Randomized Study of Domvanalimab Combined With Zimberelimab in Front-Line, PD-L1–High, Locally Advanced or Metastatic Non-Small Cell Lung Cancer (NSCLC): Results From ARC-10 Part 1

Poster 1461

ARC-10 Part 1

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Objective

- To investigate the efficacy and safety of domvanalimab and zimberelimab combination therapy in front-line, PD-L1–high, stage IIIB–IV non-small cell lung cancer (NSCLC)

Conclusions

- Combination of domvanalimab, an Fc-silent anti-TIGIT antibody, plus zimberelimab, an anti–PD-1 antibody, was associated with greater progression-free survival, overall survival, and objective response rate compared with zimberelimab monotherapy and chemotherapy in front-line, PD-L1–high, stage IIIB–IV NSCLC
- Domvanalimab plus zimberelimab was generally well tolerated, and the addition of domvanalimab to zimberelimab did not show any new safety concerns
- Ongoing phase 3 studies are evaluating domvanalimab in combination with zimberelimab and chemotherapy in NSCLC and upper gastrointestinal adenocarcinoma, as well as domvanalimab in combination with durvalumab in localized unresectable NSCLC

Introduction

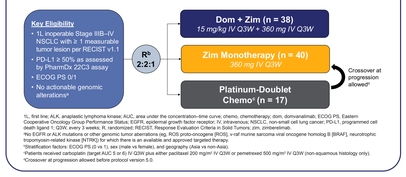
- Although targeted inhibition of the PD-1/PD-L1 pathway has demonstrated survival benefits over chemotherapy (chemo) in PD-L1–high non-small cell lung cancer (NSCLC),[1] many patients do not respond to monotherapy or develop resistance to treatment over time[2]
- Novel immunotherapy combinations are needed to improve outcomes in PD-L1–high NSCLC
- TIGIT and PD-1 have distinct non-redundant functions in controlling anti-tumor immune response, and combined inhibition may lead to enhanced immune cell activation[3]
- Dual blockade of TIGIT and PD-1 with domvanalimab (dom), an Fc-silent anti-TIGIT monoclonal antibody, and zimberelimab (zim), an anti–PD-1 monoclonal antibody, has been associated with longer progression-free survival (PFS) and greater objective response rate (ORR) vs inhibition of PD-1 alone in patients with metastatic PD-L1–high NSCLC[4]
- Dom is engineered to be Fc-silent, enabling it to activate the immune system without depleting the peripheral regulatory T cells that are crucial for avoiding immune-related toxicities
- Part 1 of the ARC-10 study evaluated the efficacy and safety of dom + zim combination therapy vs zim and also evaluated zim vs platinum-doublet chemo in front-line, PD-L1–high, stage IIIB–IV NSCLC
  - ARC-10 was initiated and conducted as a randomized, phase 3 trial; the protocol was subsequently amended to evaluate dom + zim vs pembrolizumab (Part 2)
  - Data are shown here for patients treated in Part 1 of the study

Methods

Study Design and Treatment

- ARC-10 is a global, multicenter, randomized, open-label trial (NCT04736173)
- Patients were randomized (2:2:1) to receive dom + zim combination therapy, zim monotherapy, or platinum-doublet chemo every 3 weeks **(Figure 1)**
  - At the time of protocol development, platinum-doublet chemo was selected as the control arm in countries where anti–PD-(L)1 therapy was not yet the standard of care
- Tumor assessments were performed every 9 weeks

Figure 1. ARC-10 Part 1: Randomized, Open-Label Trial in Front-Line, PD-L1–High, Stage IIIB–IV NSCLC



1L, first line; ALK, anaplastic lymphoma kinase; AUC, area under the concentration-time curve; chemo, chemotherapy; dom, domvanalimab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EGFR, epidermal growth factor receptor; IV, intravenous; NSCLC, non-small cell lung cancer; PD-L1, programmed cell death ligand 1; Q3W, every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; zim, zimberelimab.

*No EGFR or ALK mutations or other genomic tumor aberrations (eg, ROS proto-oncogene [ROS], v-raf murine sarcoma viral oncogene homolog B [BRAF], neurotrophic tropomyosin-related kinase [NTRK]) for which there is an available and approved targeted therapy.

[b]Stratification factors: ECOG PS (0 vs 1), sex (male vs female), and geography (Asia vs non-Asia).

[c]Patients received carboplatin (target AUC 5 or 6) IV Q3W plus either pemetrexed 500 mg/m² IV Q3W or pemetrexed 500 mg/m² IV Q3W (non-squamous histology only).

[d]Crossover at progression allowed before protocol version 5.0.

Assessments

- Primary endpoint
  - PFS, defined as the time from randomization to first occurrence of disease progression per RECIST v1.1 or death from any cause, whichever comes first
- Secondary endpoints
  - Overall survival (OS), defined as the time from randomization to death from any cause
  - Confirmed investigator-assessed ORR, defined as the proportion of patients with a confirmed best overall response of complete or partial response per RECIST v1.1
  - Safety
- Exploratory endpoint
  - Duration of response, defined as the time of first complete or partial response until disease progression or death, whichever comes first

Statistical Analysis

- PFS, OS, and duration of response were estimated by Kaplan-Meier methodology
- Hazard ratios (HR) were estimated by Cox proportional hazards modeling
- 95% CIs for ORR were calculated using the Clopper-Pearson exact method

Results

Patients

- Of 98 randomized patients, 95 received treatment
- Most patients were male, Asian, former or current smokers, and had stage IV lung adenocarcinoma **(Table 1)**
- Median time from randomization to data cutoff (May 17, 2024) was 24.5 months (range: 16.8–38.5 months)
- 22 patients remained on front-line treatment (dom + zim, n = 11; zim, n = 10; chemo, n = 1)

Efficacy

- PFS and OS were greater with dom + zim than with either zim or chemo **(Table 2; Figure 2)**
- OS was greater with zim than with chemo
- Median OS was not reached for dom + zim
- 12-month OS rates were 68%, 57%, and 50% for the dom + zim, zim, and chemo arms, respectively
- OS favored dom + zim over zim in patients with a PD-L1 tumor proportion score of 50%–89% (HR, 0.67 [95% CI: 0.28, 1.61]) and ≥ 90% (HR, 0.64 [95% CI: 0.21, 1.90])
- Among patients with brain metastases at baseline, the risk of death was lower for dom + zim compared with zim (HR, 0.52 [95% CI: 0.14, 1.95])
- ORR was greater for dom + zim than for either zim or chemo **(Figure 3)**
- By month 4.5, the majority of patients treated with dom + zim or zim had tumor reduction of ≥ 30% from baseline **(Figure 4)**
- Median duration of response was not reached in the dom + zim and zim arms and was 7.4 (95% CI: 4.1, not evaluable) months in the chemo arm **(Figure 5)**

Table 1. Baseline Characteristics

Characteristic	Dom + Zim (n = 38)	Zim (n = 40)	Chemo (n = 17)
Age, years			
Median (range)	62.5 (44, 83)	62.5 (41, 81)	61.0 (42, 82)
< 65 years, n (%)	20 (52.6)	25 (62.5)	10 (58.8)
Sex, n (%)			
Male	30 (78.9)	29 (72.5)	13 (76.5)
Female	8 (21.1)	11 (27.5)	4 (23.5)
Race, n (%)			
Asian	33 (86.8)	31 (77.5)	14 (82.4)
Black or African American	0	3 (7.5)	0
White	3 (7.9)	3 (7.5)	0
Multiple	1 (2.6)	2 (5.0)	0
Not reported	1 (2.6)	1 (2.5)	3 (17.6)
Smoking status, n (%)			
Never	7 (18.4)	7 (17.5)	2 (11.8)
Former	23 (60.5)	22 (55.0)	10 (58.8)
Current	8 (21.1)	11 (27.5)	5 (29.4)
ECOG PS 1, n (%)	27 (71.1)	31 (77.5)	10 (58.8)
Histology, n (%)			
Adenocarcinoma	21 (55.3)	23 (57.5)	11 (64.7)
Squamous cell carcinoma	12 (31.6)	16 (40.0)	4 (23.5)
Not specified or other	5 (13.2)	1 (2.5)	2 (11.8)
AJCC stage, n (%)			
IIIB	4 (10.5)	5 (12.5)	3 (17.6)
IIIC	3 (7.9)	1 (2.5)	2 (11.8)
IVA	14 (36.8)	18 (45.0)	9 (52.9)
IVB	17 (44.7)	16 (40.0)	3 (17.6)
Metastases at baseline, n (%)			
Brain	9 (23.7)	13 (32.5)	2 (11.8)
Liver	9 (23.7)	1 (2.5)	2 (11.8)
PD-L1 TPS, median (range)	87.5 (50, 100)	85.0 (60, 100)	90.0 (60, 100)

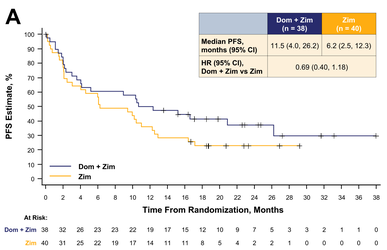
AJCC, American Joint Committee on Cancer; chemo, chemotherapy; dom, domvanalimab; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; zim, zimberelimab.

Table 2. Summary of Efficacy Endpoints

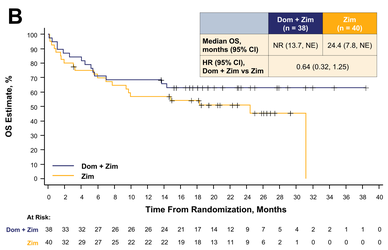
Endpoint	Dom + Zim (n = 38)	Zim (n = 40)	Chemo (n = 17)
PFS			
Median, months (95% CI)	11.5 (4.0, 26.2)	6.2 (2.5, 12.3)	9.6 (2.6, 16.4)
Events, n (%)	24 (63.2%)	30 (75.0%)	13 (76.5%)
HR (95% CI)			
Zim vs chemo	—	1.07 (0.56, 2.05)	—
Dom + zim vs zim	0.69 (0.40, 1.18)	—	—
Dom + zim vs chemo	0.69 (0.35, 1.38)	—	—
OS			
Median, months (95% CI)	NR (13.7, NE)	24.4 (7.8, NE)	11.9 (2.7, NE)
Events, n (%)	14 (36.8%)	21 (52.5%)	12 (70.6%)
HR (95% CI)			
Zim vs chemo	—	0.63 (0.30, 1.29)	—
Dom + zim vs zim	0.64 (0.32, 1.25)	—	—
Dom + zim vs chemo	0.43 (0.20, 0.93)	—	—
Confirmed ORR			
n (%)	17 (44.7%)	14 (35.0%)	6 (35.3%)
[95% CI]	[28.6, 61.7]	[20.6, 51.7]	[14.2, 61.7]
Duration of confirmed response[a]			
Median, months (95% CI)	NR (12.5, NE)	NR (6.2, NE)	7.4 (4.1, NE)
Events, n (%)	6 (35.3%)	7 (50.0%)	4 (66.7%)
HR (95% CI)			
Zim vs chemo	—	0.52 (0.15, 1.80)	—
Dom + zim vs zim	0.54 (0.18, 1.64)	—	—
Dom + zim vs chemo	0.25 (0.07, 0.96)	—	—

Chemo, chemotherapy; dom, domvanalimab; HR, hazard ratio; NE, not evaluable; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; zim, zimberelimab.
[a]Duration of confirmed response was based on confirmed responders in the treatment analysis set (dom + zim, n = 17; zim, n = 14; chemo, n = 6).

Figure 2. (A) PFS and (B) OS Were Greater With Dom + Zim Combination Therapy vs Zim Monotherapy



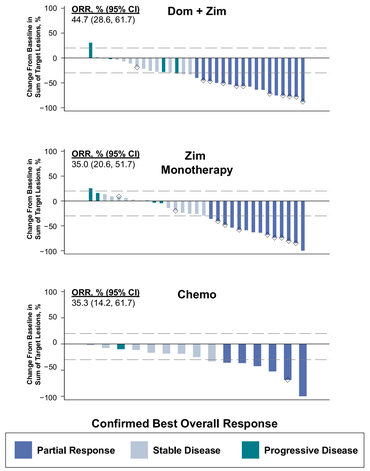
	Dom + Zim (n = 38)	Zim (n = 40)
Median PFS, months (95% CI)	11.5 (4.0, 26.2)	6.2 (2.5, 12.3)
HR (95% CI), Dom + Zim vs Zim	0.69 (0.40, 1.18)	



	Dom + Zim (n = 38)	Zim (n = 40)
Median OS, months (95% CI)	NR (13.7, NE)	24.4 (7.8, NE)
HR (95% CI), Dom + Zim vs Zim	0.64 (0.32, 1.25)	

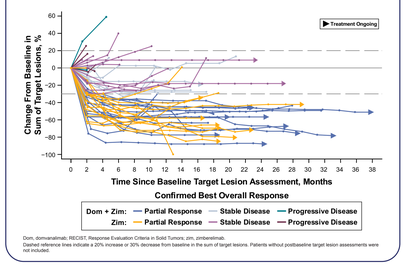
Dom, domvanalimab; HR, hazard ratio; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival; zim, zimberelimab.
Tick marks indicate censored patients.

Figure 3. Waterfall Plot of Confirmed Best Overall Response per RECIST v1.1



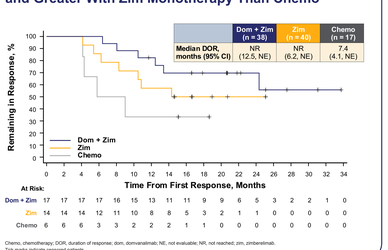
Chemo, chemotherapy; dom, domvanalimab; ORR, objective response rate; RECIST, Response Evaluation Criteria in Solid Tumors; zim, zimberelimab.
Diamond shape indicates that treatment was ongoing at the time of the data cutoff date (May 17, 2024). Dashed reference lines indicate a 20% increase or 30% decrease from baseline in the sum of target lesions. Patients without postbaseline target lesion assessments were not included.

Figure 4. Spider Plot of Changes in Tumor Size During Therapy per RECIST v1.1



Dom, domvanalimab; RECIST, Response Evaluation Criteria in Solid Tumors; zim, zimberelimab.
Dashed reference lines indicate a 20% increase or 30% decrease from baseline in the sum of target lesions. Patients without postbaseline target lesion assessments were not included.

Figure 5. Duration of Confirmed Response Was Greater With Dom + Zim Than Zim Monotherapy and Chemo, and Greater With Zim Monotherapy Than Chemo



	Dom + Zim (n = 38)	Zim (n = 40)	Chemo (n = 17)
Median DOR, months (95% CI)	NR (12.5, NE)	NR (6.2, NE)	7.4 (4.1, NE)

Chemo, chemotherapy; DOR, duration of response; dom, domvanalimab; NE, not evaluable; NR, not reached; zim, zimberelimab.
Tick marks indicate censored patients.

Safety

- Rates of treatment-emergent adverse events (TEAEs) and all-causality serious TEAEs were comparable across all 3 treatment arms **(Table 3)**
- Rates of treatment-related TEAEs leading to treatment discontinuation were greater in the chemo arm compared with the dom + zim and zim arms and were similar between dom + zim and zim
- Higher rates of treatment-related grade ≥ 3 TEAEs were observed in the chemo arm than in the dom + zim and zim arms; rates of treatment-related grade ≥ 3 TEAEs were comparable between dom + zim and zim
- Approximately one-fifth of patients who received dom + zim or zim experienced immune-mediated TEAEs
  - 1 patient who received dom + zim experienced a grade 3 immune-mediated TEAE
  - There were no grade 4 or 5 immune-mediated TEAEs
- Both dom + zim and zim displayed low rates of infusion-related reactions

Table 3. Overview of TEAEs

Parameter	Dom + Zim (n = 38)	Zim (n = 40)	Chemo (n = 17)
Treatment duration, months, median (range)	13.1 (0.7–38.6)	9.3 (0.7–29.9)	4.2 (0.7–23.5)
All-causality TEAE, n (%)			
Any	37 (97.4)	39 (97.5)	17 (100)
Serious	17 (44.7)	18 (45.0)	8 (47.1)
Grade 3 or higher	21 (55.3)	21 (52.5)	10 (58.8)
Leading to treatment discontinuation	8 (21.1)	7 (17.5)	5 (29.4)
Leading to death	5 (13.2)	7 (17.5)	3 (17.6)
Treatment-related TEAE, n (%)			
Any	31 (81.6)	23 (57.5)	14 (82.4)
Grade 3 or higher	8 (21.1)	6 (15.0)	8 (47.1)
Leading to treatment discontinuation	4 (10.5)	3 (7.5)	4 (23.5)
Leading to death	1 (2.6)[a]	4 (10.0)[b]	2 (11.8)[c]
Immune-mediated TEAE, n (%)			
Any	9 (23.7)	8 (20.0)	0
Grade 1	2 (5.3)	5 (12.5)	0
Grade 2	6 (15.8)	3 (7.5)	0
Grade 3	1 (2.6)[d]	0	0
Any infusion-related reactions, n (%)	3 (7.9)	1 (2.5)	0

Chemo, chemotherapy; dom, domvanalimab; TEAE, treatment-emergent adverse event; zim, zimberelimab.
[a]Sudden death.
[b]1 event each of sudden death, acute kidney injury, acute myocardial infarction, and intestinal perforation.
[c]1 event each of febrile neutropenia and ischemic stroke.
[d]One 81-year-old female patient experienced hepatitis, which was resolved following withdrawal of study drug.

References | Acknowledgments | Disclosures

References: 1. Mok TSK, et al. *Lancet*. 2019;393(10183):1819–1830. 2. Dehghani T, et al. *Pathol Res Pract*. 2023;246:154470. 3. Chu X, et al. *Mol Cancer*. 2023;22(1):93. 4. Johnson M, et al. Oral presentation at the 2023 ASCO Annual Meeting. June 2–June 6, 2023. Chicago, Illinois.

Acknowledgments: We extend our thanks to the patients, their families, and all participating investigators. This study was funded by Arcus Biosciences, Inc. and Gilead Sciences, Inc. Medical writing support was provided by Jay Parekh, PharmD, CMPP, of JB Ashtin, and funded by Arcus Biosciences and Gilead Sciences.

Disclosures: J Naidoo has received honoraria, research funding, and/or consulting/advisory fees from AZ, BMS, Daiichi Sankyo, Kaleido Biosciences, Lilly, MedImmune, Merck, Pfizer, Roche, and Takeda. **S Peters** has received honoraria, research funding, and/or consulting/advisory fees from AbbVie, Amgen, Arcus Biosciences, AZ, Bayer, Biocartis, Biodesix, Bioinvent, BI, Blueprint Medicines, BMS, Clovis Oncology, Daiichi Sankyo, Debiopharm Group, Ecancer, F-Star Biotechnology, Fishawack Facilitate, Foundation Medicine, Genentech, Genzyme, Gilead Sciences, GSK, Illumina, Imedex, Incyte, Iovance Biotherapeutics, Janssen, Lilly, Medscape, Merck, Novartis, OncologyEducation, PER, Pfizer, PharmaMar, Prospidyn Therapeutics, Prime Oncology, Regeneron, Research to Practice, RMEI Medical Education, Roche, Sanofi, Seattle Genetics, Takeda, and Vaccibody. **Y Runglodvatana** has received honoraria, research funding, and/or consulting/advisory fees from AZ, Arcus Biosciences, Beigene, Eisai, GSK, Novartis, Merck, MSD, Pfizer, Regeneron, Roche, and Takeda. **J Yu-Chung Li** has received honoraria, research funding, and/or consulting/advisory fees from AZ, Daiichi Sankyo, Merck, MSD, Novartis, and Roche. **C Heng Fong** has no conflicts of interest to report. **G Fuang Ho** has received fees paid to his institution from AB Science, Arcus Biosciences, Astellas, AZ, Lilly, Merck, Pfizer, Regeneron, Roche, Tessa Therapeutics, and has received personal fees from AZ, BI, BMS, Ipsen, Janssen, Merck, Novartis, Pfizer, Roche, and Taiho. **S Hin How** has received clinical trial grants to his institution from AZ, BI, Janssen, Merck, Novartis, and Roche; has received payment for attending advisory board meetings from AZ, Janssen, Merck, and Roche; has received payment for publication of clinical trial results from AZ and Janssen; and has received support to attend the World Conference on Lung Cancer 2023 from Merck. **J Juengsamarn** has received honoraria and research funding from Arcus Biosciences, AZ, BeiGene, Eisai, MSD, and Roche. **T Todd, N Marina, D Patel, S Han, C Bermingham, and D Nuyten** are employees of Arcus Biosciences, Inc. and may hold stock and/or stock options. **T Dang** is an employee of Gilead Sciences, Inc. and may hold stock and/or stock options. **ML Johnson** has received honoraria, research funding, and/or consulting/advisory fees from AbbVie, Acerta Pharma, Adaptimmune, Amgen, Apexigen, Arcus Biosciences, Artiva, Astellas Pharma, AZ, Atreca, Axelia Oncology, BeiGene, BerGenBio, BioAtla, Black Diamond Therapeutics, BI, Calithera Biosciences, Carisma Therapeutics, Checkpoint Therapeutics, Corvus Pharmaceuticals, Curis, CytomX Therapeutics, Daiichi Sankyo, Dracen, Dynavax Technologies, Eisai, Elicio Therapeutics, EMD Serono, EQRx, Eracea, Exelixis, Fate Therapeutics, Genentech/Roche, Genmab, Genoscea Biosciences, Gilead Sciences, GSK, Gritstone Bio, Guardant Health, Harpoon, Helsinn Healthcare, Hengrui Pharmaceutical, Hutchison MediPharma, IDEAYA Biosciences, IGM Biosciences, Immunocore, Incyte, IMPAC Medical Systems, Janssen Oncology, Kadmon, Kartos Therapeutics, Loxo, Lycera, Memorial Sloan-Kettering Cancer Center, Lilly, Merck, Merus, Mirati Therapeutics, Molecular Axiom, NeoImmuneTech, Nexvia Oncology, Novartis, Numab, Nuvalent, OncoMed, Oncorus, Palleon Pharmaceuticals, Pfizer, PMV Pharma, Rain Therapeutics, RasCal, Regeneron, Relay Therapeutics, Revolution Medicines, Ribon Therapeutics, Rubius Therapeutics, Sanofi, Seven and Eight Biopharmaceuticals, Shattuck Labs, Silicon Therapeutics, Stem CentRx, Syndax, TCR2 Therapeutics, Takeda, Tarveda Therapeutics, Tempest Therapeutics, Tessa Therapeutics, Tizona Therapeutics, Trmunity Therapeutics, Turning Point Therapeutics, University of Michigan, VBL Therapeutics, Vyriad, and Y-mAbs Therapeutics.

Presented at the SITC 2024 Annual Meeting, November 8–10, 2024, Houston, Texas