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Ivonescimab Versus Pembrolizumab for PD-L1–Positive NSCLC: A Subgroup Analysis of HARMONi-2 by PD-L1 Expression Level

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BACKGROUND

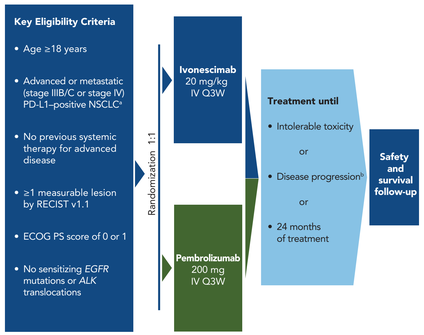
- Ivonescimab is a first-in-class, investigational, bispecific antibody against programmed cell death protein 1 (PD-1) and vascular endothelial growth factor[1]
- The phase 3 HARMONi-2 (NCT05499390) trial compared ivonescimab with pembrolizumab as monotherapy (N = 398) in patients with previously untreated, programmed cell death ligand 1 (PD-L1)–positive (tumor proportion score [TPS] ≥1%) advanced non–small cell lung cancer (NSCLC)[1]
  - In the primary analysis, progression-free survival (PFS) improved significantly in patients who received ivonescimab compared with pembrolizumab (median PFS, 11.1 and 5.8 months, respectively; hazard ratio [HR], 0.51 [95% CI, 0.38-0.69]; $P < 0.0001$)
- The overall PFS results were consistent across prespecified subgroups of patients, including those with TPS 1-49% and TPS ≥50%
- The objective of the current analysis of HARMONi-2 was to further assess the efficacy and safety outcomes by level of tumor PD-L1 expression based on TPS

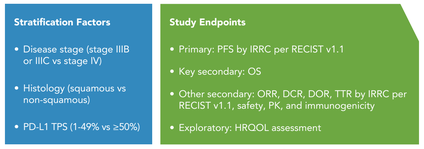
METHODS

Design

- HARMONi-2 (NCT05499390) was a randomized, double-blind, phase 3 trial that compared the efficacy and safety of ivonescimab with pembrolizumab monotherapy in 55 hospitals across China[1] (**Figure 1**)

Figure 1. Trial Design





ALK, anaplastic lymphoma kinase; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, endothelial growth factor receptor; HRQOL, health-related quality of life; 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; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; TPS, tumor proportion score; TTR, time to response.

[a]Squamous or non-squamous NSCLC subtype confirmed histologically or cytologically.

[b]Confirmed by the masked IRRC.

- This exploratory analysis of HARMONi-2 further evaluated outcomes by PD-L1 expression level, as measured by TPS 1-49% versus ≥50% versus ≥90%

RESULTS

Patient Characteristics

- The TPS 1-49% subgroup included 230 patients, the TPS ≥50% subgroup included 168 patients, and the TPS ≥90% subgroup included 55 patients (**Table 1**)
- At the January 29, 2024, data cutoff, the overall median duration of follow-up was 8.7 months[1]

Table 1. Baseline Characteristics by PD-L1 Expression Subgroup

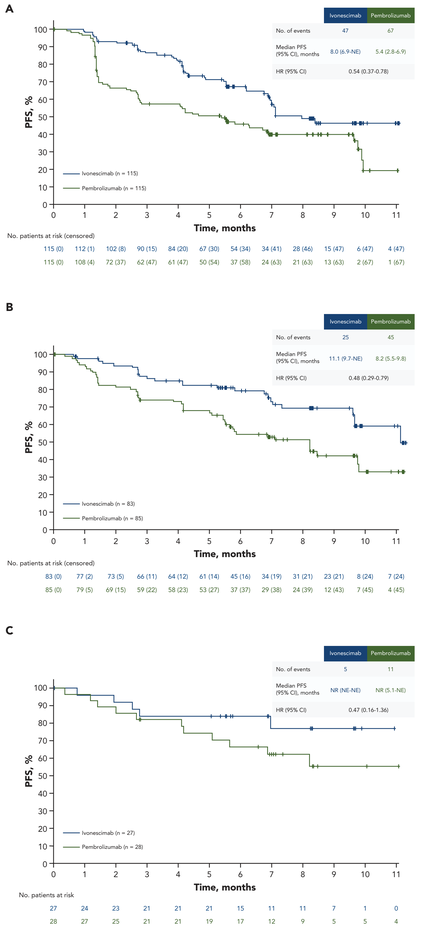
	PD-L1 TPS 1-49%		PD-L1 TPS ≥50%		PD-L1 TPS ≥90%	
	Ivonescimab n = 115	Pembrolizumab n = 115	Ivonescimab n = 83	Pembrolizumab n = 85	Ivonescimab n = 27	Pembrolizumab n = 28
Age, n (%)						
<65 years	51 (44.3)	51 (44.3)	46 (55.4)	34 (40.0)	13 (48.1)	11 (39.3)
≥65 years	64 (55.7)	64 (55.7)	37 (44.6)	51 (60.0)	14 (51.9)	17 (60.7)
Sex, n (%)						
Male	91 (79.1)	92 (80.0)	73 (88.0)	77 (90.6)	24 (88.9)	27 (96.4)
Female	24 (20.9)	23 (20.0)	10 (12.0)	8 (9.4)	3 (11.1)	1 (3.6)
Ethnicity, n (%)						
Han Chinese	113 (98.3)	114 (99.1)	80 (96.4)	84 (98.8)	27 (100)	28 (100)
Other	2 (1.7)	1 (0.9)	3 (3.6)	1 (1.2)	0	0
Smoking status, n (%)						
Never	27 (23.5)	28 (24.3)	12 (14.5)	10 (11.8)	3 (11.1)	2 (7.1)
Current	24 (20.9)	25 (21.7)	15 (18.1)	17 (20.0)	5 (18.5)	5 (17.9)
Former	64 (55.7)	62 (53.9)	56 (67.5)	58 (68.2)	19 (70.4)	21 (75.0)
ECOG PS, n (%)						
0	13 (11.3)	15 (13.0)	12 (14.5)	11 (12.9)	6 (22.2)	2 (7.1)
1	102 (88.7)	100 (87.0)	71 (85.5)	74 (87.1)	21 (77.8)	26 (92.9)
Pathology, n (%)						
Squamous	55 (47.8)	54 (47.0)	35 (42.2)	37 (43.5)	11 (40.7)	11 (39.3)
Non-squamous	60 (52.2)	61 (53.0)	48 (57.8)	48 (56.5)	16 (59.3)	17 (60.7)
Liver metastases, n (%)						
Yes	10 (8.7)	17 (14.8)	15 (18.1)	11 (12.9)	4 (14.8)	5 (17.9)
No	105 (91.3)	98 (85.2)	68 (81.9)	74 (87.1)	23 (85.2)	23 (82.1)
Brain metastases, n (%)						
Yes	25 (21.7)	25 (21.7)	8 (9.6)	14 (16.5)	4 (14.8)	5 (17.9)
No	90 (78.3)	90 (78.3)	75 (90.4)	71 (83.5)	23 (85.2)	23 (82.1)

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed cell death ligand 1; TPS, tumor proportion score.

Efficacy

- As previously reported, median PFS in the PD-L1 TPS 1-49% subgroup was 8.0 months versus 5.4 months for patients receiving ivonescimab or pembrolizumab, respectively (HR, 0.54 [95% CI, 0.37-0.78]); in the TPS ≥50% subgroup, median PFS was 11.1 months versus 8.2 months, respectively (HR, 0.48 [95% CI, 0.29-0.79]) (**Figures 1A, B**)[1]
- In this additional analysis, the median PFS in patients with PD-L1 TPS ≥90% was not reached for either treatment group (HR, 0.47 [95% CI, 0.16-1.36]) (**Figure 1C**)
- The objective response rate (ORR) in the PD-L1 TPS 1-49% subgroup was 43% versus 31% for patients treated with ivonescimab or pembrolizumab, respectively (**Table 2**)
- In the TPS ≥50% subgroup, ORR was 60% versus 48% for patients treated with ivonescimab or pembrolizumab, respectively, and in the TPS ≥90% subgroup was 63% versus 64%, respectively

Figure 2. Kaplan-Meier Curves of IRRC-Assessed PFS in Patients by PD-L1 Expression Subgroup. (A) PD-L1 TPS 1-49%[1]; (B) PD-L1 TPS ≥50%[1]; (C) PD-L1 TPS ≥90%



HR, hazard ratio; IRRC, independent radiology review committee; NE, not estimable; NR, not reached; PD-L1, programmed cell death ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

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Table 2. Summary of Overall Response by PD-L1 Expression Subgroup

	PD-L1 TPS 1-49%		PD-L1 TPS ≥50%		PD-L1 TPS ≥90%	
	Ivonescimab n = 115	Pembrolizumab n = 115	Ivonescimab n = 83	Pembrolizumab n = 85	Ivonescimab n = 27	Pembrolizumab n = 28
ORR, % (95% CI)	42.6 (33-52)[a]	31.3 (23-41)[a]	60.2 (49-71)[a]	48.2 (37-59)[a]	63.0 (42.4-80.6)	64.3 (44.1-81.4)
BOR, n (%)						
CR	0	0	1 (1.2)	0	1 (3.7)	0
PR	49 (42.6)	36 (31.3)	49 (59.0)	41 (48.2)	16 (59.3)	18 (64.3)
SD	54 (47.0)	39 (33.9)	25 (30.1)	25 (29.4)	7 (25.9)	6 (21.4)
PD	6 (5.2)	32 (27.8)	3 (3.6)	13 (15.3)	1 (3.7)	3 (10.7)
DCR, % (95% CI)	89.6 (82.5-94.5)	65.2 (55.8-73.9)	90.4 (81.9-95.7)	77.6 (67.3-86.0)	88.9 (70.8-97.6)	85.7 (67.3-96.0)
TTR, median (IQR), months	1.48 (1.38-2.79)	2.40 (1.41-2.83)	1.48 (1.38-2.76)	2.56 (1.38-2.92)	1.41 (1.38-1.51)	1.45 (1.38-2.79)

BOR, best overall response; CR, complete response; DCR, disease control rate; IQR, interquartile range; ORR, objective response rate; PD, disease progression; PD-L1, programmed cell death ligand 1; PR, partial response; SD, stable disease; TPS, tumor proportion score; TTR, time to response.

[a]The ORR for PD-L1 TPS 1-49% and ≥50% was previously published.[1]

Safety

- In the PD-L1 TPS ≥50% and ≥90% subgroups, the frequency of serious treatment-related adverse events (TRAEs) was similar across treatment groups; in the TPS 1-49% subgroup, TRAE frequency was higher in patients who received ivonescimab than with pembrolizumab (**Table 3**)

Table 3. Summary of TRAEs by PD-L1 Expression Subgroup

	PD-L1 TPS 1-49%		PD-L1 TPS ≥50%		PD-L1 TPS ≥90%	
	Ivonescimab n = 115	Pembrolizumab n = 114	Ivonescimab n = 82	Pembrolizumab n = 85	Ivonescimab n = 26	Pembrolizumab n = 28
TRAEs (all grades), n (%)	99 (86.1)	87 (76.3)	78 (95.1)	76 (89.4)	25 (96.2)	26 (92.9)
Grade ≥3	31 (27.0)	12 (10.5)	27 (32.9)	19 (22.4)	10 (38.5)	7 (25.0)
Serious TRAEs	23 (20.0)	13 (11.4)	18 (22.0)	19 (22.4)	8 (30.8)	7 (25.0)
Leading to discontinuation	1 (0.9)	2 (1.8)	2 (2.4)	4 (4.7)	2 (7.7)	2 (7.1)
Leading to death	0	1 (0.9)[a]	1 (1.2)[b]	1 (1.2)[c]	0	0

PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; TRAE, treatment-related adverse event.

[a]1 patient had respiratory failure that resulted in death.

[b]1 patient had disease progression that resulted in death.

[c]1 patient had an unknown cause of death.

- In the overall population, the most common (occurring in ≥20% of patients) TRAEs occurring in patients receiving ivonescimab were proteinuria and aspartate aminotransferase increased[1]
- When stratified by PD-L1 expression level, the most common TRAEs in patients receiving ivonescimab were proteinuria, aspartate aminotransferase increased, anemia, hypercholesterolemia, hypertriglyceridemia, and blood bilirubin increased (**Table 4**)
  - Importantly, the rates of grade ≥3 hemorrhage were similar in patients who received ivonescimab across the TPS 1-49%, ≥50%, and ≥90% subgroups (1 [1%], 1 [1%], and 1 [4%], respectively) and were similar to the rates seen in patients who received pembrolizumab (0, 1 [1%], and 0, respectively)

Table 4. Most Common TRAEs (≥20% in Either Treatment Group) by PD-L1 Expression Subgroup

	PD-L1 TPS 1-49%				PD-L1 TPS ≥50%				PD-L1 TPS ≥90%			
	Ivonescimab n = 115		Pembrolizumab n = 114		Ivonescimab n = 82		Pembrolizumab n = 85		Ivonescimab n = 26		Pembrolizumab n = 28	
Event, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Proteinuria	35 (30.4)	2 (1.7)	6 (5.3)	0	27 (32.9)	4 (4.9)	14 (16.5)	0	10 (38.5)	2 (7.7)	5 (17.9)	0
Aspartate aminotransferase increased	19 (16.5)	0	15 (13.2)	0	20 (24.4)	1 (1.2)	16 (18.8)	0	7 (26.9)	1 (3.8)	3 (10.7)	0
Anemia	15 (13.0)	2 (1.7)	12 (10.5)	0	11 (13.4)	1 (1.2)	17 (20.0)	1 (1.2)	6 (23.1)	0	2 (7.1)	0
Hypercholesterolemia	14 (12.2)	0	10 (8.8)	0	18 (22.0)	0	10 (11.8)	0	8 (30.8)	0	1 (3.6)	0
Blood bilirubin increased	12 (10.4)	0	11 (9.6)	0	19 (23.2)	2 (2.4)	12 (14.1)	1 (1.2)	6 (23.1)	1 (3.8)	4 (14.3)	1 (3.6)
Rash	10 (8.7)	1 (0.9)	16 (14.0)	0	5 (6.1)	0	12 (14.1)	0	3 (11.5)	0	6 (21.4)	0
Hypertriglyceridemia	9 (7.8)	2 (1.7)	7 (6.1)	1 (0.9)	11 (13.4)	2 (2.4)	7 (8.2)	0	7 (26.9)	1 (3.8)	0	0

PD-L1, programmed cell death ligand 1; TPS, tumor proportion score; TRAE, treatment-related adverse event.

CONCLUSIONS

- Although the study was not powered to analyze efficacy by PD-L1 subgroup, results of this analysis show evidence of numerically greater PFS benefit and higher response rate with a manageable safety profile for ivonescimab compared with pembrolizumab across all PD-L1 expression subgroups
- Results of this analysis support further evaluation of ivonescimab as monotherapy for first-line treatment of PD-L1–positive NSCLC, regardless of PD-L1 expression level

REFERENCES

1. Xiong A, et al. *Lancet*. 2025;405(10481):839-849.

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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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