIGIT, or anti-adenosine therapies

AJCC, American Joint Committee on Cancer staging; CrCl, creatinine clearance; ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small cell lung cancer; PD, progressive disease; PD-L1, programmed cell death ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; TC, tumor cell; TIGIT, T cell immunoglobulin and ITIM domain; TPS, tumor proportion score.
[a]Testing is mandatory for patients with non-squamous histology and optional for those with squamous histology.

Outcomes and Endpoints

- Treatment will be continued until unacceptable toxicity, loss to follow-up, disease progression, study withdrawal, death, or study termination
- Key study endpoints are listed in **Table 2**

Table 2. Key Study Endpoints

Primary Endpoints	Secondary Endpoints	Exploratory Endpoints
• Objective response rate[a] • Safety	• Disease control rate[a] • Progression-free survival[a] • Duration of response[a] • Overall survival • Pharmacokinetics • Immunogenicity	• Biomarkers • Pharmacodynamics

RECIST, Response Evaluation Criteria in Solid Tumors.
[a]Assessed by the investigator according to RECIST v1.1.

Statistical Considerations

- Efficacy and safety will be analyzed for all enrolled patients who received any amount of study treatment
- For quemliclustat-containing arms that include a safety run-in, patients will be evaluable for the safety run-in phase if they have received at least 1 dose of treatment and completed safety follow-up assessments for at least 1 full 21-day treatment cycle

Status

- The study is currently planned to enroll patients in Asia-Pacific, Europe, and North America

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