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Phase III study of ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy as first-line treatment for advanced squamous non-small cell lung cancer (HARMONi-6)

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Declaration of Interests

Shun Lu

- Received research support from AstraZeneca, Hutchison, BMS, Heng Rui, Beigene and Hansoh
- Received speaker fees from Astra Zeneca, Roche, Hansoh, Hengrui Therapeutics
- An advisor and consultant of Astra Zeneca, Pfizer, Hutchison MediPharma, ZaiLab,Yuhan Corporation, Menarini, InventisBio Co., Ltd., Shanghai Fosun Pharmaceutical (Group) Co., Ltd., Simcere Zaiming Pharmaceutical Co., Ltd.
- Independent Board member of Innovent Biologics, INC

The HARMONi-6 study was sponsored by Akeso Biopharma Inc.

Backgroud

- Several PD-(L)1 inhibitors including tislelizumab plus chemotherapy have been approved by NMPA and EMA as first-line treatment for advanced sq-NSCLC.

- Ivonescimab is a bispecific antibody targeting PD-1 and VEGF.
  - Approved in patients with non-squamous NSCLC who have experienced disease progression on EGFR-TKI therapy in China (HARMONi-A)
  - Approved in patients with PD-L1 TPS≥1% advanced NSCLC as first-line treatment in China (HARMONi-2).[1-2]

- HARMONi-6 (NCT05840016) is a randomized phase 3 study of ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy as first-line treatment for advanced sq-NSCLC.

Abbreviation: PD-(L)1, programmed death-(ligand) 1; NMPA,National Medical Products Administration; EMA, European Medicines Agency; sq, squamous; NSCLC, non-small cell lung cancer; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; TPS, tumor proportion score

1. Fang W, et al. JAMA. 2024;332(7):561-570. 2. Xiong A, et al. Lancet. 2025;405(10481):839-849.

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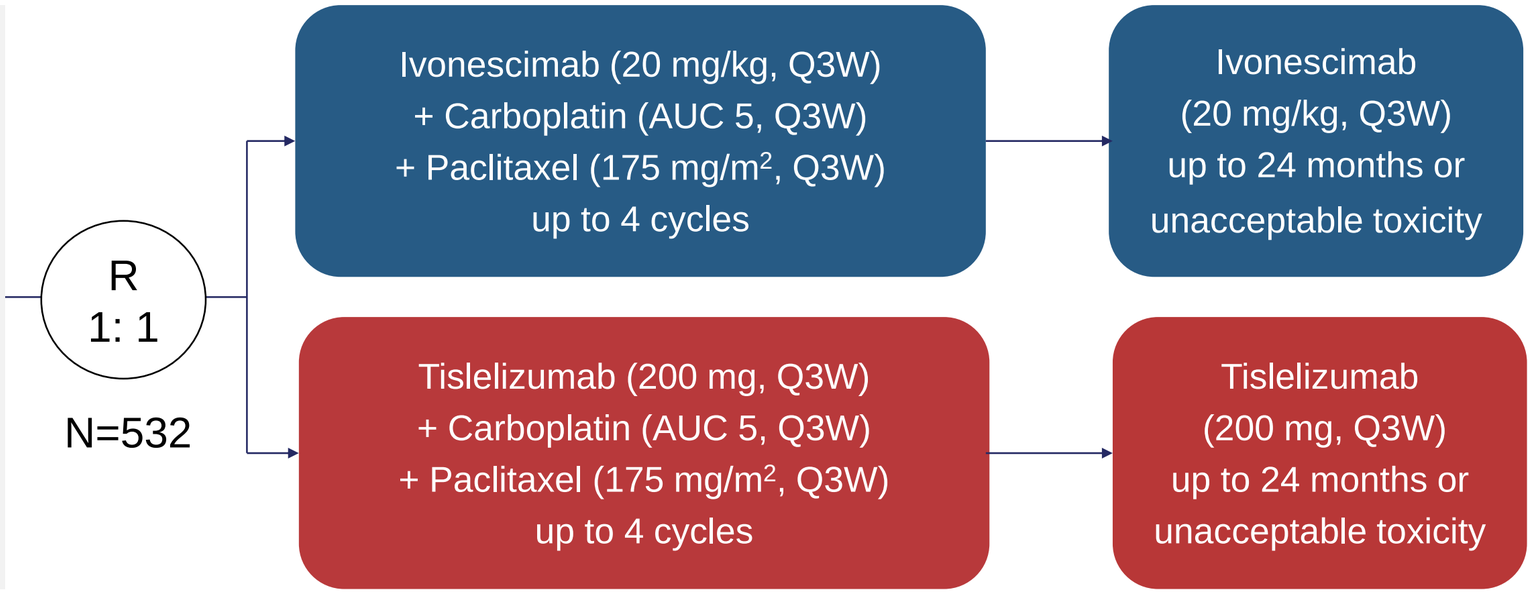
Study Design

A multicenter, randomized, double-blind, parallel-controlled phase III study

Key Eligibility Criteria

- Pathologically confirmed sq-NSCLC
- Stage IIIB-IV
- No prior systemic therapy
- No EGFR mutations or ALK rearrangements
- ECOG PS 0 or 1



Stratification Factors:

- Stage: IIIB/IIIC vs. IV
- PD-L1 TPS: ≥1% vs. <1%

Endpoints:

- **Primary endpoint: PFS by IRRC per RECIST v1.1**
- Key secondary endpoint: OS
- Secondary endpoints: PFS by INV, ORR, DCR, DoR, TTR and safety

Data cutoff date: February 28, 2025

Abbreviation: ALK, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance score; R, randomization; AUC, area under the curve; Q3W, every three weeks; IRRC, independent radiology review committee; RECIST v1.1, response evaluation criteria in solid tumors version 1.1; PFS, progression-free survival; OS, overall survival; INV, investigator; ORR, overall response rate; DCR, disease control rate; DoR, duration of response; TTR, time to response.

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Statistical Consideration

- Estimated sample size

  - N=528 were planned to provide 86.3% power for PFS assuming PFS HR=0.70 and 80% power for OS assuming OS HR=0.73.

- Hierarchical testing approach to test PFS first and OS second both at a one-sided α level of 0.025.

  - One interim PFS analysis was planned.

- This presentation is based on the prespecified PFS interim analysis:

  - Planed at 208 PFS events.

  - Actually observed 221 PFS events.

  - Corresponding statistical significant efficacy boundary: p≤ 0.0094

- OS was not mature at this time

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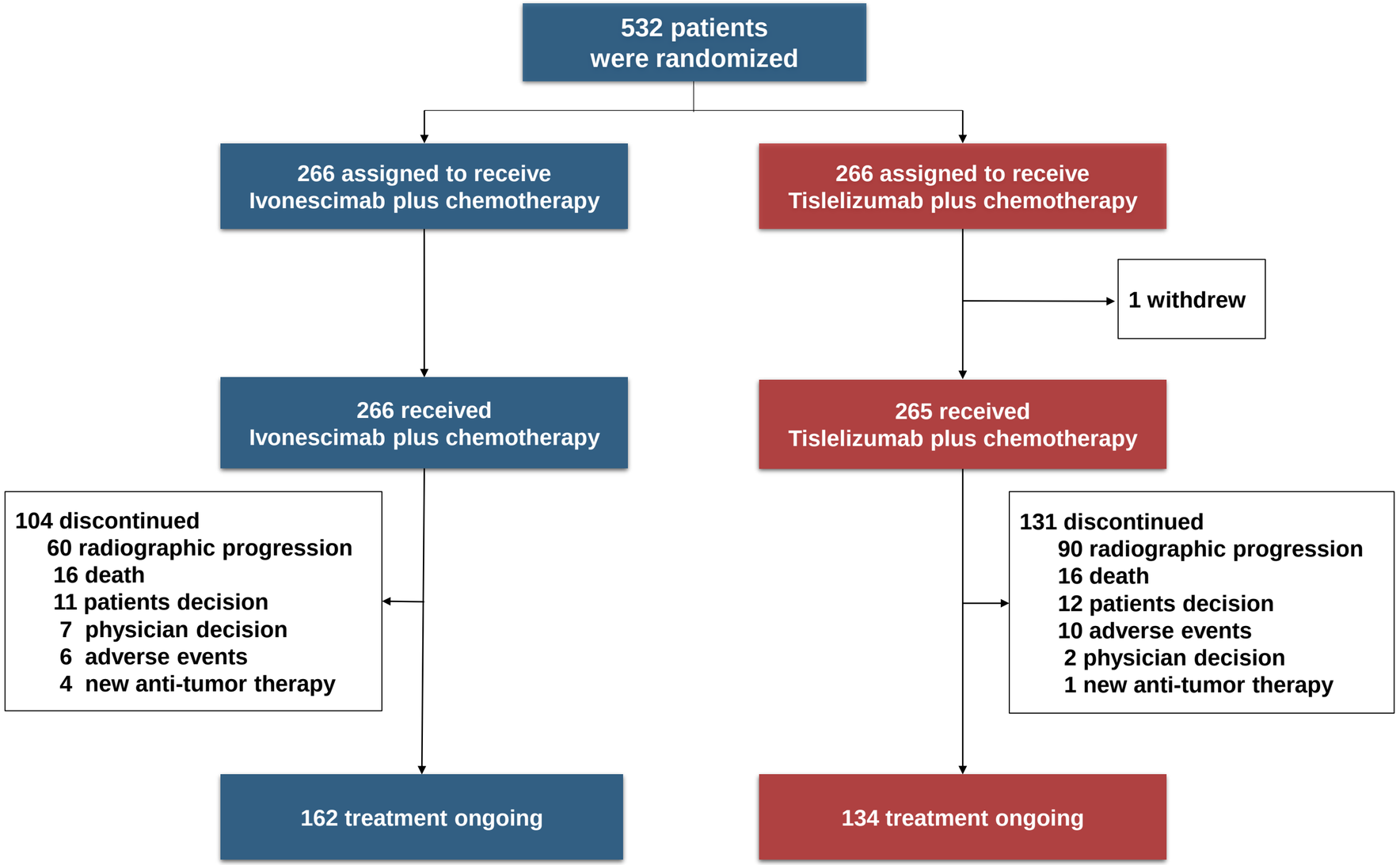
Patient Disposition



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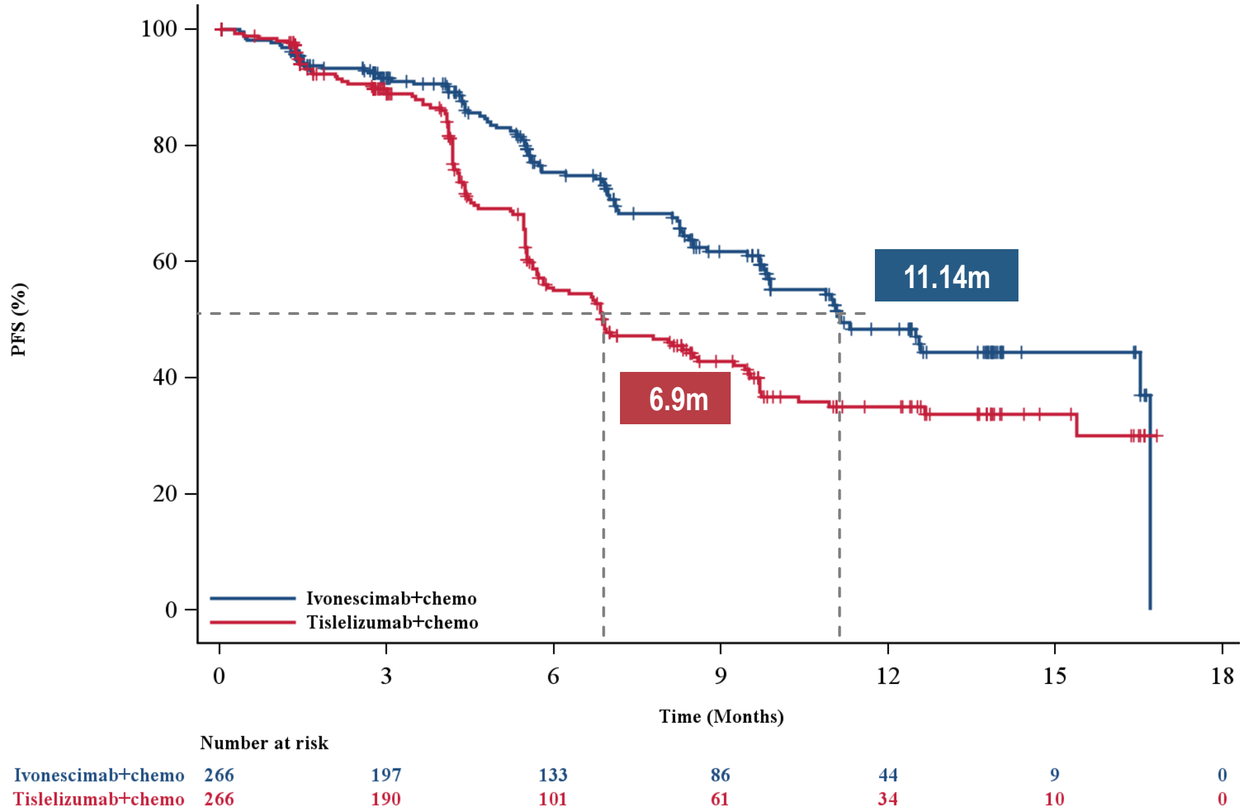
Baseline Characteristics

Characteristics, n(%)		Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=266)
Age, years	< 65	135 (50.8)	139 (52.3)
	≥ 65	131 (49.2)	127 (47.7)
Sex	Male	256 (96.2)	238 (89.5)
	Female	10 (3.8)	28 (10.5)
ECOG PS*	0	42 (15.8)	42 (15.8)
	1	224 (84.2)	222 (83.5)
Smoking history	Never	21 (7.9)	37 (13.9)
	Current/Former	245 (92.1)	229 (86.1)
Disease stage	IIIB/IIIC	21 (7.9)	20 (7.5)
	IV	245 (92.1)	246 (92.5)
Tumor characteristics	Central type	178 (66.9)	158 (59.4)
	Major blood vessel encasement	49 (18.4)	44 (16.5)
	With cavity	24 (9.0)	23 (8.6)
	With hemoptysis history	86 (32.3)	79 (29.7)
PD-L1 TPS	<1%	105 (39.5)	105 (39.5)
	≥ 1%	161 (60.5)	161 (60.5)
	1-49%	112 (42.1)	99 (37.2)
	≥ 50%	49 (18.4)	62 (23.3)
Metastases sites	≥3 metastatic sites	42 (15.8)	39 (14.7)
	Liver metastases	28 (10.5)	45 (16.9)
	Brain metastases	9 (3.4)	17 (6.4)

*Two patients' ECOG PS were missing in the tislelizumab plus chemotherapy arm.

Primary endpoint: PFS by IRRC

Ivonescimab+chemo demonstrated a statistically significant improvement in PFS vs. tislelizumab+chemo with HR=0.60, representing a 4.2 months improvement in mPFS.



	Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=266)
mPFS, months (95% CI)	**11.14** (9.86, NE)	6.90 (5.82, 8.57)
Stratified HR (95% CI)	**0.60** (0.46, 0.78)	
p-value	**<0.0001**	

Median Follow-up: 10.28 months

Consistent PFS benefit by investigator-assessment: HR = 0.64 (95% CI: 0.50, 0.84)

Abbreviation: mPFS, median progression-free survival; NE, not estimable; HR, hazard ratio; CI, confidence interval.

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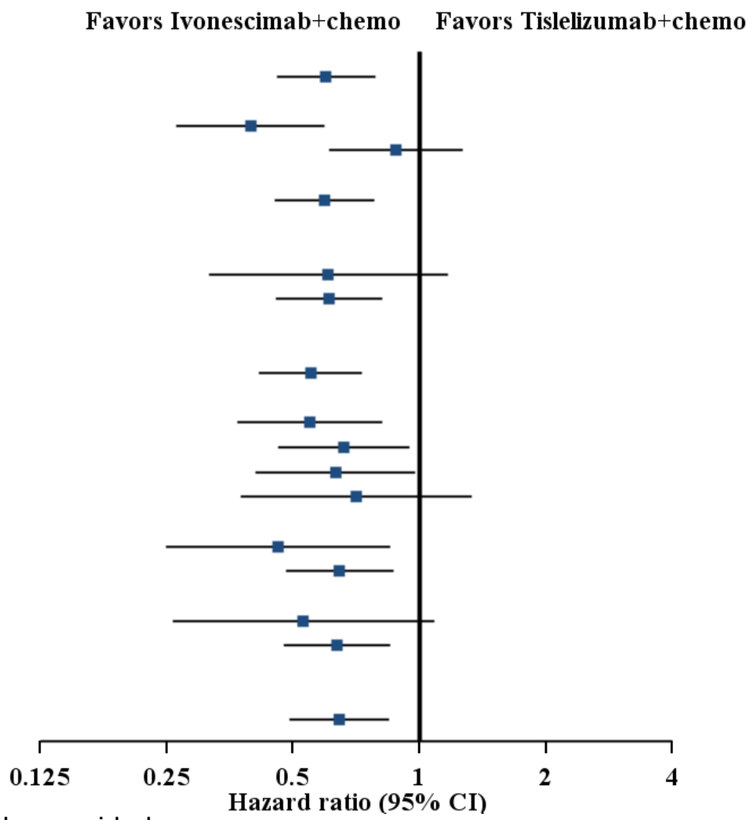
Subgroup Analysis of PFS by IRRC

- PFS benefit favored ivonescimab across all key subgroups.
- Observed important baseline imbalances in the older patient subgroup (Age ≥65), such as target lesion size, brain metastases. After adjusting for these covariates, the adjusted HR for Age ≥65 was 0.69.

Characteristic	Ivonescimab+chemo Events/Number of Subjects	Tislelizumab+chemo Events/Number of Subjects	Hazard ratio (95% CI)
Overall	94/266	127/266	0.60 (0.46, 0.78)
Age, years			
<65	37/135	69/139	0.40 (0.26, 0.59)
≥65	57/131	58/127	0.88 (0.61, 1.27)
Sex			
Male	90/256	118/238	0.59 (0.45, 0.78)
Female	4/10	9/28	
ECOG PS			
0	16/42	21/42	0.61 (0.32, 1.17)
1	78/224	106/222	0.61 (0.45, 0.82)
Disease Stage			
IIIB/IIIC	12/21	8/20	
IV	82/245	119/246	0.55 (0.41, 0.73)
PD-L1 TPS			
<1%	42/105	58/105	0.55 (0.37, 0.82)
≥1%	52/161	69/161	0.66 (0.46, 0.95)
1-49%	35/112	47/99	0.63 (0.41, 0.98)
≥50%	17/49	22/62	0.71 (0.37, 1.33)
≥3 metastases sites			
Yes	17/42	26/39	0.46 (0.25, 0.85)
No	77/224	101/227	0.64 (0.48, 0.87)
Liver metastases			
Yes	11/28	24/45	0.53 (0.26, 1.08)
No	83/238	103/221	0.64 (0.48, 0.85)
Brain metastases			
Yes	2/9	11/17	
No	92/257	116/249	0.64 (0.49, 0.85)



If the number of events at a level of a subgroup is less than 10, the median PFS and hazard ratio will not be provided.

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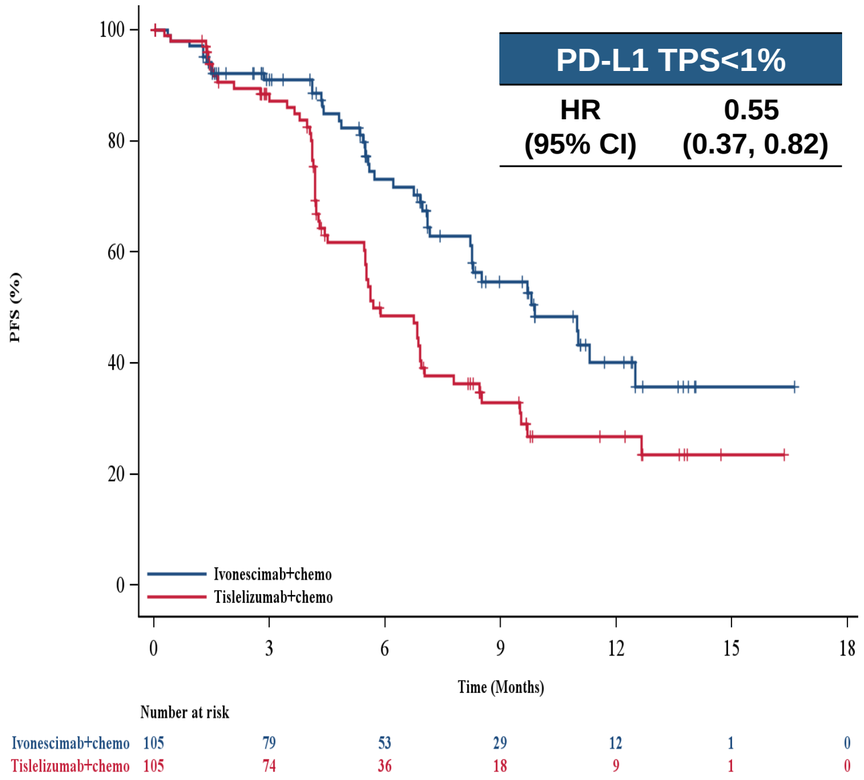
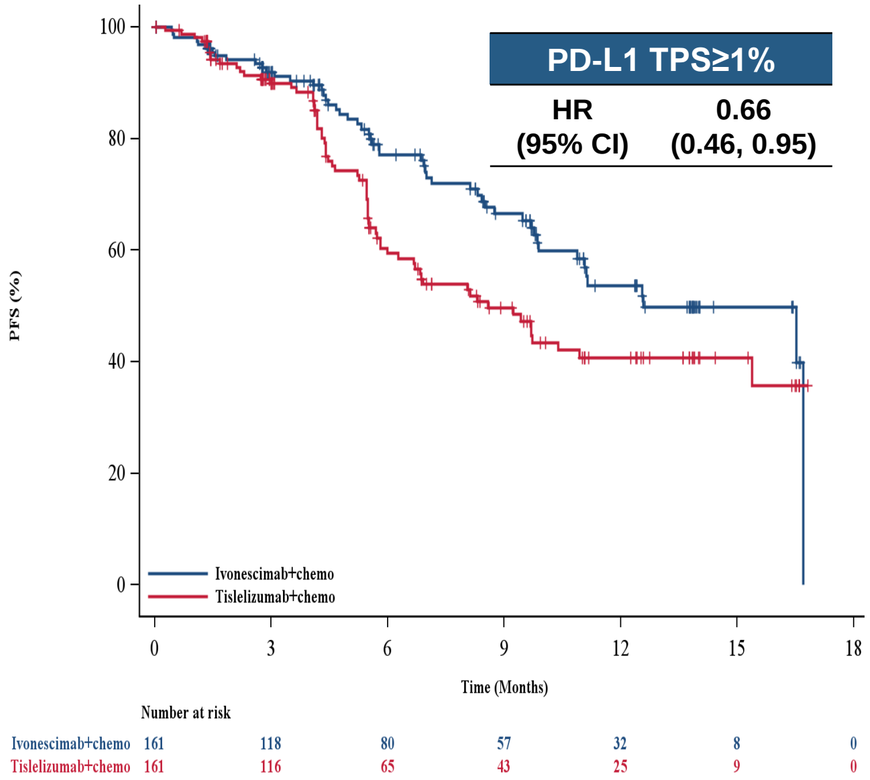
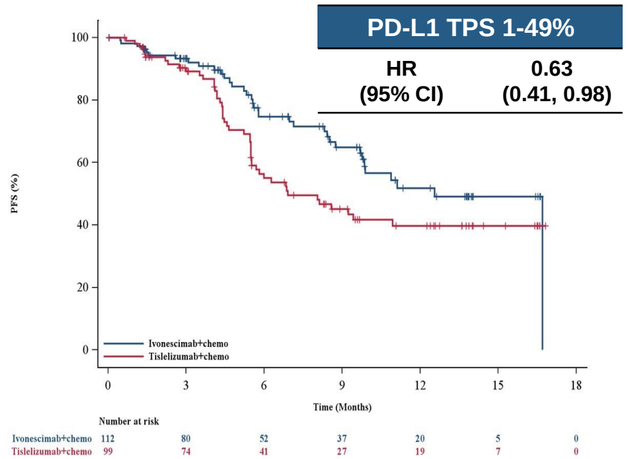
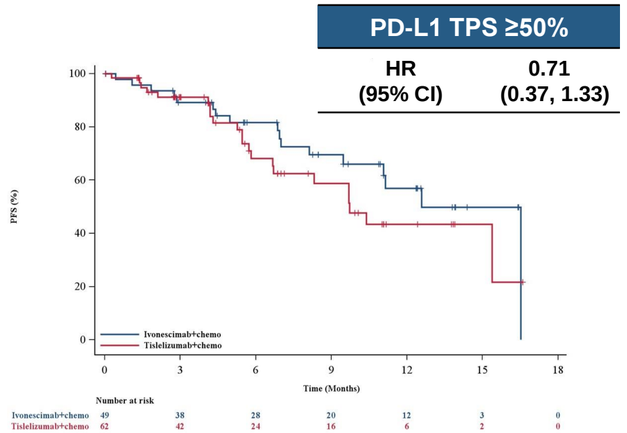
PFS in different PD-L1 expression Subgroups

Ivonescimab showed meaningful PFS improvement over tislelizumab regardless of PD-L1 expression.









Median Follow-up: 10.28 months

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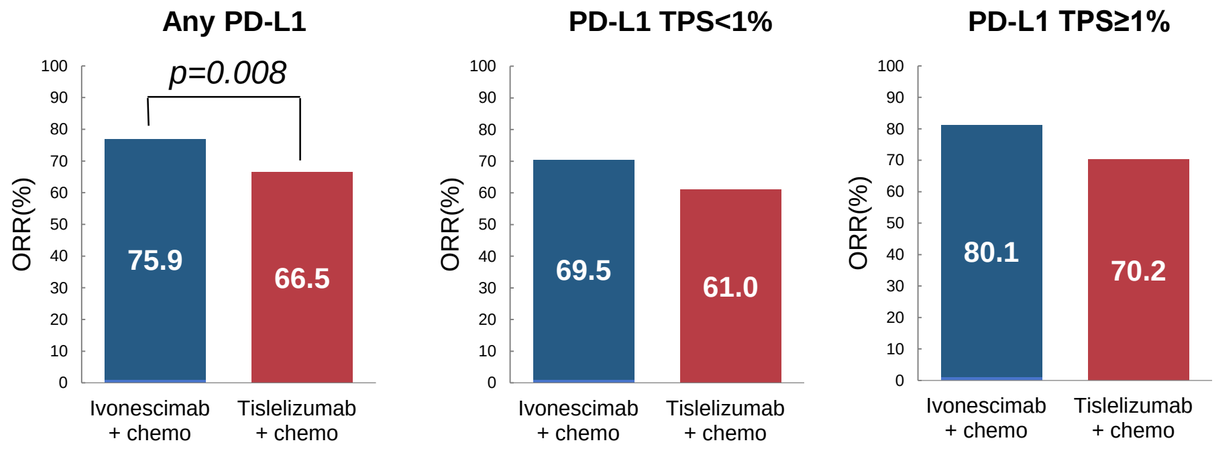
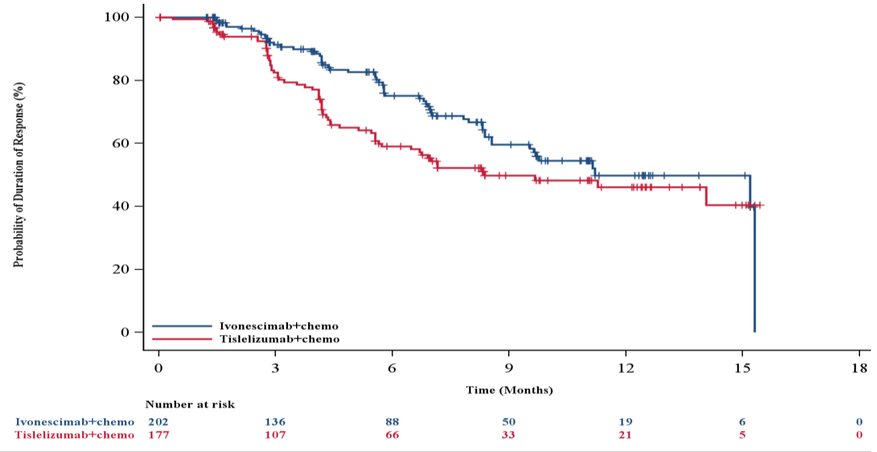
ORR and DoR by IRRC

Tumor response was higher and more durable in the ivonescimab arm.

ORR by IRRC



DoR by IRRC



	Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=266)
BOR, n (%)		
CR	1 (0.4)	0
PR	201 (75.6)	177 (66.5)
SD	39 (14.7)	60 (22.6)
PD	6 (2.3)	15 (5.6)

	Ivonescimab + chemo (N=202)	Tislelizumab + chemo (N=177)
mDoR, months (95% CI)	**11.20** (8.54, NE)	8.38 (5.72, NE)
p-value	0.0219	

Abbreviation: BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not estimated.

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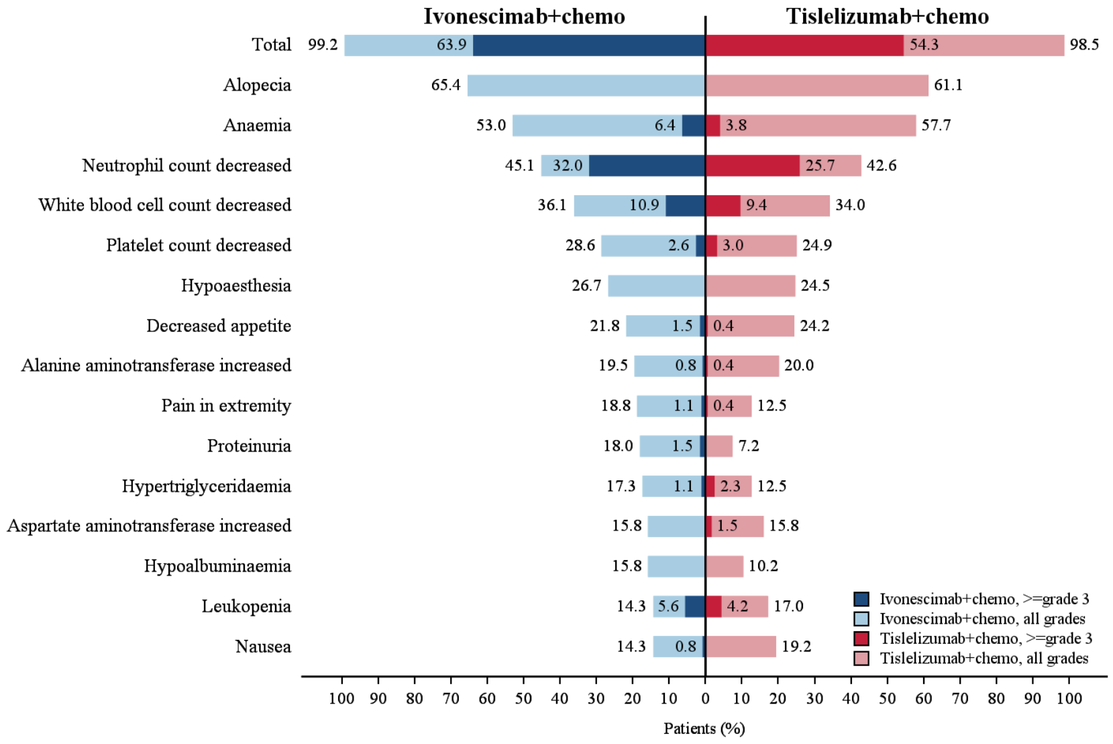
Safety Summary

Ivonescimab plus chemotherapy showed a manageable safety profile in sq-NSCLC.

	Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=265)
TRAE	264 (99.2)	261 (98.5)
Grade ≥ 3 TRAE	170 (63.9)	144 (54.3)
Serious TRAE	86 (32.3)	80 (30.2)
Leading to ivonescimab or tislelizumab discontinuation	9 (3.4)	11 (4.2)
Leading to death	8 (3.0)	10 (3.8)

Most common TRAEs (incidence ≥15%)



Abbreviation: TRAE, treatment-related adverse events.

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Immune-Related and VEGF-Related AEs

Ivonescimab exhibited similar irAEs to tislelizumab.

Immune-related AEs	Ivonescimab + chemo (N=266)	Tislelizumab + chemo (N=265)
Any grade	73 (27.4)	67 (25.3)
Grade ≥3 irAE	24 (9.0)	27 (10.2)
Serious irAE	23 (8.6)	26 (9.8)
Leading to ivonescimab or tislelizumab discontinuation	3 (1.1)	6 (2.3)
Leading to death	0	1 (0.4)

Possibly VEGF-related AEs occurred more frequently in the ivonescimab arm, most of which were grade 1-2.

Possibly VEGF-Related AEs[#]	Ivonescimab + chemo (N=266)		Tislelizumab + chemo (N=265)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	123 (46.2)	20 (7.5)	60 (22.6)	6 (2.3)
Proteinuria	72 (27.1)	6 (2.3)	29 (10.9)	0
Haemorrhage	57 (21.4)	5 (1.9)	25 (9.4)	2 (0.8)
Hypertension	27 (10.2)	8 (3.0)	12 (4.5)	3 (1.1)
Arterial thromboembolism	3 (1.1)	3 (1.1)	0	0
Venous thromboembolism	2 (0.8)	0	3 (1.1)	1 (0.4)
Fistula	1 (0.4)	0	0	0

[#] AE terms were grouped terms.

Abbreviation: VEGF, vascular endothelial growth factor; AEs, adverse events; irAEs, immune-related adverse events.

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Conclusion

- Ivonescimab plus chemotherapy significantly improved PFS for advanced sq-NSCLC first-line treatment compared with tislelizumab plus chemotherapy.
  - **mPFS: 11.14 vs. 6.90, HR=0.60 (95%CI: 0.46, 0.78), p<0.0001**
  - PFS benefit favored ivonescimab plus chemotherapy across all key subgroup
    - **PD-L1 TPS＜1%: HR=0.55; TPS≥ 1%: HR=0.66**
- Tumor response was higher and more durable in the ivonescimab plus chemotherapy arm.
- OS was not matured at this time and will be reported later.
- Ivonescimab plus chemotherapy showed a manageable safety profile in sq-NSCLC, consistent with previous experience.

Ivonescimab plus chemothrapy showed significant efficacy improvement with manageable safety profile and might be a new standard of care for advanced sq-NSCLC.

Shun Lu

Acknowledgement

- All patients participating in the study as well as their families.
- All investigators and team members involved in this trial.
- Akeso Biopharma Inc. who sponsored this study.

Ivonescimab plus chemotherapy versus tislelizumab plus chemotherapy as first-line treatment for advanced squamous non-small-cell lung cancer (HARMONi-6): a randomised, double-blind, phase 3 trial

Zhiwei Chen, Fang Yang*, Zhou Jiang*, Longhua Sun*, Lin Wu*, Zhengxiang Han, Yun Fan, Yanqiu Zhao, Xingya Li, Haipeng Xu, Xiangjiao Meng, Ying Liu, Zhiye Zhang, Hui Luo, Xuelei Ma, Xuezhen Ma, Qin Shi, Zhongmin Zhang, Runxiang Yang, Pingli Wang, Pinhua Pan, Xiaohong Ai, Jie Li[1], Xingxiang Pu, Zhiwu Wang, Jian Fang, Ming He, Yong He, Shuliang Guo, Juan Li, Hongbiao Wang, Junqiang Zhang, Qian Chu, Xuewen Liu, Shenpeng Ying, Hongcheng Wu, Hongmei Sun, Yinghua Ji, Ming Zhou, Chao Cao, Kejing Tang, Zhengguo Li, Dairong Li, Zhihong Zhang, Jie Li[2], Jianya Zhou, Hongzhong Yang, Yingying Du, Hui Yang, Jian Shi, Hualin Chen, Wenting Li, Dongmei Lu, Mingxiu Hu, Zhongmin Maxwell Wang, Baiyong Li, Michelle Xia, Shun Lu*

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