Current Trial Report

STAR-121: A Phase III Randomized Study of Domvanalimab and Zimberelimab in Combination With Chemotherapy Versus Pembrolizumab With Chemotherapy in Untreated Metastatic Non–Small Cell Lung Cancer With No Actionable Gene Alterations

Delvys Rodriguez-Abreu,[1] Joaquim Bosch-Barrera,[2] Jhanelle E. Gray,[3] Myung-Ju Ahn,[4] Melissa Johnson,[5] Xinwei Yu,[6] Saad Mohammad,[6] Xueying Chen,[6] Trever Todd,[7] Jongseok Kim,[6] Martin Reck[8]

Abstract

Introduction: Dual inhibition with a T-cell immunoreceptor with immunoglobulin and ITIM domains plus programmed death (ligand)-1 (PD[L]-1) inhibitors, with or without chemotherapy, is an emerging therapeutic strategy in metastatic non–small cell lung cancer (mNSCLC). The STAR-121 (NCT05502237) phase III, global, randomized, open-label study will investigate first-line domvanalimab (anti-TIGIT) and zimberelimab (anti–PD-1) plus chemotherapy versus pembrolizumab plus chemotherapy in mNSCLC with no actionable gene alterations. **Participants and Methods:** Approximately 720 participants (≥18 years old) with untreated mNSCLC and no *EGFR* and *ALK* mutations will be randomized into 3 groups (A, B, or C) in a 4:4:1 ratio and stratified by baseline PD-L1 expression (tumor cells <50% vs. ≥50%), histology (squamous vs. nonsquamous), and geographic region (East Asia vs. non-East Asia). Group A will receive domvanalimab 1200 mg plus zimberelimab 360 mg plus platinum-doublet chemotherapy (PT), group B will receive pembrolizumab 200 mg plus PT, and group C will receive zimberelimab 360 mg plus PT, every 3 weeks. Treatment will be administered until disease progression or intolerable toxicity. Dual primary endpoints are progression-free survival (by blinded independent central review [BICR]) and overall survival for group A versus B. Key secondary endpoints comprise overall response rate (by BICR), safety, and quality of life. Exploratory endpoints include efficacy and safety between groups A and C, pharmacokinetics, patient-reported outcomes, and biomarkers. **Conclusion:** Enrollment in the STAR-121 study commenced on October 12, 2022, and is currently ongoing with completion planned by September 2024. The study completion is expected by December 2027.

Clinical Lung Cancer, Vol. 000, No.xxx, 1–6 © 2023 Published by Elsevier Inc.
Keywords: Immunotherapy, TIGIT, PD-1, Clinical trial, NSCLC

Introduction

In non–oncogene-driven metastatic non–small cell lung cancer (mNSCLC), preferred frontline treatment is a programmed death (ligand)-1 (PD-[L]1) inhibitor either alone in patients with high PD-L1 expression (≥50% tumor proportion score) or in combination with platinum-doublet chemotherapy (PT), regardless of histol-

ClinicalTrials.gov number: NCT05502237

[1]Complejo Hospitalario Universitario Insular-Materno Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Gran Canaria, Spain
[2]Department of Medical Oncology, Catalan Institute of Oncology, Doctor Josep Trueta University Hospital; Precision Oncology Group (OncoGIR-Pro), Institut d'Investigació Biomèdica de Girona (IDIBGI); Department of Medical Sciences, Medical School, University of Girona, Girona, Spain
[3]Moffitt Cancer Center, Tampa, FL
[4]Department of Hemato-Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, The Republic of Korea
[5]Sarah Cannon Research Institute, Nashville, TN
[6]Gilead Sciences, Inc., Foster City, CA
[7]Arcus Biosciences, Hayward, CA
[8]Lung Clinic Grosshansdorf, Airway Research Center North, German Center for Lung Research, Grosshansdorf, Germany

Submitted: Dec 13, 2023; Accepted: Dec 17, 2023; Epub: xxx

Address for correspondence: Delvys Rodriguez-Abreu, MD, PhD, Medical Oncology Department Head, Hospital Universitario Insular de Gran Canaria, 13 35016, Las Palmas de Gran Canaria, Gran Canaria, Spain, Tel.: +34 928318867.
E-mail contact: drodabr@gobiernodecanarias.org

1525-7304/$ - see front matter © 2023 Published by Elsevier Inc.
https://doi.org/10.1016/j.cllc.2023.12.010

ogy or PD-L1 expression.[1,2] Despite improved clinical outcomes with these agents, long-term prognosis for mNSCLC remain poor. Many patients do not respond or experience disease progression after initial clinical response, emphasizing an urgent need for more effective combination treatments.[3]

The T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine inhibitory motif ITIM domains (TIGIT) is an immune checkpoint and an emerging target in cancer immunotherapy. TIGIT is expressed on T-cells and natural killer (NK) cells.[4,5] TIGIT high-affinity ligands include CD155 and CD112.[5] Activation of the TIGIT/CD155 pathway leads to reduced T-cell receptor expression, resulting in impairment of NK cells and CD8 T-cell effector functions.[5] TIGIT also competes with the costimulatory receptor CD226 for binding to CD155 ligands. This impairs the CD226-mediated costimulatory signal to the immune cells resulting in reduced antitumor immunity.[5]

TIGIT and PD-(L)1 have distinct, nonredundant roles in regulating antitumor immune response.[5] In preclinical studies, dual blockade of PD-(L)1 and TIGIT has been shown to induce $CD8^+$ T-cell responses, resulting in increased, synergistic antitumor activity relative to PD-(L)1 inhibition alone.[5] Several anti-TIGIT and anti–PD-(L)1 combination therapies are being investigated for untreated mNSCLC.[5] In a phase II randomized study with untreated PD-L1 positive mNSCLC patients, tiragolumab (anti-TIGIT) in combination with atezolizumab (anti–PD-L1) demonstrated improved clinical benefit compared with atezolizumab alone. A subsequent phase III study (NCT04294810) is ongoing to confirm the clinical benefit with this combination.[6]

Domvanalimab (AB154) is an Fc-silent humanized IgG1 anti-TIGIT monoclonal antibody that blocks interaction between TIGIT and its ligand CD155, thus reducing immunosuppression of T-cells and NK cells, promoting antitumor activity.[7-10] In preclinical studies, combination of domvanalimab with an anti–PD-1 antibody significantly increased interferon-gamma secretion relative to anti–PD-1 alone.[9] Further, domvanalimab blocked TIGIT/CD155 interaction at <1 nM potency.[9] As domvanalimab is Fc-silent, it does not stimulate antibody-dependent cytotoxicity or complement dependent cytotoxicity, thus minimizing potential depletion of TIGIT-expressing immune cells.[11] Zimberelimab is an anti–PD-1 humanized IgG4 monoclonal antibody with demonstrated clinical efficacy and manageable safety in tumor types including cervical cancer and Hodgkin lymphoma.[12,13]

The antitumor effect of the domvanalimab and zimberelimab combination through dual blockade of TIGIT and PD-1 was demonstrated in the ARC-7 phase II randomized study in previously untreated patients with stage IV PD-L1-high mNSCLC.[10] At median follow-up of 18.5 months, domvanalimab plus zimberelimab demonstrated improved efficacy versus zimberelimab monotherapy with an overall response rate of 40% versus 30% and median progression-free survival (PFS) of 9.3 months versus 5.4 months (hazard ratio [HR] = 0.67), respectively.[10]

Here, we present the design of STAR-121, a global, phase III, randomized, open-label study investigating domvanalimab and zimberelimab plus chemotherapy versus pembrolizumab plus chemotherapy as first-line treatment in mNSCLC with no actionable gene alterations.

Methods

Study Design and Endpoints

In STAR-121 (NCT05502237), approximately 720 participants with mNSCLC will be randomized in a 4:4:1 ratio to groups A (domvanalimab plus zimberelimab plus PT), B (pembrolizumab plus chemotherapy), and C (zimberelimab plus chemotherapy), respectively (Figure 1). Participants will be stratified by baseline PD-L1 expression (tumor cells [TC] <50% vs. ≥50%), histology (squamous vs. nonsquamous), and geographic region (East Asia vs. non-East Asia).

The dual primary endpoints are groups A versus B PFS (by blinded independent central review [BICR] per Response Evaluation Criteria in Solid Tumors version 1.1 [RECIST v1.1]) and overall survival (OS). Secondary endpoints are groups A versus B overall response rate (RECIST v1.1), safety, tolerability, and quality of life (QoL; per Non–Small Cell Lung Cancer Symptom Assessment Questionnaire [NSCLC-SAQ]), and duration of response (RECIST v1.1). Exploratory endpoints include safety (Group A vs. C), pharmacokinetics, patient-reported outcomes, biomarkers, and incidence of antidrug antibodies

Participants

Study participants must be ≥18 years of age with documented evidence of stage IV NSCLC and measurable disease per RECIST v1.1. Detailed inclusion and exclusion criteria are described in Table 1.

Treatments

Participants will receive domvanalimab 1200 mg plus zimberelimab 360 mg (both intravenous [I.V.]) in group A, pembrolizumab 200 mg I.V. in group B, zimberelimab 360 mg I.V. in group C, on day 1 of each 21-day cycle. In all 3 study groups, participants will also receive IV PT in each 21-day cycle. Chemotherapy will be selected by the investigator based on histology and administered during the first 4 cycles. Participants with squamous or adenosquamous mNSCLC will receive carboplatin (day 1, maximum dose 900 mg) plus paclitaxel 200 mg/m^2 (day 1) or nab-paclitaxel 100 mg/m^2 (days 1, 8, and 15). For nonsquamous histology, participants will receive carboplatin (maximum dose 750 mg) or cisplatin 75 mg/m^2, plus pemetrexed 500 mg/m^2. After the first 4 cycles, participants with nonsquamous histology may continue with maintenance pemetrexed until disease progression or intolerable toxicities.

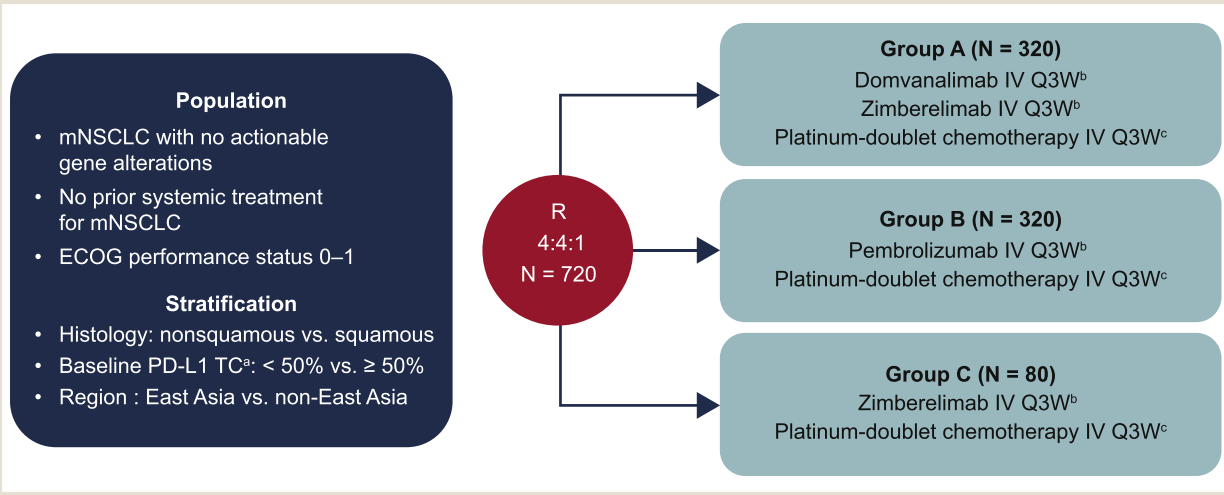
Participants will remain on treatment until disease progression (by BICR per RECIST v1.1), death, intolerable toxicity, withdrawal of consent, or for a maximum of 35 doses (approximately 2 years). Treatment beyond initial disease progression will be permitted if there is evidence of investigator-assessed clinical benefit and tolerability.

Assessments

Tumor imaging will be performed at screening, weeks 6 and 12, then every 9 weeks through week 57, followed by every 12 weeks until disease progression (by BICR) or initiation of subsequent

Please cite this article as: Delvys Rodriguez-Abreu et al, STAR-121: A Phase III Randomized Study of Domvanalimab and Zimberelimab in Combination With Chemotherapy Versus Pembrolizumab With Chemotherapy in Untreated Metastatic Non–Small Cell Lung Cancer With No Actionable Gene

Figure 1 STAR-121 Study Design. ECOG PS = Eastern Cooperative Oncology Group performance status; IV= intravenous; mNSCLC = metastatic non–small cell lung cancer; PD-L1 = programmed death ligand-1; Q3W = every 3 weeks; R = randomized; TC = tumor cells (SP263 scoring method).
[a]PD- L1 TC 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 wk (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 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 was conducted after a safety run-in period, defined as approximately 20 participants randomized in group A completing at least 1 full study cycle.



anticancer therapy. Adverse events will be monitored throughout the study and a safety follow-up visit will occur 30 days (±7 days) after last study dose. QoL assessments will be collected on day 1 of each cycle, end of treatment, and safety follow-up. Pharmacokinetic and immunogenicity samples will be taken from groups A and C on day 1 of cycles 1 to 4, 8, 12, 18, 24, 30, and end of treatment. PD-L1 TC will be tested by the sponsor's central laboratory at screening for stratification at randomization. PD-L1 expression status will be tested centrally using Ventana PD-L1 (SP263) assay (Roche Diagnostics Crop., IN).

Statistical Analysis

Efficacy analysis will be conducted in all randomized participants (intention-to-treat population [ITT]). PFS and OS will be analyzed using a log-rank test stratified by randomization stratification factors in groups A and B. A COX regression model will be used to estimate HR, and 2-sided 95% CI and Kaplan-Meier estimates of median PFS and median OS will be presented. Safety analysis will include all participants who received ≥1 dose of any study drug. Treatment-emergent period is defined as the time period from first dose of study treatment to 30 days following the last dose of study treatment or initiation of post-treatment anticancer therapy, whichever occurs earlier. Descriptive statistics will be used to summarize treatment-emergent adverse events by treatment group. Analysis of time to first symptom deterioration in NSCLC-SAQ total score will be conducted between groups A and B using a log-rank test stratified by randomization stratification factors in the QoL analysis set (all ITT patients with baseline and ≥1 postbaseline QoL assessment).

The primary analysis of PFS and OS will be conducted for group A versus B. The family-wise type I error rate for the primary and key secondary efficacy endpoint comparisons between groups A and B will be controlled using the graphic approach of Maurer and Bretz.[14] No formal hypothesis testing will be conducted to compare groups A and C.

Current Status

The study enrollment commenced October 12, 2022, and is currently ongoing globally, including in North America, South America, Europe, and Asia, with completion planned by September 2024. The estimated study completion is December 2027.

Discussion

The hypothesis of the STAR-121 study is that domvanalimab and zimberelimab in combination with chemotherapy will improve clinical outcomes compared with zimberelimab or pembrolizumab plus chemotherapy in participants with untreated mNSCLC without *EGFR* or *ALK* aberrations, regardless of PD-L1 expression.[15] Anti–PD-(L)1 agents induce enhanced T-cell responses and antitumor activity, and chemotherapy can further enhance immune responses by increasing the immunogenicity of the tumor microen-

Please cite this article as: Delvys Rodriguez-Abreu et al, STAR-121: A Phase III Randomized Study of Domvanalimab and Zimberelimab in Combination With Chemotherapy Versus Pembrolizumab With Chemotherapy in Untreated Metastatic Non–Small Cell Lung Cancer With No Actionable Gene

Table 1 Key Participant Eligibility Criteria for STAR-121

Inclusion Criteria

- Patients aged ≥18 y able to understand and give written informed consent with pathologically documented stage IV NSCLC at the time of enrollment (based on AJCC, 8th edition), documented negative test results for *EGFR* and *ALK* (for participants with nonsquamous histology), and a life expectancy ≥3 mo
- Adequate tumor tissue from locations not radiated prior to biopsy to evaluate PD-L1 status prior to randomization
- No prior systemic treatment of metastatic NSCLC[a]
- Measurable disease per RECIST v1.1 criteria by investigator assessment[b]
- Bone scan required for participants with known or suspected bone metastasis within 6 wk before randomization
- ECOG performance 0 or 1
- Adequate organ function
  - Adequate hematologic counts: Without transfusion or growth factor within 2 wk of study drug initiation; hemoglobin ≥9 g/dL, absolute neutrophil count ≥1500/mm^3, and platelets ≥100,000/μL
  - Adequate hepatic function: Total bilirubin ≤1.5 ULN, aspartate aminotransferase and alanine aminotransferase ≤2.5 ULN or ≤5 ULN if known liver metastases, and serum albumin >3 g/dL
  - Creatinine clearance: At least 45 mL/min (60 mL/min for participants receiving cisplatin) as assessed by the Cockcroft-Gault equation
- Must agree to use protocol-specified method(s) of contraception from screening visit until 6 mo after last dose of chemotherapy and 120 d after the last dose of domvanalimab, zimberelimab, and pembrolizumab (or longer according to local regulatory requirements)
- Willing and able to comply with the requirements and restrictions in this protocol

Exclusion Criteria

- Mixed SCLC and NSCLC histology
- Known gene alterations in *ROS1, NTRK, BRAF, RET*, or other actionable driver oncogenes with approved therapies
- Positive serum pregnancy test or breastfeeding or have plans to breastfeed
- Prior treatment with any anti–PD-1, anti–PD-L1, or any other antibody targeting an immune checkpoint
- Known hypersensitivity to study drug(s), metabolites, or formulation excipients
- Requirement for ongoing therapy with prohibited drugs per study protocol
- Have an active second malignancy or an active second malignancy within 3 y prior to enrollment[c]
- Active autoimmune disease that required systemic treatment in the past 2 y[d]
- Receiving chronic systemic steroids (> 10 mg/d prednisone equivalent)
- Significant third space fluid retention not amenable for required repeated drainage
- Untreated CNS metastases and/or carcinomatous meningitis[e]
- Cardiac disease: MI or unstable angina within 6 mo of enrollment, history of cardiac arrhythmias requiring medication except for well-controlled AF, or NYHA class ≥ III CHF or LVEF <40%
- Active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) or gastrointestinal perforation within 6 mo prior to enrollment
- History of non-infectious pneumonitis/ILD that required steroid treatment or current pneumonitis/ILD
- RT within 2 wk prior to first dose of study treatment or RT to the lung with >30 Gy within 6 mo of the first dose of the study; patients must have recovered to grade 1 or lower from all radiation-related toxicities, not require corticosteroids, and have not had radiation pneumonitis
- Allogenic tissue/solid organ transplant
- Active infection requiring treatment
- Live virus vaccination within 30 d of planned treatment start; seasonal flu and COVID-19 vaccines not containing live virus are permitted
- Known history of HIV-1 or -2 with uncontrolled viral load or taking medications that may interfere with the metabolism of study drugs
- Known acute hepatitis B, known chronic hepatitis B infection with active untreated disease, or known active hepatitis C infection; in patients with a history of hepatitis B virus or hepatitis C virus, patients with detectable viral loads will be excluded
- Concurrent medical or psychiatric conditions that may be likely to confound study interpretation or prevent completion of study procedures

Abbreviations: AF = atrial fibrillation; AJCC = American Joint Committee on Cancer; CHF = congestive heart failure; CNS = central nervous system; COVID-19 = coronavirus disease 2019; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; ILD = interstitial lung disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSCLC = non–small cell lung cancer; NYHA = New York Heart Association; PD-1 = programmed death-1; PD-L1 = programmed death ligand-1; RECIST = Response Evaluation Criteria in Solid Tumors version 1.1; RT = radiation therapy; SCLC = small cell lung cancer; ULN = upper limit of normal.
[a] Patients who received chemotherapy for nonmetastatic disease are eligible if the treatment was completed at least 12 mo prior to the start of study treatment.
[b] Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
[c] Patients with a history of malignancy that has been completely treated, with no evidence of active cancer for at least 3 y prior to enrollment, or with surgically cured tumors with low risk of recurrence (eg, nonmelanoma skin cancer, histologically confirmed complete excision of carcinoma in situ, or similar) are allowed to enroll.
[d] Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.
[e] Patients with previously treated brain metastases may participate provided they have stable CNS disease for at least 4 wk prior to enrollment.

vironment,[16] resulting in tumor regression and more durable therapeutic effect compared with either agent alone.[16]

TIGIT is associated with immunosuppression and T-cell exhaustion and has emerged as a promising target for coinhibition with PD-(L)1 in mNSCLC.[5] The combined use of frontline domvanalimab and zimberelimab is supported by results from the phase II ARC-7 study demonstrating improved outcomes with this combination compared with zimberelimab monotherapy PD-L1–high mNSCLC. The combination was well tolerated with a safety profile similar to that of zimberelimab mononotherapy.[10] ARC-10 is an ongoing, phase III, randomized study investigating domvanalimab plus zimberelimab versus pembrolizumab monotherapy in participants with untreated locally advanced or mNSCLC with PD-L1 TC ≥50% and no actionable gene alterations.[17] The results of the

Please cite this article as: Delvys Rodriguez-Abreu et al, STAR-121: A Phase III Randomized Study of Domvanalimab and Zimberelimab in Combination With Chemotherapy Versus Pembrolizumab With Chemotherapy in Untreated Metastatic Non–Small Cell Lung Cancer With No Actionable Gene

STAR-121 study are expected to provide much needed evidence on the use of dual immune checkpoint inhibitors, in particular dual TIGIT and PD-1 inhibition, plus chemotherapy as first-line treatment option in non–oncogene-driven mNSCLC.

Disclosure

DR-A has provided consulting services to Roche, Bristol-Myers Squibb, MSD, AstraZeneca, and Novartis; participated in a speaker's bureau for Roche, Bristol-Myers Squibb, and MSD; and received travel accommodations from Roche, Bristol-Myers Squibb, MSD, and Novartis. **JB-B** reports grants and personal fees from Roche and Pfizer; personal fees from MSD, BMS, AstraZeneca, Vifor, and Sanofi, outside the submitted work; and has received support for attending meetings and/or travel from Takeda, MSD, and Roche. **JEG** has received honoraria from Jazz Pharmaceuticals, Merck, and Oncocyte; has provided consulting services to AstraZeneca, Blueprint Medicines, Bristol-Myers Squibb, EMD Serono, Eli Lilly, Sanofi, Merck, Loxo, Jazz Pharmaceuticals, Novartis, MedImmune, Janssen, and the National Comprehensive Cancer Network; and has received travel accommodations from Novartis, Oncocyte, Jazz Pharmaceuticals, and Merck. **MJA** has provided consulting services to AstraZeneca, Eli Lilly, MSD, Takeda, Alpha Pharmaceutical, Amgen, Merck, Pfizer, and Yuhan and has received honoraria from AstraZeneca, Eli Lilly, MSD, Takeda, Merck, and Yuhan. Her institution has received research funding from Yuhan. **MJ** has provided consulting services to Genentech/Roche, AstraZeneca, Calithera Biosciences, Merck, Sanofi, Mirati Therapeutics, Ribon Therapeutics, Abbvie, GlaxoSmithKline, Gristone Bio, Janssen, Eli Lilly, Amgen, Daiichi Sankyo, Eisai, Axelia Oncology, Black Diamond Therapeutics, CytomX Therapeutics, EcoR1 Capital, Editas Medicine, Genmab, IDEAYA Biosciences, ITeos Therapeutics, Oncorus, Regeneron, Turning Point Therapeutics, Astellas Pharma, Checkpoint Therapeutics, Genocea Biosciences, Molecular Axiom, Novartis, Revolution Medicines, Takeda, VBL Therapeutics, ArriVent Biopharma, Pyramid Biosciences, and Seagen and has received travel accommodations from Abbvie, AstraZeneca, Genentech, Incyte, Merck, Pfizer, and Sanofi. Her institution has received research funding from EMD Serono, Kadmon, Janssen, Mirati Therapeutics, Genmab, Pfizer, AstraZeneca, Stem CentRX, Novartis, Array Biopharma, Regeneron, Merck, Hengrui Pharmaceutical, Lycera, BeiGene, Tarveda Therapeutics, Loxo, Abbvie, Boehringer Ingelheim, Guardant Health, Daiichi Sankyo, Sanofi, CytomX Therapeutics, Dynavax Technologies, Corvus Pharmaceuticals, Incyte, Genocea Biosciences, Gristone Bio, Amgen, Genentech/Roche, Adaptimmune, Syndax, Neovia Oncology, Acerta Pharma, Takeda, Shattuck Labs, GlaxoSmithKline, Apexigen, Atreca, OncoMed, Eli Lilly, Immunocore, University of Michigan, TCR2 Therapeutics, Arcus Biosciences, Ribon Therapeutics, BerGenBio, Calithera Biosciences, Tmunity Therapeutics, Seven and Eight Biopharmaceuticals, Curis, Silicon Therapeutics, Dracen, PMV Pharma, Artios, BioAtla, Elicio Therapeutics, Erasca Inc., Harpoon, Helsinn Healthcare, Hutchinson MediPharma, IDEAYA Biosciences, IGM Biosciences, Memorial Sloan-Kettering Cancer Center, NeoImmuneTech, Numab, Relay Therapeutics, Revolution Medicines, Tempest Therapeutics, Tizona Therapeutics Inc., Turning Point Therapeutics, Vyriad, Y-mAbs Therapeutics, Exelixis, Fate Therapeutics, Merus, Black Diamond Therapeutics, Kartos Therapeutics, Carisma Therapeutics, Rain Therapeutics, Nuvalent Inc., Palleon Pharmaceuticals, EQRx, and Immunitas. **XY** is a current employee of, and receives stock options from, Gilead Sciences, Inc. **SM** is a current employee of, and receives stock options from, Gilead Sciences, Inc. **XC** is a previous employee of Novartis and Innovent Biologics, and a current employee of Gilead Sciences, Inc. and has received stock options from Novartis and Gilead Sciences, Inc. **TT** is a current employee of, and receives stock options from, Arcus Biosciences. **JK** is a current employee of, and receives stock options from, Gilead Sciences, Inc. **MR** has provided consulting services to Eli Lilly, MSD Oncology, Merck Serono, Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim, Pfizer, Novartis, Genentech/Roche, Abbvie, Amgen, Mirati Therapeutics, Samsung Bioepis, Sanofi, Regeneron, and Daiichi Sankyo and has also participated in a speaker's bureau for Genentech/Roche, Eli Lilly, MSD Oncology, Merck Serono, AstraZeneca, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Pfizer, Novartis, Amgen, Mirati Therapeutics, and Sanofi/Aventis.

CRediT authorship contribution statement

Delvys Rodriguez-Abreu: Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. **Joaquim Bosch-Barrera:** Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. **Jhanelle E. Gray:** Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. **Myung-Ju Ahn:** Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. **Melissa Johnson:** Conceptualization, Investigation, Methodology, Resources, Writing – review & editing. **Xinwei Yu:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Saad Mohammad:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Xueying Chen:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Trever Todd:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Jongseok Kim:** Conceptualization, Investigation, Methodology, Writing – review & editing. **Martin Reck:** Conceptualization, Investigation, Methodology, Resources, Writing – review & editing.

Acknowledgments

The authors thank the patients and their caregivers for helping us realize the possibilities of this research. The authors thank the dedicated clinical study investigators and their devoted team members for participating in the STAR-121 study. This study is funded by Gilead Sciences, Inc. and Arcus Biosciences, Inc. Medical writing and editorial support was provided by Madeeha Aqil, PhD, MWC, CMPP of Parexel and funded by Gilead Sciences, Inc. and Arcus Biosciences, Inc.

References

1. Hendriks LE, Kerr KM, Menis J, et al. Non-oncogene-addicted metastatic non-small-cell lung cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol.* 2023;34(4):358–376. doi:10.1016/j.annonc.2022.12.013.

Please cite this article as: Delvys Rodriguez-Abreu et al, STAR-121: A Phase III Randomized Study of Domvanalimab and Zimberelimab in Combination With Chemotherapy Versus Pembrolizumab With Chemotherapy in Untreated Metastatic Non–Small Cell Lung Cancer With No Actionable Gene

2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for non-small cell lung cancer V.5.2023. © National Comprehensive Cancer Network, Inc. 2023. All rights reserved. Accessed November 19, 2023.
3. Heo JY, Yoo SH, Suh KJ, et al. Clinical pattern of failure after a durable response to immune checkpoint inhibitors in non-small cell lung cancer patients. *Sci Rep*. 2021;11(1):2514. doi:10.1038/s41598-021-81666-x.
4. Banta KL, Xu X, Chitre AS, et al. Mechanistic convergence of the TIGIT and PD-1 inhibitory pathways necessitates co-blockade to optimize anti-tumor CD8+ T cell responses. *Immunity*. 2022;55(3) 512-526.e9. doi:10.1016/j.immuni.2022.02.005.
5. Chu X, Tian W, Wang Z, Zhang J, Zhou R. Co-inhibition of TIGIT and PD-1/PD-L1 in cancer immunotherapy: mechanisms and clinical trials. *Mol Cancer*. 2023;22(1):1–31. doi:10.1186/s12943-023-01800-3.
6. Cho BC, Rodriguez-Abreu D, Hussein M, et al. Tiragolumab plus atezolizumab versus placebo plus atezolizumab as a first-line treatment for PD-L1-selected non-small-cell lung cancer (CITYSCAPE): primary and follow-up analyses of a randomised, double-blind, phase 2 study. *Lancet Oncol*. 2022;23(6):781–792. doi:10.1016/S1470-2045(22)00226-1.
7. Anderson AE, Lopez A, Udyavar A, et al. *Presented at: Society for Immunotherapy of Cancer*. Characterization of AB154, a humanized, non-depleting α-TIGIT antibody undergoing clinical evaluation in subjects with advanced solid tumors; 2019.
8. Anderson AE, Becker A, Yin F, et al. Abstract A124: preclinical characterization of AB154, a fully humanized anti-TIGIT antibody, for use in combination therapies. *Cancer Immunol Res*. 2019;7(suppl 2):A124. doi:10.1158/2326-6074.CRICIMTEATIAACR18-A124.
9. Anderson AE, DiRenzo D, Lee S, et al. Characterization of AB154, a humanized anti-TIGIT antibody, for use in combination studies. *Cancer Res*. 2019;79(suppl 13):1557. doi:10.1158/1538-7445.AM2019-1557.
10. Johnson ML, Fox W, Lee Y-G, et al. ARC-7: randomized phase 2 study of domvanalimab+ zimberelimab±etrumadenant versus zimberelimab in first-line, metastatic, PD-L1-high non-small cell lung cancer (NSCLC). *J Clin Oncol*. 2022;40(36):397600. Presented at: ASCO 2023 Plenary Series: Rapid Abstract Updates session.
11. Kang TH, ST Jung. Boosting therapeutic potency of antibodies by taming Fc domain functions. *Exp Mol Med*. 2019;51(11):1–9. doi:10.1038/s12276-019-0345-9.
12. Lin N, Zhang M, Bai H, et al. Efficacy and safety of GLS-010 (zimberelimab) in patients with relapsed or refractory classical Hodgkin lymphoma: a multicenter, single-arm, phase II study. *Eur J Cancer*. 2022;164:117–126. doi:10.1016/j.ejca.2021.07.021.
13. Wu X, Xia L, Wang J, et al. 180O Efficacy and safety of zimberelimab (GLS-010) monotherapy in patients with recurrent or metastatic cervical cancer: a multicenter, open-label, single-arm, phase II study. *Ann Oncol*. 2022;33:S1506. doi:10.1016/j.annonc.2022.10.216.
14. Maurer W, Bretz F. Multiple testing in group sequential trials using graphical approaches. *Stat Biopharm Res*. 2013;5(4):311–320. doi:10.1080/19466315.2013.807748.
15. Rodriguez-Abreu D, Gray JE, Ahn M-J, et al. 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. TPS9141.. *J Clin Oncol*. 2023;41(16) TPS9141. Presented at ASCO 2023.
16. Zhang L, Zhou C, Zhang S, et al. Chemotherapy reinforces anti-tumor immune response and enhances clinical efficacy of immune checkpoint inhibitors. *Front Oncol*. 2022;12:939249. doi:10.3389/fonc.2022.939249.
17. Chouaid C, Ho GF, Runglodvatana Y, et al. *Presented at: American Society of Clinical Oncology*. ARC-10: a phase 3 study to evaluate zimberelimab+ domvanalimab versus pembrolizumab in front-line, PD-L1-high, locally advanced or metastatic non–small-cell lung cancer; 2023.

Please cite this article as: Delvys Rodriguez-Abreu et al, STAR-121: A Phase III Randomized Study of Domvanalimab and Zimberelimab in Combination With Chemotherapy Versus Pembrolizumab With Chemotherapy in Untreated Metastatic Non–Small Cell Lung Cancer With No Actionable Gene