Efficacy and Safety of Ivonescimab-Chemotherapy Versus Placebo-Chemotherapy in EGFR-Tyrosine Kinase Inhibitor–Resistant, *EGFR*-Mutated Non–Small Cell Lung Cancer in the Phase 3 HARMONi Study

Xiuning Le,[1] Antonio Passaro,[2] Janessa Laskin,[3] Delvys Rodriguez-Abreu,[4] Antonio Calles Blanco,[5] Lyudmila Bazhenova,[6] Giuseppe Lo Russo,[7] Natasha Leighl,[8] Federico Cappuzzo,[9] Nicolas Girard,[10] Sanjay Popat,[11] Wenfeng Fang,[12] Yongzhong Luo,[13] Runxiang Yang,[14] Howard West,[15] Jianling Li,[15] Jonathan W. Goldman,[16] Li Zhang[12]

[1]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [2]European Institute of Oncology IRCCS, Milan, Italy; [3]British Columbia Cancer and University of British Columbia, Vancouver, BC, Canada; [4]Complejo Hospitalario Universitario Insular-Materno Infantil de Gran Canaria, Universidad de Las Palmas de Gran Canaria, Las Palmas de Gran Canaria, Spain; [5]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [6]UC San Diego Moores Cancer Center, San Diego, CA, USA; [7]Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [8]Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada; [9]Regina Elena National Cancer Institute, Rome, Italy; [10]Institut Curie, Paris, France; [11]Royal Marsden Hospital, London, United Kingdom; [12]Sun Yat-sen University Cancer Center, Guangzhou, China; [13]Hunan Cancer Hospital, Changsha, China; [14]The Third Affiliated Hospital of Kunming Medical University/Yunnan Cancer Hospital, Kunming, China; [15]Summit Therapeutics Inc., Palo Alto, CA, USA; [16]UCLA Health, Los Angeles, CA, USA

BACKGROUND

- Ivonescimab is a first-in-class, bispecific antibody that cooperatively targets both programmed cell death protein 1 (PD-1) and vascular endothelial growth factor (VEGF)[1]
- In patients with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)–pretreated, advanced or metastatic *EGFR*-mutated non–small cell lung cancer (NSCLC), ivonescimab + chemotherapy significantly prolonged progression-free survival (PFS) and overall survival (OS) compared with chemotherapy alone in the phase 3 HARMONi-A (NCT05184712) trial conducted in China[2,3]
  - Based on this study, ivonescimab + chemotherapy was approved in China for the second-line treatment of EGFR-mutated NSCLC[4]

OBJECTIVE

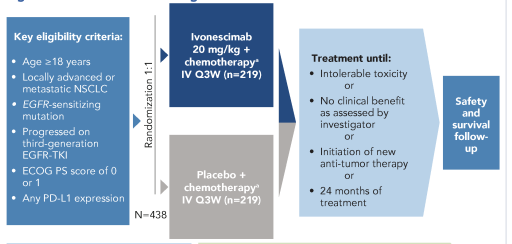
- To assess the efficacy and safety of ivonescimab + chemotherapy versus placebo + chemotherapy in patients with *EGFR*-mutated non-squamous NSCLC whose disease has progressed on a third-generation EGFR-TKI[5]

METHODS

Design

- In the global, randomized, double-blind, phase 3 HARMONi (NCT06396065) study, eligible patients were randomly assigned (1:1) to receive ivonescimab (20 mg/kg) or placebo with pemetrexed and carboplatin intravenously every 3 weeks for up to 4 cycles, followed by maintenance therapy with ivonescimab or placebo + pemetrexed for up to 24 months of treatment (**Figure 1**)[5]
  - Patients with symptomatic metastases of the central nervous system (CNS) were excluded[5]

Figure 1. HARMONi Trial Design[5]



AUC, area under the curve; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor; IRRC, independent radiology review committee; IV, intravenously; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.
Carboplatin was discontinued after an induction phase of 4 cycles.
[a]Chemotherapy was pemetrexed 500 mg/m² and carboplatin AUC 5 mg/mL/min.

- Planned efficacy analyses were primary PFS (~231 events), interim OS (at the time of the primary PFS analysis), and primary OS (~261 events)[5]
  - Due to delayed enrollment in North America and Europe, follow-up in these patients was shorter compared with patients from Asia in the primary OS analysis[5]
  - For this reason, a post hoc longer-term analysis of OS was conducted[5]
- A subgroup analysis was also conducted evaluating intracranial PFS (as assessed by independent radiology review committee [IRRC] based on Response Evaluation Criteria in Solid Tumors version 1.1) and probability of intracranial progression (defined as occurrence of a new brain lesion or progression of an existing brain lesion), in patients with and without brain metastases at baseline[5]
  - At screening, an enhanced (if not contraindicated) scan of the brain by computed tomography or magnetic resonance imaging (MRI) was performed to evaluate for brain metastases; if suspected, an MRI scan of the brain was required to confirm or reject the diagnosis[5]
  - For patients with brain metastases at baseline, brain imaging was performed with repeat MRI every 6 weeks (±7 days) for 54 weeks after the first dose of study treatment, then every 12 weeks (±7 days)[5]
  - If clinically indicated, the investigators were allowed to perform additional scans or more frequent evaluations[5]

RESULTS

Patient Characteristics

- Of the 438 patients who were randomized to receive ivonescimab + chemotherapy (n=219) or placebo + chemotherapy (n=219), 54 (24.7%) in each arm had brain metastases at baseline (**Table 1**)
  - The demographics and baseline disease characteristics were generally balanced between treatment arms for patients with and without brain metastases (Table 1), consistent with that of the intention-to-treat (ITT) population[5]

Table 1. Baseline Characteristics

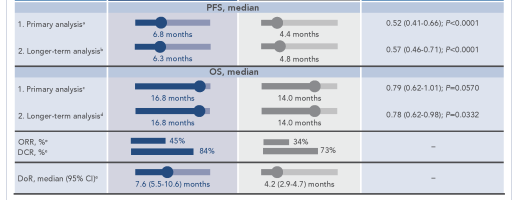
Characteristic	Patients with brain metastases		Patients without brain metastases	
	Ivo + chemo (n=54)	Pbo + chemo (n=54)	Ivo + chemo (n=165)	Pbo + chemo (n=165)
Age, median (range), years	63 (40.0-84.0)	58 (37.0-84.0)	62 (32.0-82.0)	62 (36.0-81.0)
Age ≥65 years, n (%)	21 (38.9)	19 (35.2)	62 (37.6)	69 (41.8)
Female sex, n (%)	33 (61.1)	30 (55.6)	97 (58.8)	97 (58.8)
Region, n (%)				
Asia	29 (53.7)	31 (57.4)	107 (64.8)	106 (64.2)
Europe	10 (18.5)	9 (16.7)	30 (18.2)	23 (13.9)
North America	15 (27.8)	14 (25.9)	28 (17.0)	36 (21.8)
Race, n (%)				
American Indian or Alaska Native	0	0	0	1 (0.6)
Asian	34 (63.0)	36 (66.7)	119 (72.1)	117 (70.9)
Black or African American	2 (3.7)	0	0	3 (1.8)
White	13 (24.1)	16 (29.6)	38 (23.0)	38 (23.0)
Other[a]	5 (9.3)	2 (3.7)	8 (4.8)	6 (3.6)
Never-smoker, n (%)	39 (72.2)	41 (75.9)	104 (63.0)	114 (69.1)
Liver metastasis, n (%)	10 (18.5)	10 (18.5)	22 (13.3)	13 (7.9)
Prior lines of systemic anti-cancer therapy, median (range)	1 (1.0-3.0)	1 (1.0-3.0)	1 (1.0-4.0)	1 (1.0-4.0)

chemo, chemotherapy; ivo, ivonescimab; pbo, placebo.
[a]Other includes unknown and not permitted per regulation.

Efficacy in the ITT Population

- In the primary analysis, PFS assessed by IRRC was longer with ivonescimab + chemotherapy versus placebo + chemotherapy[a] (**Figure 2**); this PFS benefit was consistent across predefined subgroups[5]
  - PFS was longer with ivonescimab + chemotherapy versus placebo + chemotherapy in patients with brain metastases at baseline (hazard ratio [HR] = 0.34; 95% CI, 0.20-0.57) and patients without brain metastases at baseline (HR = 0.59; 95% CI, 0.45-0.77)[5]
- In both the primary and longer-term analyses, OS was longer with ivonescimab + chemotherapy versus placebo + chemotherapy[a] (**Figure 2**); this OS benefit was consistent across predefined subgroups in the longer-term analysis[5]
- The objective response rate and disease control rate were numerically greater in the ivonescimab + chemotherapy arm versus the placebo + chemotherapy arm[5] (**Figure 2**)
  - Duration of response was numerically longer with ivonescimab + chemotherapy versus placebo + chemotherapy[5]

Figure 2. Efficacy Analysis in the ITT Population[5]

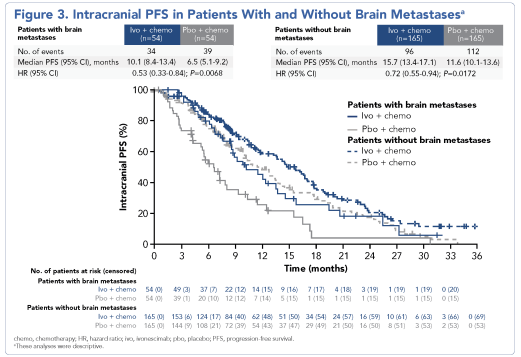


chemo, chemotherapy; DCR, disease control rate; DoR, duration of response; EU, European Union; IRRC, independent radiology review committee; ITT, intention to treat; ivo, ivonescimab; NA, North America; ORR, objective response rate; OS, overall survival; pbo, placebo; PFS, progression-free survival.
[a]Data cutoff: June 10, 2024; median follow-up: 22.3 months; N=345. Assessed by IRRC
[b]Data cutoff: April 12, 2025; median follow-up: 29.7 months; N=438. Assessed by IRRC. *P* value was exploratory.
[c]Data cutoff: April 12, 2025; median follow-up: Overall, 29.7 months; Asia, 32.7 months; NA & EU, 9.2 months.
[d]Data cutoff: April 12, 2025 (Asia); Sept 5, 2025 (NA & EU); median follow-up: Overall, 29.7 months; Asia, 32.7 months; NA & EU, 13.7 months. *P* value was exploratory.
[e]Data cutoff: April 12, 2025. Assessed by IRRC.

Intracranial PFS

- At the data cutoff of April 12, 2025, median intracranial PFS was longer in the ivonescimab + chemotherapy arm versus the placebo + chemotherapy arm in patients with and without brain metastases at baseline (**Figure 3**)

Figure 3. Intracranial PFS in Patients With and Without Brain Metastases[a]

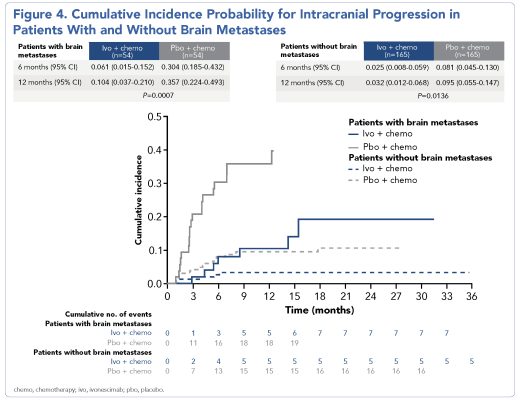


chemo, chemotherapy; HR, hazard ratio; ivo, ivonescimab; pbo, placebo; PFS, progression-free survival.
[a]These analyses were descriptive.

Cumulative Incidence Probability for Intracranial Progression

- The cumulative incidence probability (95% CI) for intracranial progression at 6 months and 12 months was significantly lower with ivonescimab + chemotherapy versus placebo + chemotherapy in both subgroups (**Figure 4**)
  - For patients without brain metastases at baseline, the benefit continued for more than 27 months

Figure 4. Cumulative Incidence Probability for Intracranial Progression in Patients With and Without Brain Metastases



chemo, chemotherapy; ivo, ivonescimab; pbo, placebo.

Safety

- In the safety analysis population, grade ≥3 treatment-related adverse events (TRAEs) occurred in 109 patients (50%) in the ivonescimab + chemotherapy arm versus 92 (42%) in the placebo + chemotherapy arm[5]
- The frequencies of grade ≥3 TRAEs were generally similar in subgroups of patients with and without brain metastases at baseline for each treatment arm (**Table 2**)
- In the safety analysis population, grade ≥3 immune-related TRAEs occurred in 21 patients (10%) in the ivonescimab + chemotherapy arm and 13 (6%) in the placebo + chemotherapy arm[5]
  - Immune-related TRAEs of any grade occurring in ≥3% of patients were hypothyroidism, hyperthyroidism, increased aspartate aminotransferase, and rash[5]
- Immune-related TRAEs of any grade occurred at similar frequencies in subgroups of patients with and without brain metastases within each treatment arm (**Table 2**)
  - In the ivonescimab + chemotherapy arm, grade ≥3 immune-related TRAEs that occurred in >1 patient were increased alanine aminotransferase (1 patient in each subgroup), drug eruption (2 patients without brain metastases), and increased lipase (2 patients without brain metastases)
  - Grade ≥3 interstitial lung toxicity (including pneumonitis, interstitial lung disease, and immune-mediated lung disease) occurred in 1 patient with and 2 patients without brain metastases, respectively, in the ivonescimab + chemotherapy arm
- In the safety analysis population, grade ≥3 VEGF-related TRAEs occurred in 16 (7%) patients in the ivonescimab + chemotherapy arm and 7 (3%) patients in the placebo + chemotherapy arm[5]
  - The most common VEGF-related TRAEs of any grade occurring in ≥3% of patients were proteinuria, hypertension, and hemorrhage[5]
- VEGF inhibition-associated TRAEs of any grade also occurred at similar frequencies in patients with and without brain metastases within each treatment arm (**Table 2**)
  - For patients in the ivonescimab + chemotherapy arm, grade ≥3 VEGF-related TRAEs by classification that occurred in >1 patient were hypertension (2 patients with and 6 patients without brain metastases), proteinuria (2 patients without brain metastases), hemorrhage (2 patients without brain metastases), congestive heart failure (2 patients without brain metastases), and venous thrombotic events (4 patients without brain metastases)
- The frequencies of TRAEs in patients in the ivonescimab + chemotherapy arm were generally consistent across subgroups (**Table 3**)

Table 2. Summary of TRAEs in Patients With and Without Brain Metastases

Characteristic, n (%)	Patients with brain metastases		Patients without brain metastases	
	Ivo + chemo (n=54)	Pbo + chemo (n=54)	Ivo + chemo (n=164)	Pbo + chemo (n=164)
TRAEs (all grades)	48 (88.9)	49 (90.7)	159 (97.0)	154 (93.9)
Grade ≥3	26 (48.1)	23 (42.6)	83 (50.6)	69 (42.1)
Serious TRAEs	11 (20.4)	7 (13.0)	50 (30.5)	26 (15.9)
Leading to discontinuation of any study drug	6 (11.1)	1 (1.9)	21 (12.8)	16 (9.8)
Leading to death[b]	1 (1.9)[c]	1 (1.9)[c]	3 (1.8)[d]	4 (2.4)[e]
Immune-related TRAEs	18 (33.3)	10 (18.5)	54 (32.9)	29 (17.7)
Grade ≥3	5 (9.3)	3 (5.6)	16 (9.8)	10 (6.1)
VEGF-related TRAEs	16 (29.6)	7 (13.0)	57 (34.8)	26 (15.9)
Grade ≥3	2 (3.7)	2 (3.7)	14 (8.5)	5 (3.0)

chemo, chemotherapy; ivo, ivonescimab; pbo, placebo; TRAE, treatment-related adverse event; VEGF, vascular endothelial growth factor.
[a]As assessed by investigator.
[b]TRAE leading to death was hepatic failure.
[c]TRAE leading to death was cognitive disorder.
[d]TRAEs leading to death were 1 patient with disease progression, 1 patient with multiple organ dysfunction, and 1 patient with gastrointestinal hemorrhage and pulmonary embolism.
[e]TRAEs leading to death were pneumonitis, myocardial infarction, cerebrovascular accident, and embolic stroke, each in 1 patient.

Table 3. Most Common TRAEs (≥20% in Either Treatment Group) in Patients With and Without Brain Metastases

Characteristic,[a] n (%)	Patients with brain metastases				Patients without brain metastases(			
	Ivo + chemo (n=54)		Pbo + chemo (n=54)		Ivo + chemo (n=164)		Pbo + chemo (n=164)	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Anemia	22 (40.7)	5 (9.3)	28 (51.9)	7 (13.0)	85 (51.8)	17 (10.4)	95 (57.9)	20 (12.2)
White blood cell count decreased	21 (38.9)	8 (14.8)	20 (37.0)	6 (11.1)	77 (47.0)	20 (12.2)	76 (46.3)	18 (11.0)
Neutrophil count decreased	19 (35.2)	10 (18.5)	22 (40.7)	10 (18.5)	74 (45.1)	32 (19.5)	70 (42.7)	26 (15.9)
AST increased	18 (33.3)	1 (1.9)	12 (22.2)	1 (1.9)	50 (30.5)	1 (0.6)	45 (27.4)	1 (0.6)
Nausea	17 (31.5)	1 (1.9)	17 (31.5)	0	44 (26.8)	2 (1.2)	44 (26.8)	0
Platelet count decreased	16 (29.6)	7 (13.0)	13 (24.1)	2 (3.7)	55 (33.5)	20 (12.2)	48 (29.3)	12 (7.3)
ALT increased	14 (25.9)	2 (3.7)	12 (22.2)	1 (1.9)	45 (27.4)	3 (1.8)	50 (30.5)	5 (3.0)
Decreased appetite	13 (24.1)	0	13 (24.1)	0	41 (25.0)	0	26 (15.9)	1 (0.6)
Vomiting	11 (20.4)	1 (1.9)	6 (11.1)	0	34 (20.7)	2 (1.2)	35 (21.3)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; chemo, chemotherapy; ivo, ivonescimab; pbo, placebo; TRAE, treatment-related adverse event.
[a]Events are listed according to decreasing incidence in the "Any grade" column of the ivo + chemo treatment arm with brain metastases present.

CONCLUSIONS

- Ivonescimab + chemotherapy showed significant PFS benefit and a manageable safety profile in patients with *EGFR*-mutated NSCLC post–third-generation EGFR-TKI[5]
- Intracranial PFS benefit and reduced risk for intracranial progression were seen in patients with and without brain metastases at baseline
- The intracranial benefit of adding ivonescimab to standard of care in patients with NSCLC, regardless of brain metastases at baseline, suggests a potential role for this novel treatment modality in the subset of patients with *EGFR*-mutated NSCLC after third-generation TKI

REFERENCES

1. Zhong T, et al. *J Immunother Cancer*. 2022;10(suppl 2). Abstract 521.
2. Fang W, et al. *JAMA*. 2024;332(7):561-570.
3. Zhang L, et al. Presented at the Society for Immunotherapy of Cancer (SITC) Annual Meeting; November 5-9, 2025; National Harbor, MD, USA. Abstract 1348.
4. PR Newswire. Published June 1, 2024. Accessed August 3, 2026. https://www.prnewswire.com/news-releases/ivonescimab-in-combination-with-chemotherapy-approved-in-china-by-nmpa-for-2l-egfrm-nsclc-based-on-harmoni-a-clinical-trial-positive-trend-observed-in-overall-survival-towards-ivonescimab-plus-chemotherapy-302161109.html.
5. Le X, et al. *Lancet Oncol*. 2026;27(9):1094-1109.

ACKNOWLEDGMENTS

The authors thank the participants and their caregivers, the investigators, the site staff who have been and are participating in this study, and Lori Styles for her contributions to the study. This study is sponsored by Summit Therapeutics Inc., and Akeso Biopharma funded data collection in China. Medical writing assistance was provided by MEDiSTRAVA (San Francisco, CA, USA) and was funded by Summit Therapeutics Inc.

Disclaimer: This poster is an encore and has been reused with permission from the European Society for Medical Oncology (ESMO). This abstract was accepted and previously presented by Xiuning Le, et al. at the European Lung Cancer Congress (ELCC), FPN (Final Publication Number): 106322, ESMO Open, Volume 11, 2026 Supplement 3. All rights reserved. Previously presented at World Conference on Lung Cancer (WCLC) 2025, September 6-9, 2025, Barcelona, Spain; European Lung Cancer Congress (ELCC) 2026, March 25-28, 2026, Copenhagen, Denmark; Fall 2026 ONCare Alliance National Leadership Summit, September 30-October 2, 2026; Charlotte, NC.; and AMCP Nexus 2026, October 26-29, 2026, San Diego, CA, USA.

DISCLOSURES

Xiuning Le declares consulting/advisory fees from AbbVie, Abion, Akeso, Allist, ArriVent Biopharma, AstraZeneca, Avistone, Bayer, BioNTech, BlossomHill, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Dizal, Eli Lilly, EMD Serono (Merck KGaA), Hengrui, Innovent, Johnson & Johnson (Janssen), Merck, Novartis, Pfizer, Regeneron, Summit, SystImmune, Taiho, and Teligene; and research funding to institution from ArriVent Biopharma, Dizal, Eli Lilly, EMD Serono, Johnson & Johnson (Janssen), Regeneron, Takeda, Teligene, and Thermo Fisher.

Disclosures for all other authors can be found in the Supplementary Information, accessible via the QR code.

Ivonescimab is an investigational therapy not approved by any regulatory authority other than China's National Medical Products Administration (NMPA).

CONTACT INFORMATION

Please contact the presenting author, Deanna Phillips, at deanna.phillips@smmttx.com for questions or comments.

Copies of this poster and supplementary information obtained through QR (Quick Response) Code are for personal use only and may not be reproduced without written permission from the authors. By use of the QR Code, you agree to the Summit privacy notice, located at smmttx.com.

Presented at the Network for Collaborative Oncology Development & Advancement (NCODA) 2026 International Fall Summit; October 28-30, 2026; Orlando, FL