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Intracranial Progression-Free Survival With Ivonescimab Compared to Placebo in the HARMONi-A Trial of Patients With Previously Treated *EGFR* Mutation–Positive Non–Small Cell Lung Cancer

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BACKGROUND

- First-line treatment for advanced or metastatic non–small cell lung cancer (NSCLC) with activating epidermal growth factor receptor (*EGFR*) gene variants includes third-generation EGFR tyrosine kinase inhibitors (EGFR TKIs) such as osimertinib[1,2]
- However, NSCLC tumors often develop acquired resistance to EGFR TKIs, which leads to disease progression, leaving patients with limited treatment options[3]
- Ivonescimab is a novel, investigational, bispecific antibody against programmed cell death protein 1 (PD-1) and vascular endothelial growth factor (VEGF); it has exhibited cooperative binding in vitro that could produce complementary and synergistic antitumor effects through the PD-1 and the VEGF pathways[4-6]
- The phase 3 HARMONi-A trial compared the efficacy and safety of ivonescimab plus chemotherapy with chemotherapy in patients with advanced or metastatic *EGFR* mutation–positive NSCLC that progressed after EGFR TKI treatment[7]
  - In the first preplanned interim analysis (March 10, 2023 data cutoff), ivonescimab plus chemotherapy significantly improved progression-free survival (PFS) versus chemotherapy (hazard ratio [HR], 0.46 [95% CI, 0.34-0.62]; $P < 0.001$); median PFS was 7.1 (95% CI, 5.9-8.7) vs 4.8 (95% CI, 4.2-5.6) months[7]
  - The PFS benefit observed with ivonescimab plus chemotherapy compared with chemotherapy was consistent in patients with and without brain metastases at baseline, with HRs of 0.40 (95% CI, 0.22-0.73) and 0.48 (95% CI, 0.34-0.69), respectively[7]
- This post hoc analysis evaluated the efficacy of ivonescimab plus chemotherapy on intracranial disease progression in HARMONi-A

OBJECTIVE

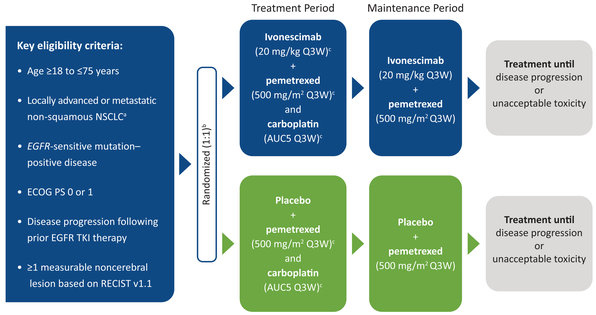
- To assess the effects of ivonescimab plus chemotherapy on intracranial PFS in patients with locally advanced or metastatic NSCLC in the HARMONi-A trial

METHODS

Study Design

- The HARMONi-A trial (NCT05184712) was a randomized, double-blind, placebo-controlled phase 3 trial in China, which included adult patients with locally advanced or metastatic, *EGFR* mutation–positive NSCLC whose disease had progressed after EGFR TKI therapy (**Figure 1**)[8]

Figure 1. Study Design



AUC5, area under the concentration time-curve value of 5 mg/mL/min; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non–small cell lung cancer; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1.; TKI, tyrosine kinase inhibitor.
[a]Histologically or cytologically confirmed non-squamous NSCLC (stage IIIB/C or stage IV; ineligible for surgery or local therapy).
[b]With stratification by exposure to third-generation EGFR TKIs (yes/no) and presence of brain metastases at baseline (yes/no).
[c]4 cycles (3 weeks/cycle).

Assessments and Outcomes

- Computed tomography or magnetic resonance imaging of the brain were performed for all patients at baseline
- In patients with brain metastases at baseline, tumor assessments via brain imaging were conducted every 6 weeks during the first 54 weeks and every 12 weeks thereafter
  - In patients without brain metastases at baseline, subsequent brain imaging was conducted at the discretion of the investigators on the basis of central nervous system symptoms
- The primary efficacy end point in the HARMONi-A trial was overall PFS by independent radiologic review committee (IRRC)
- For the current analysis, intracranial PFS was assessed by IRRC per Response Evaluation Criteria in Solid Tumors, version 1.1 in all patients enrolled (intention-to-treat [ITT] population) and in those with brain metastases at baseline
  - Intracranial PFS was defined as the time from randomization until intracranial progression or death from any cause in the absence of known intracranial progression
  - At the time of analysis, patients who were alive without intracranial disease progression were censored at their last evaluable scan

RESULTS

Participants

- As of March 10, 2023, a total of 322 patients were enrolled (161 in each arm) in the trial
  - The median duration of follow-up for all patients was 7.1 months (interquartile range [IQR], 5.4-9.0) for the ivonescimab plus chemotherapy arm and 8.2 months (IQR, 5.5-9.5) for the placebo plus chemotherapy arm
  - The median duration of exposure was 8.8 cycles (range, 1.0-16.9) and 7.3 cycles (range, 1.0-16.2) for ivonescimab and placebo, respectively
- Of the patients enrolled, 35 (21.7%) and 37 (23.0%) in the ivonescimab plus chemotherapy and placebo plus chemotherapy arms, respectively, had brain metastases at baseline (**Table 1**)
  - For patients with brain metastases at baseline, the median duration of follow up was 7.9 months (IQR, 7.1-8.4) and 8.2 months (IQR, 6.2-8.9) for the ivonescimab plus chemotherapy and placebo plus chemotherapy arms, respectively

Table 1. Baseline Characteristics

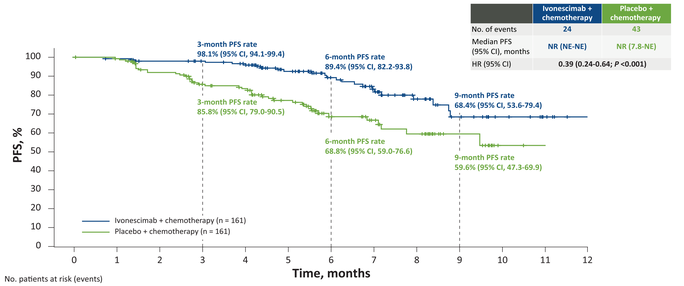
Characteristic	ITT population[a]		Patients with brain metastases at baseline	
	Ivonescimab plus chemotherapy n = 161	Placebo plus chemotherapy n = 161	Ivonescimab plus chemotherapy n = 35	Placebo plus chemotherapy n = 37
Age, median (range), years	59.6 (32.3-74.9)	59.4 (36.2-74.2)	59.2 (43.1-74.9)	57.7 (37.6-71.9)
Age ≥65 years, n (%)	50 (31.1)	51 (31.7)	10 (28.6)	11 (29.7)
Sex, n (%)				
Male	77 (47.8)	79 (49.1)	16 (45.7)	19 (51.4)
Female	84 (52.2)	82 (50.9)	19 (54.3)	18 (48.6)
ECOG PS, n (%)[b]				
0	24 (14.9)	34 (21.1)	7 (20.0)	7 (18.9)
1	137 (85.1)	127 (78.9)	28 (80.0)	30 (81.1)
Disease stage, n (%)[c]				
IIIB/C	3 (1.9)	5 (3.1)	0	0
IV	158 (98.1)	156 (96.9)	35 (100)	37 (100)
Patients with brain metastases, n (%)	35 (21.7)	37 (23.0)	35 (100)	37 (100)
Patients with liver metastases, n (%)	21 (13.0)	17 (10.6)	6 (17.1)	6 (16.2)
Patients with ≥3 distant metastases, n (%)	74 (46.0)	68 (42.2)	24 (68.6)	23 (62.2)
***EGFR* variant, n (%)**				
Exon 19 deletion	92 (57.1)	78 (48.4)	19 (54.3)	18 (48.6)
L858R	60 (37.3)	78 (48.4)	15 (42.9)	19 (51.4)
Other	35 (21.7)	25 (15.5)	7 (20.0)	6 (16.2)
Previous EGFR TKI therapy, n (%)				
1st/2nd generation TKI only	22 (13.7)	24 (14.9)	6 (17.1)	6 (16.2)
3rd generation TKI only	49 (30.4)	58 (36.0)	14 (40.0)	13 (35.1)
1st/2nd generation TKI, then 3rd generation TKI	90 (55.9)	79 (49.1)	15 (42.9)	18 (48.6)

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; ITT, intention to treat; NA, not applicable; TKI, tyrosine kinase inhibitor.
All patients were enrolled in China, but race/ethnicity demographic information was not collected.
[a]Baseline characteristics for the patients in this analysis were previously published.[7]
[b]ECOG PS scores range from 0 to 5 (higher scores indicate greater disability).
[c]Stage at diagnosis was based on *AJCC Cancer Staging Manual*, 8th edition.[9]

Efficacy

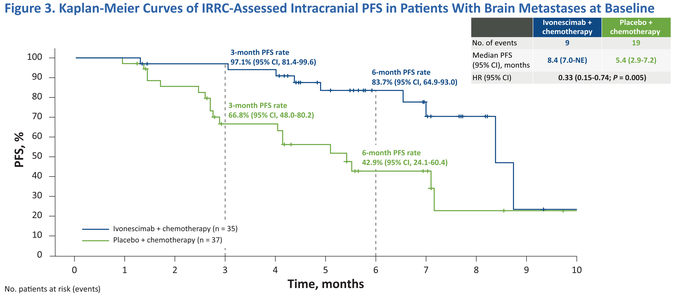
- In the ITT population, the median intracranial PFS was not reached in either arm; HR was 0.39 (95% CI, 0.24-0.64; $P < 0.001$), favoring the ivonescimab plus chemotherapy arm
  - The 6-month PFS rates were 89.4% and 68.8% in the ivonescimab plus chemotherapy and placebo plus chemotherapy arms, respectively (**Figure 2**)
- In patients with brain metastases at baseline, median intracranial PFS was 8.4 months (95% CI, 7.0-NE) in the ivonescimab plus chemotherapy and 5.4 months (95% CI, 2.9-7.2) in the placebo plus chemotherapy arms; HR was 0.33 (95% CI, 0.15-0.74; $P = 0.005$), favoring the ivonescimab plus chemotherapy arm
  - The 6-month PFS rates were 83.7% and 42.9% in the ivonescimab plus chemotherapy and placebo plus chemotherapy arms, respectively (**Figure 3**)

Figure 2. Kaplan-Meier Curves of IRRC-Assessed Intracranial PFS (ITT Set)



HR, hazard ratio; IRRC, independent radiologic review committee; ITT, intention to treat; NE, not evaluable; NR, not reached; PFS, progression-free survival.

Figure 3. Kaplan-Meier Curves of IRRC-Assessed Intracranial PFS in Patients With Brain Metastases at Baseline



HR, hazard ratio; IRRC, independent radiologic review committee; NE, not estimated; NR, not reached; PFS, progression-free survival.

CONCLUSIONS

- Ivonescimab combined with chemotherapy significantly improved intracranial PFS in patients with advanced *EGFR* mutation–positive NSCLC whose disease had progressed after previous EGFR-TKI therapy
- Results of this analysis support further evaluation of ivonescimab combined with chemotherapy for the treatment of *EGFR*-sensitive mutation–positive NSCLC

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REFERENCES

1. Riely GJ et al. *J Natl Comp Canc Netw*. 2024;22:249-274.
2. Hendriks LE et al. *Ann Oncol*. 2023;34:339-357.
3. Fu K et al. *J Hematol Oncol*. 2022;15:173.
4. Zhao Y et al. *EClinicalMedicine*. 2023;62:102106.
5. Wang L et al. *J Thorac Oncol*. 2024;19:465-474.
6. Frentzas S et al. *J Immunother Cancer*. 2024;12:e008037.
7. HARMONi-A study investigators. *JAMA*. 2024;332:561-570.
8. Amin MB et al. *CA Cancer J Clin*. 2017;67(2):93-99.

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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