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Intracranial Efficacy of Ivonescimab Plus Chemotherapy in Epidermal Growth Factor Receptor (EGFR) Tyrosine Kinase Inhibitor–Resistant, *EGFR*-Mutated Non–Small Cell Lung Cancer in the HARMONi Study

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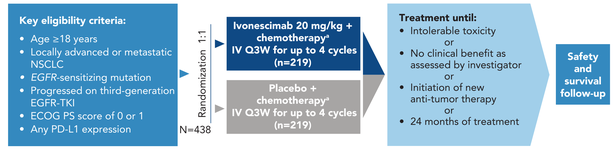
BACKGROUND

- Ivonescimab is an investigational bispecific antibody against programmed cell death protein 1 (PD-1) and vascular endothelial growth factor (VEGF)[1]
- In patients with 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 trial (NCT05184712) 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]
- HARMONi is a global, randomized, double-blind, phase 3 trial evaluating 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[5,6]
  - In the primary analysis of HARMONi, PFS as assessed by independent radiology review committee (IRRC) was longer with ivonescimab + chemotherapy compared with placebo + chemotherapy (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.41-0.66)[6]
    - The PFS HR was 0.34 (95% CI, 0.20-0.57) in patients with brain metastases at baseline and 0.59 (95% CI, 0.45-0.77) in patients without brain metastases at baseline[6]
  - Grade ≥3 treatment-related adverse events (TRAEs) were reported in 50.0% and 42.2% of patients and serious TRAEs in 28.0% and 15.1% of patients in the ivonescimab + chemotherapy and placebo + chemotherapy arms, respectively[6]
    - Rates of TRAEs leading to study drug discontinuation (7.3% vs 5.0%) and TRAEs leading to death (1.8% vs 2.3%) were comparable with ivonescimab + chemotherapy versus placebo + chemotherapy[6]
- To explore intracranial disease control, we assessed intracranial PFS and cumulative incidence of intracranial progression by baseline brain metastases status
  - Intracranial endpoints were evaluated in prespecified exploratory analyses of HARMONi and were not part of the primary multiplicity-controlled testing hierarchy

METHODS

- In HARMONi (NCT06396065), eligible patients were randomly assigned (1:1) to receive ivonescimab (20 mg/kg) or placebo with pemetrexed and carboplatin intravenously every 3 weeks for 4 cycles, followed by maintenance therapy with ivonescimab or placebo + pemetrexed for up to 24 months of treatment (**Figure 1**)[5,6]
  - Patients with symptomatic metastases of the central nervous system were excluded

Figure 1. Trial Design



Stratification factors:
- Geographic region
- Brain metastases at baseline (present or absent)

Study endpoints:
- **Primary:** OS, PFS by IRRC per RECIST v1.1
- **Secondary:** ORR by IRRC per RECIST v1.1, DoR, safety and tolerability

AUC, area under the concentration-time 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; 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.
[a]Chemotherapy was pemetrexed 500 mg/m² and carboplatin AUC 5 mg/mL/min. Carboplatin was discontinued after an induction phase of 4 cycles.

- This subgroup analysis evaluated intracranial PFS (as assessed by IRRC based on Response Evaluation Criteria in Solid Tumors, version 1.1 [RECIST v1.1]) and cumulative incidence 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
  - The probability of a first event being an intracranial progression, non-intracranial progression, or death was estimated by cumulative incidences using a competing risks approach in patients
  - At screening, an enhanced scan of the brain by computed tomography or magnetic resonance imaging (MRI) was performed (if not contraindicated) to evaluate for brain metastases; if suspected, an MRI scan of the brain was required to confirm or reject the diagnosis
  - During the study, if brain metastases were present at baseline, brain imaging was performed with repeat MRI per the tumor imaging schedule: every 6 weeks (±7 days) for 54 weeks after the first dose of study treatment, then every 12 weeks (±7 days)
  - If clinically indicated, the investigators were allowed to perform additional scans or more frequent evaluations

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

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 (**Figure 2**)

Cumulative Incidence Probability for Intracranial Progression

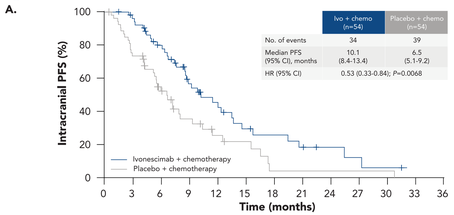
- The cumulative incidence probability (95% CI) for intracranial progression at 6 months and 12 months was significantly lower with ivonescimab + chemotherapy versus placebo + chemotherapy in both subgroups (**Figure 3**)
  - For patients without brain metastases, the benefit continued for more than 27 months

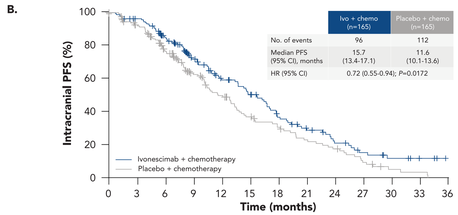
Table 1. Baseline Characteristics

Characteristic	Patients with brain metastases		Patients without brain metastases	
	Ivo + chemo n=54	Placebo + chemo n=54	Ivo + chemo n=165	Placebo + 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)

[a]Other includes unknown and not permitted per regulation.

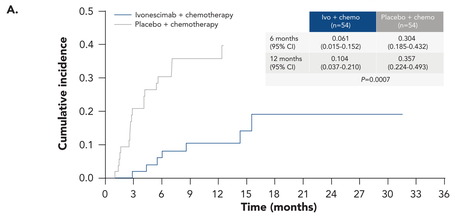
Figure 2. Intracranial PFS in Patients (A) With and (B) Without Brain Metastases[a]

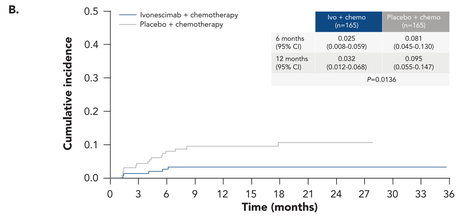




Chemo, chemotherapy; HR, hazard ratio; ivo, ivonescimab; PFS, progression-free survival.
[a]These analyses were descriptive.

Figure 3. Cumulative Incidence Probability for Intracranial Progression in Patients (A) With and (B) Without Brain Metastases





Chemo, chemotherapy; HR, hazard ratio; ivo, ivonescimab.

Safety

- The frequencies of grade 3 or higher TRAEs were generally similar in subgroups of patients with and without brain metastases for each treatment arm (**Table 2**)
- Immune-related TRAEs of any grade occurred at similar frequencies in 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
- 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

Characteristic, n (%)	Patients with brain metastases		Patients without brain metastases	
	Ivo + chemo n=54	Placebo + chemo n=54	Ivo + chemo n=164	Placebo + 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[a]	1 (1.9)[b]	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; 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)

Characteristic,[a] n (%)	Patients with brain metastases				Patients without brain metastases			
	Ivo + chemo n=54		Placebo + chemo n=54		Ivo + chemo n=164		Placebo + 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; TRAE, treatment-related adverse event.
[a]Events are listed according to decreasing incidence in the 'Any grade' column of the ivonescimab + chemotherapy treatment arm with brain metastases present.

CONCLUSIONS

- Ivonescimab + chemotherapy treatment was associated with numerically longer intracranial PFS benefit and a lower incidence of intracranial progression compared with placebo + chemotherapy in patients with and without brain metastases at baseline
- The safety profile of ivonescimab + chemotherapy was generally consistent with the known profiles of PD-L1 and VEGF pathway inhibition combined with chemotherapy,[7-9] and no new safety signals were identified across baseline brain metastases subgroups
- 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 progressed after third-line TKI

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DISCLOSURES

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

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