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

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BACKGROUND

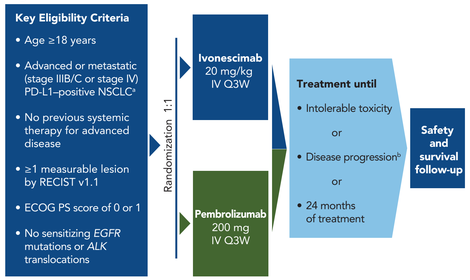
- Although immune checkpoint inhibitor–based therapy is the current first-line treatment approach for most patients with advanced non–small cell lung cancer (NSCLC) without targetable mutations, disparities remain in outcomes for squamous versus non-squamous subtypes[1]
- Ivonescimab, a first-in-class, investigational, bispecific antibody against programmed cell death protein 1 (PD-1) and vascular endothelial growth factor, was compared with pembrolizumab as first-line treatment in the phase 3 HARMONi-2 trial in patients with programmed cell death ligand 1 (PD-L1)–positive (tumor proportion score [TPS] ≥1%) advanced NSCLC[2]
  - In the primary analysis of HARMONi-2, progression-free survival (PFS) was significantly prolonged in patients treated with ivonescimab compared with pembrolizumab (median PFS, 11.14 and 5.82 months, respectively; hazard ratio, 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 squamous and non-squamous NSCLC[2]
- The objective of the current analysis of HARMONi-2 was to further assess the efficacy and safety outcomes by tumor histology subgroup

METHODS

Design

- HARMONi-2 (NCT05499390) is a randomized, double-blind, phase 3 trial comparing the efficacy and safety of ivonescimab with pembrolizumab across 55 hospitals in China (**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 nonsquamous NSCLC subtype confirmed histologically or cytologically.

[b]Confirmed by masked IRRC.

- This exploratory analysis evaluated outcomes by histology in subgroups of patients with squamous and non-squamous NSCLC

RESULTS

Patient Characteristics

- Baseline demographics and disease characteristics for the squamous (181 patients) and non-squamous (217 patients) subgroups are reported in **Table 1**
- At the January 29, 2024, data cutoff date for this analysis, the overall median duration of follow-up was 8.7 months[2]
- Median duration of exposure in the squamous subgroup for ivonescimab versus pembrolizumab was 10.8 cycles (range, 1.0-21.0 cycles) versus 8.2 cycles (range, 0.8-17.0 cycles), respectively, and in the non-squamous subgroup was 9.5 cycles (range, 0.9-19.5 cycles) versus 9.0 cycles (range, 1.0-19.6 cycles), respectively

Table 1. Baseline Patient Demographics and Disease Characteristics by Tumor Histology

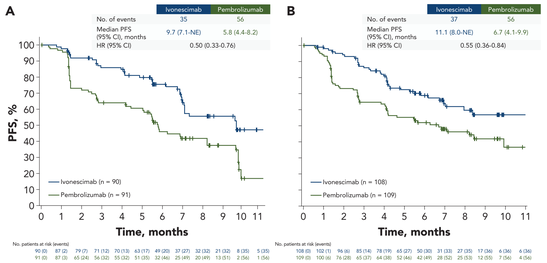
Characteristic	Squamous		Non-squamous	
	Ivonescimab n = 90	Pembrolizumab n = 91	Ivonescimab n = 108	Pembrolizumab n = 109
Age, n (%)				
<65 years	39 (43.3)	39 (42.9)	58 (53.7)	46 (42.2)
≥65 years	51 (56.7)	52 (57.1)	50 (46.3)	63 (57.8)
Sex, n (%)				
Male	80 (88.9)	86 (94.5)	84 (77.8)	83 (76.1)
Female	10 (11.1)	5 (5.5)	24 (22.2)	26 (23.9)
Ethnicity, n (%)				
Han Chinese	89 (98.9)	90 (98.9)	104 (96.3)	108 (99.1)
Other	1 (1.1)	1 (1.1)	4 (3.7)	1 (0.9)
Smoking status, n (%)				
Never	10 (11.1)	9 (9.9)	29 (26.9)	29 (26.6)
Current	21 (23.3)	23 (25.3)	18 (16.7)	19 (17.4)
Former	59 (65.6)	59 (64.8)	61 (56.5)	61 (56.0)
ECOG PS, n (%)				
0	7 (7.8)	15 (16.5)	18 (16.7)	11 (10.1)
1	83 (92.2)	76 (83.5)	90 (83.3)	98 (89.9)
PD-L1 TPS, n (%)				
1-49%	55 (61.1)	54 (59.3)	60 (55.6)	61 (56.0)
≥50%	35 (38.9)	37 (40.7)	48 (44.4)	48 (44.0)
Liver metastases, n (%)				
Yes	13 (14.4)	7 (7.7)	12 (11.1)	21 (19.3)
No	77 (85.6)	84 (92.3)	96 (88.9)	88 (80.7)
Brain metastases, n (%)				
Yes	4 (4.4)	12 (13.2)	29 (26.9)	27 (24.8)
No	86 (95.6)	79 (86.8)	79 (73.1)	82 (75.2)

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

Efficacy

- As previously reported,[2] median PFS was longer with ivonescimab than with pembrolizumab in both the squamous and the non-squamous subgroups (**Figure 2**)
- In the squamous subgroup, the objective response rate (ORR) was 53.3% versus 30.8% in patients treated with ivonescimab or pembrolizumab, respectively[2]; median duration of response (DOR) was not reached (NR; 95% CI, 8.25-not estimable [NE]) versus 8.38 months (95% CI, 5.55-NE), respectively, and median time to response (TTR) was 1.43 months (interquartile range [IQR], 1.38-2.79) versus 1.45 months (IQR, 1.38-2.76), respectively
- In the non-squamous histology subgroup, ORR was 47.2% versus 45.0% in patients treated with ivonescimab or pembrolizumab, respectively[2]; median DOR was NR (95% CI, NE-NE) versusNR (7.69-NE), and median TTR was 1.54 months (IQR, 1.38-2.76) versus 2.69 months (IQR, 1.41-3.09)
- In both the squamous and the non-squamous histology subgroups, median PFS was longer with ivonescimab than with pembrolizumab for patients who had a TPS 1-49% and those who had a TPS ≥50% (**Figures 3, 4**)

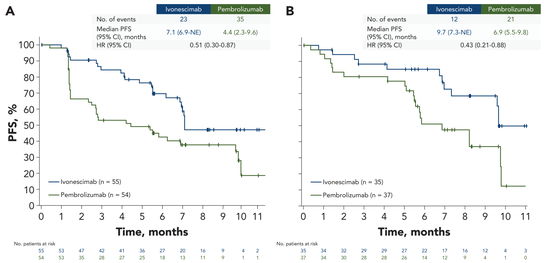
Figure 2. Kaplan-Meier Curves of IRRC-Assessed PFS. (A) Squamous and (B) Non-squamous Subgroups[2]



HR, hazard ratio; IRRC, independent radiology review committee; NE, not estimable; PFS, progression-free survival.

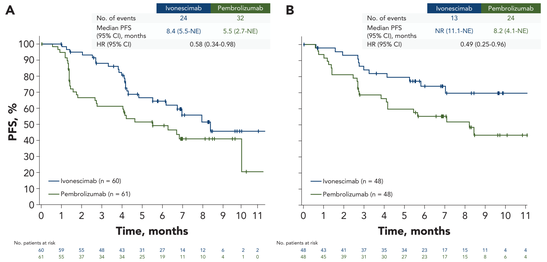
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Figure 3. Kaplan-Meier Curves of IRRC-Assessed PFS in the Squamous Subgroup. (A) TPS 1-49% and (B) TPS ≥50%



HR, hazard ratio; IRRC, independent radiology review committee; NE, not estimable; PFS, progression-free survival; TPS, tumor proportion score.

Figure 4. Kaplan-Meier Curves of IRRC-Assessed PFS in the Non-squamous NSCLC Subgroup. (A) TPS 1-49% and (B) TPS ≥50%



HR, hazard ratio; IRRC, independent radiology review committee; NE, not estimable; NR, not reached; PFS, progression-free survival; TPS, tumor proportion score.

Safety

- In the squamous subgroup, the frequency of serious treatment-related adverse events (TRAEs) was similar for patients who received either treatment; in the non-squamous subgroup, TRAE frequency was higher with ivonescimab than with pembrolizumab (**Table 2**)

Table 2. Summary of Safety Results by Tumor Histology Subgroup

	Squamous		Non-squamous	
	Ivonescimab n = 90	Pembrolizumab n = 91	Ivonescimab n = 107	Pembrolizumab n = 108
TRAEs (all grades), n (%)	77 (85.6)[a]	73 (80.2)[a]	100 (93.5)	90 (83.3)
Grade ≥3	20 (22.2)[a]	17 (18.7)[a]	38 (35.5)	14 (13.0)
Serious	17 (18.9)[a]	17 (18.7)[a]	24 (22.4)	15 (13.9)
Leading to discontinuation	2 (2.2)[a]	3 (3.3)[a]	1 (0.9)	3 (2.8)
Leading to death[a]	0	1 (1.1)[b]	1 (0.9)[c]	1 (0.9)[d]

TRAE, treatment-related adverse event.

[a]TRAEs for squamous histology were previously published.[2]

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

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

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

- In the overall population, the most common (occurring in ≥15% of patients) TRAEs that occurred in patients who received ivonescimab were proteinuria, aspartate aminotransferase increased, hypercholesterolemia, blood bilirubin increased, hypertension, alanine aminotransferase increased, and hemorrhage[1]
- When stratified by histology subgroup, the most common TRAEs that occurred in patients who received ivonescimab were proteinuria, hypothyroidism, aspartate aminotransferase increased, hypertension, hypercholesterolemia, and blood bilirubin increased (**Table 3**)
  - Importantly, the rates of grade ≥3 hemorrhage were similar in the squamous and non-squamous subgroups who received ivonescimab: 0 versus 2 patients (2%), respectively,[2] and were similar to the rates seen with pembrolizumab: 1 (1%) versus 0, respectively

Table 3. Most Common (≥15% in Either Treatment Group) TRAEs

Event, n (%)	Squamous				Non-squamous			
	Ivonescimab n = 90		Pembrolizumab n = 91		Ivonescimab n = 107		Pembrolizumab n = 108	
	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3	Any grade	Grade ≥3
Proteinuria	22 (24.4)	2 (2.2)	12 (13.2)	0	40 (37.4)	4 (3.7)	8 (7.4)	0
Hypothyroidism	21 (23.3)	0	11 (12.1)	0	7 (6.5)	0	8 (7.4)	0
Blood bilirubin increased	19 (21.1)	1 (1.1)	9 (9.9)	1 (1.1)	12 (11.2)	1 (0.9)	14 (13.0)	0
Aspartate aminotransferase increased	16 (17.8)	0	10 (11.0)	0	23 (21.5)	1 (0.9)	21 (19.4)	0
Hypertension	16 (17.8)	4 (4.4)	3 (3.3)	0	15 (14.0)	6 (5.6)	2 (1.9)	1 (0.9)
Anemia	13 (14.4)	0	16 (17.6)	0	13 (12.1)	3 (2.8)	13 (12.0)	1 (0.9)
Hypercholesterolemia	13 (14.4)	0	8 (8.8)	0	19 (17.8)	0	12 (11.1)	0
Rash	6 (6.7)	0	10 (11.0)	0	9 (8.4)	1 (0.9)	18 (16.7)	0

TRAE, treatment-related adverse event.

CONCLUSIONS

- The analysis of histology subgroups from the HARMONi-2 study shows a consistent numerically greater PFS benefit and response rate and a manageable safety profile for ivonescimab compared with pembrolizumab
- Results of this analysis support further evaluation of ivonescimab as monotherapy for first-line treatment of squamous or non-squamous PD-L1–positive NSCLC

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1. Hendriks LE, et al. *Ann Oncol*. 2023;34:358-376.
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ACKNOWLEDGMENTS

The authors thank the participants and their caregivers, the investigators, and all the site staff who have been and are participating in this study. This study is sponsored by Summit Therapeutics, Inc. Medical writing assistance was provided by MEDiSTRAVA (San Francisco, CA, USA) and was funded by Summit Therapeutics.

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

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Presented at the IASLC 2025 World Conference on Lung Cancer (WCLC); September 6-9, 2025; Barcelona, Spain