YUMC Yeungnam University Medical Center

Emerging Treatment Options and Future Strategies in Advanced Lung Squamous Cell Carcinoma

제21회 대한결핵 및 호흡기학회 폐암 심포지엄

영 남 의 대
안 준 홍

Contents

- Unmet needs in treatment of LUSC
- Bispecific antibody
- ICI combinations
- ADC
- Summary

Contents

- Unmet needs in treatment of LUSC
- Bispecific antibody
- ICI combinations
- ADC
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NCCN guideline

PD-L1 ≥50% FIRST-LINE THERAPY (PS 0–2)

Preferred
- Pembrolizumab (category 1)[54,55]
- Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[66]
- Atezolizumab[e] (category 1)[58]
- Cemiplimab-rwlc (category 1)[59]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[60]

Other Recommended
- Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)[63]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel (category 2B)[64]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine (category 2B)[64]

Useful in Certain Circumstances
- Nivolumab + ipilimumab (category 1)[65]

PD-L1 ≥1%–49% FIRST-LINE THERAPY (PS 0–2)

Preferred
- Carboplatin + (paclitaxel or albumin-bound paclitaxel) + pembrolizumab (category 1)[66]
- Cemiplimab-rwlc + paclitaxel + (carboplatin or cisplatin) (category 1)[60]

Other Recommended
- Nivolumab + ipilimumab + paclitaxel + carboplatin (category 1)[63]
- Nivolumab + ipilimumab (category 1)[65]
- Tremelimumab-actl + durvalumab + carboplatin + albumin-bound paclitaxel[64]
- Tremelimumab-actl + durvalumab + (carboplatin or cisplatin) + gemcitabine[64]

Useful in Certain Circumstances
- Pembrolizumab (category 2B)[n,54,55]

SQUAMOUS CELL CARCINOMA (PS 0–2)

Preferred (no previous IO)

Systemic ICIs
- Nivolumab (category 1)
- Pembrolizumab[k] (category 1)
- Atezolizumab (category 1)

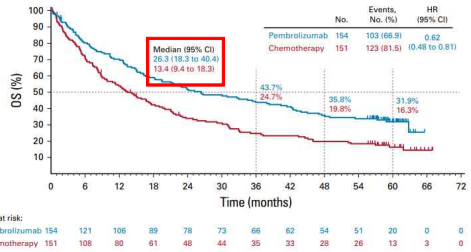
Other Recommended (no previous IO or previous IO)[n]
- Docetaxel
- Gemcitabine
- Docetaxel + Ramucirumab
- Albumin-bound Paclitaxel
- Fam-trastuzumab deruxtecan-nxki (HER2 IHC 3+)

INITIAL

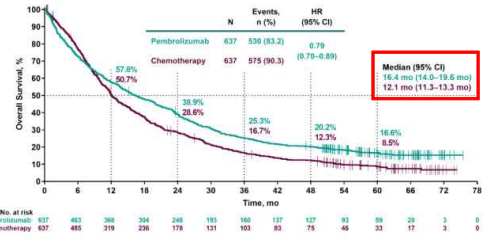
SUBSEQUENT

Advancing LUSC Therapy: Progress and Remaining Challenges

KEYNOTE-024 (PD-L1 ≥50%), mPFS 7.7 months
mOS 26.3 months



KEYNOTE-042 (PD-L1 ≥1%), mPFS 5.6 months
mOS 16.4 months

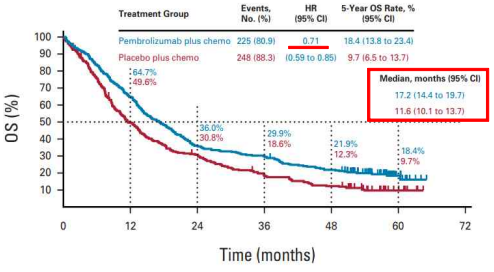


Subgroup HR for OS (SQ 0.76 vs. NSQ 0.81)

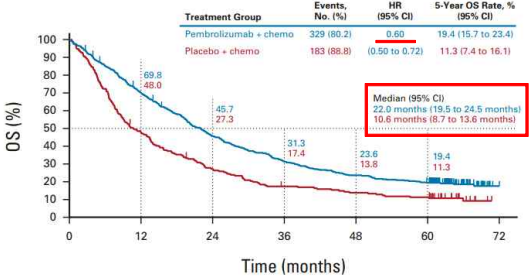
J Clin Oncol. 2023 Apr 10;41(11):1986-1991
J Clin Oncol. 2021 Jul 20;39(21):2339-2349

Advancing LUSC Therapy: Progress and Remaining Challenges

KEYNOTE-407 (LUSC), mPFS 8.0 months
mOS 17.2 months



KEYNOTE-189 (LUAD), mPFS 9.0 months
mOS 22.0 months



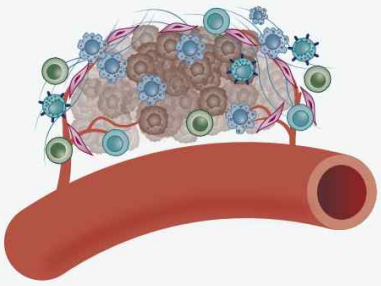
J Clin Oncol. 2023 Apr 10;41(11):1992-1998
J Clin Oncol. 2023 Apr 10;41(11):1999-2006

Current unmet needs in treatment of LUSC

- Lack of actionable driver mutations
- Limited 2L options post-IO Failure
- Resistance mechanisms & "cold tumors"
- Safety & comorbidity challenges

Speaker's Perspective

Molecular biology of LUSC



③ Tumor immune microenvironment

3.1 Cold TIME with high CNV burden

3.2 Higher immune heterogeneity than LUAD

3.3 Cellular composition

Neutrophils, Th1/2 cells, TILs, SPP1-macrophage, and CAFs

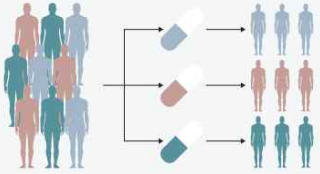
3.4 Therapeutic strategies

Current checkpoint targets: PD-1, PD-L1, CTLA-4

Emerging checkpoint targets: TIGIT, TIM-3, LAG-3, CD73, B7-H3

Anti-angiogenesis: VEGF, VEGFR

CIK cell therapy, TIL therapy, and FMT



⑤ TAA-based immunotherapy

5.1 Targeting membrane receptors

EGFR, ERBB2, FGFR1, DDR2, MET, ALK, ROS1, and TROP2

5.2 ACT immunotherapy

CAR T cell therapy and TIL therapy

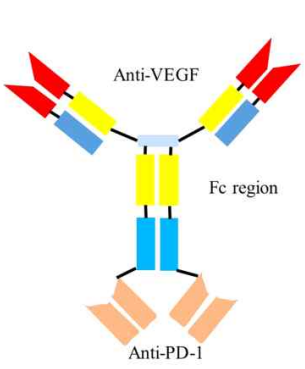
5.3 Cancer vaccines

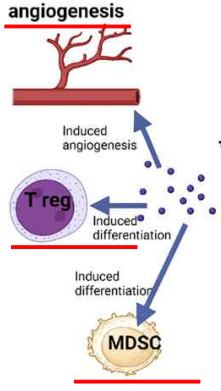
Ann Oncol. 2026 Mar;37(3):289-313

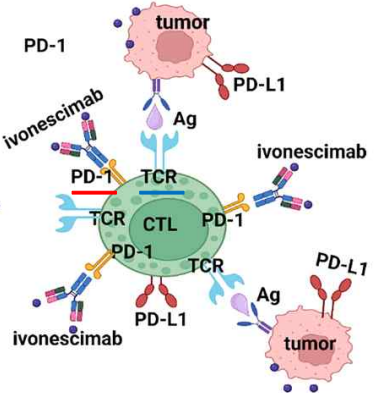
Contents

Ivonescimab

A first-in-class, investigational, bispecific antibody targeting **PD-1 and VEGF**







Front Immunol. 2025 Nov 17:16:1599181

Phase 3 Study of Ivonescimab (AK112) vs. Pembrolizumab as First-line Treatment for PD-L1-positive Advanced NSCLC: HARMONi-2

C. Zhou[1,2], J. Chen[3], L. Wu[3], L. Wang[1], A. Xiong[1], B. Liu[4], J. Yao[5], H. Zhong[6], J. Li[7], Y. Cheng[8], Y. Sun[9], H. Ge[10], Q. Shi[11], M. Zhou[12], Z. Han[13], J. Wang[14], Q. Bu[15], Y. Zhao[16], J. Chen[17], J. Yang[18], M. Xia[18]

[1]Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai/CN; [2]East Hospital Affiliated To Tongji University, shanghai/CN; [3]Hunan Cancer Hospital, Changsha/CN; [4]Harbin Medical University Cancer Hospital, Harbin/CN; [5]The First Affiliated Hospital of Henan University of Science and Technology, Luoyang/CN; [6]Shanghai Chest Hospital, Shanghai/CN; [7]The First Affiliated Hospital of Gannan Medical University, Ganzhou/CN; [8]Jilin Cancer Hospital, Changchun/CN; [9]Shandong Cancer Hospital and Institute, Jinan/CN; [10]The Fourth Hospital of Hebei Medical University, Shijiazhuang/CN; [11]Fuzhou Tuberculosis Prevention and Treatment Hospital, Fuzhou/CN; [12]Affiliated Cancer Hospital and Institute of Guangzhou Medical University, Guangzhou/CN; [13]The Affiliated Hospital of Xuzhou Medical University, Xuzhou/CN; [14]The Fifth Medical Center of the General Hospital of Chinese People's Liberation Army, Beijing/CN; [15]The First affiliated hospital of Guangxi Medical University, Nanning/CN; [16]Henan Cancer Hospital, Zhengzhou/CN; [17]Fujian Cancer Hospital, Fuzhou/CN; [18]Akeso Biopharma, Inc., Zhongshan/CN

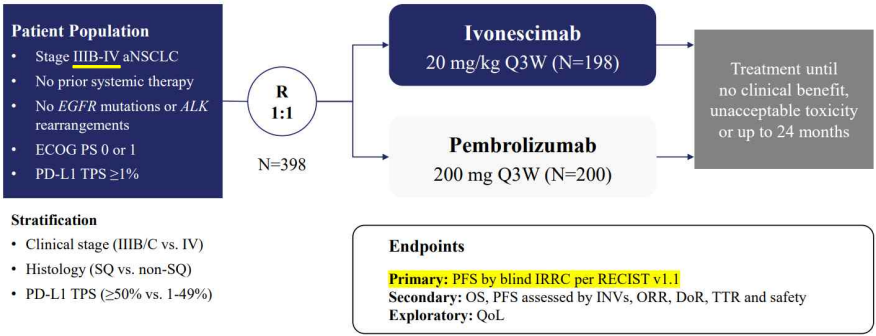
Ivonescimab versus pembrolizumab for PD-L1-positive non-small cell lung cancer (HARMONi-2): a randomised, double-blind, phase 3 study in China

Aiwen Xiong*, Lei Wang*, Jianhua Chen*, Lin Wu*, Baogang Liu, Jun Yao, Hua Zhang, Jie Li, Ying Cheng, Yulan Sun, Hui Ge, Jijiang Yao, Qin Shi, Ming Zhou, Bolin Chen, Zhengxiang Han, Jinliang Wang, Qing Bu, Yanqiu Zhao, Junjiang Chen, Lijiang Mei, Gaofeng Li, Xingyu Li, Xinmin Yu, Yinghua Ji, Daqiang Sun, Xiaohang Ai, Qian Chu, Yu Lin, Jiqing Hao, Dengfu Huang, Chengzhi Zhao, Jielu Shen, Hongzhuang Yang, Xuewen Liu, Jing Wang, Yanhong Deng, Xiaodong Mu, Jin Yang, Dongmei Lu, Mingyao Hu, Zhongmin Maxwell Wang, Baiyang Li, Michelle Xia, Caicun Zhou

Lancet. 2025 Mar 8;405(10481):839-849
WCLC 2024 Congress

Study design

A randomized, double-blind, phase 3 study[a]



[a] Patients were randomized from November 2022 to August 2023. Data cut off: January 29, 2024.

Abbreviations: aNSCLC, advanced non-small cell lung cancer; *EGFR*, epidermal growth factor receptor; *ALK*, anaplastic lymphoma kinase; ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death ligand 1; TPS, tumor proportion score; R, randomization; SQ, squamous cell carcinoma; Q3W, every three weeks; PFS, progression-free survival; IRRC, independent radiology review committee; OS, overall survival; INV, investigator; ORR, overall response rate; DoR, duration of response; TTR, time to response; QoL, quality of life.

Lancet. 2025 Mar 8;405(10481):839-849
WCLC 2024 Congress

Baseline characteristics

Characteristics, n (%)		Ivonescimab (n = 198[a])	Pembrolizumab (n = 200[a])	Total (n = 398[a])
Age (years)	<65	97 (49.0)	85 (42.5)	182 (45.7)
	≥65	101 (51.0)	115 (57.5)	216 (54.3)
Sex	Male	164 (82.8)	169 (84.5)	333 (83.7)
	Female	34 (17.2)	31 (15.5)	65 (16.3)
ECOG PS	0	25 (12.6)	26 (13.0)	51 (12.8)
	1	173 (87.4)	174 (87.0)	347 (87.2)
Smoker	Never	39 (19.7)	38 (19.0)	77 (19.3)
	Current	39 (19.7)	42 (21.0)	81 (20.4)
	Former	120 (60.6)	120 (60.0)	240 (60.3)
Clinical stage	IIIB/C	15 (7.6)	16 (8.0)	31 (7.8)
	IV	183 (92.4)	184 (92.0)	367 (92.2)
Pathology	SQ	90 (45.5)	91 (45.5)	181 (45.5)
	Tumor centrally located[b]	65 (72.2)	57 (62.6)	122 (67.4)
	Tumor with cavitation/necrosis[b]	9 (10.0)	7 (7.7)	16 (8.8)
	Tumor encasing large blood vessel[b]	6 (6.7)	1 (1.1)	7 (3.9)
	Non-SQ	108 (54.5)	109 (54.5)	217 (54.5)
PD-L1 TPS	≥50%	83 (41.9)	85 (42.5)	168 (42.2)
	1-49%	115 (58.1)	115 (57.5)	230 (57.8)
Liver metastases	Yes	25 (12.6)	28 (14.0)	53 (13.3)
	No	173 (87.4)	172 (86.0)	345 (86.7)
Brain metastases	Yes	33 (16.7)	39 (19.5)	72 (18.1)
	No	165 (83.3)	161 (80.5)	326 (81.9)

KN042

38%

47%

5%

[a] Patients who received randomization. [b] In 181 patients with SQ.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance score; PD-L1, programmed death ligand 1; TPS, tumor proportion score; SQ, squamous ce

Lancet. 2025 Mar 8;405(10481):839-849
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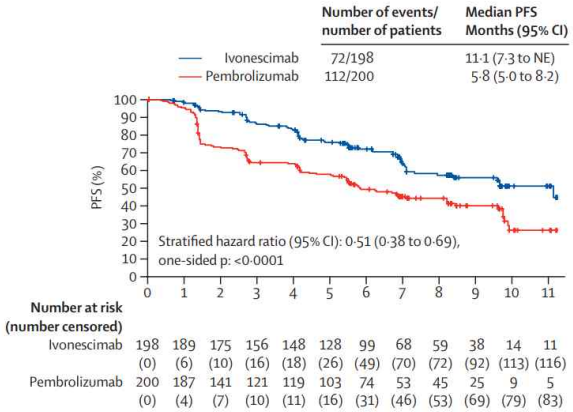
Primary endpoint: PFS by IRRC

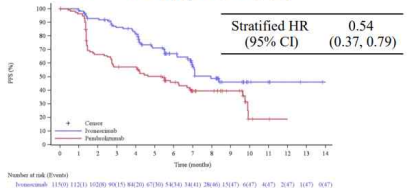


Lancet. 2025 Mar 8;405(10481):839-849
WCLC 2024 Congress

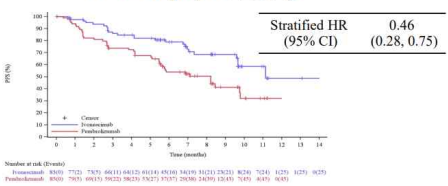
Key PFS subgroup analysis

PD-L1 expression

PD-L1 Low (TPS 1-49%)

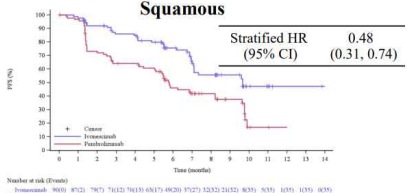


PD-L1 High (TPS ≥50%)

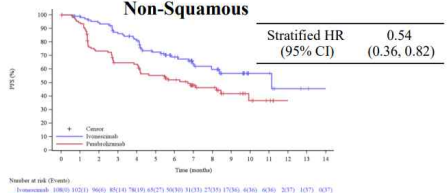


NSCLC Histology

Squamous

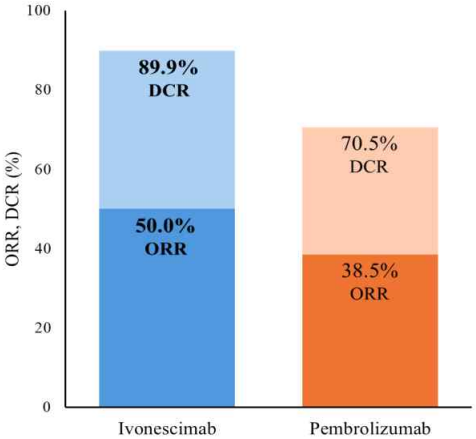


Non-Squamous



Lancet. 2025 Mar 8;405(10481):839-849
WCLC 2024 Congress

ORR and DoR by IRRC



	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
ORR, % (95% CI)	**50.0** (42.8, 57.2)	38.5 (31.7, 45.6)
DCR, % (95% CI)	**89.9** (84.8, 93.7)	70.5 (63.7, 76.7)
Median DoR, mos (95% CI)	**NR** (NE, NE)	NR (8.28, NE)

ORR and DCR were higher with ivonescimab vs. pembrolizumab.

Lancet. 2025 Mar 8;405(10481):839-849
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Safety Summary

TRAEs

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
TRAEs (all grades)	177 (89.8)	163 (81.9)
Grade≥3	58 (29.4)	31 (15.6)
Serious TRAEs	41 (20.8)	32 (16.1)
Leading to discontinuation	3 (1.5)	6 (3.0)
Leading to death	1 (0.5)	2 (1.0)

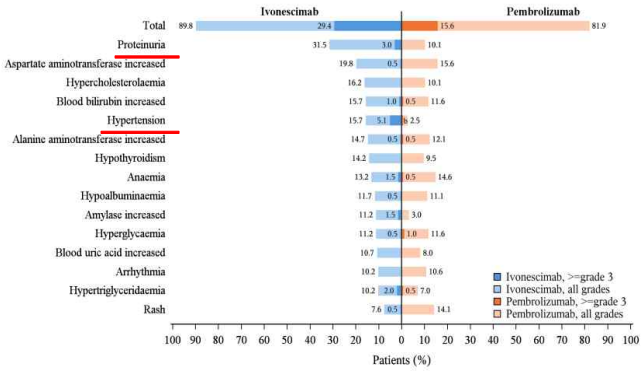
Ivonescimab showed a manageable safety profile, which was consistent with previous studies.

TRAEs in SQ Subgroup

Safety Summary, n (%)	Ivonescimab (n = 90[a])	Pembrolizumab (n = 91[a])
TRAEs (all grades)	77 (85.6)	73 (80.2)
Grade≥3	20 (22.2)	17 (18.7)
Serious TRAEs	17 (18.9)	17 (18.7)
Leading to discontinuation	2 (2.2)	3 (3.3)
Leading to death	0	1 (1.1)

Ivonescimab also demonstrated a tolerable safety profile in SQ patients.

The Most Common TRAEs (incidence ≥10%)



The differences in AEs were predominantly proteinuria, hypertension, and laboratory abnormalities.

Lancet. 2025 Mar 8;405(10481):839-849
WCLC 2024 Congress

irAE and VEGF-Related AEs

irAEs

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
irAEs (all grades)	59 (29.9)	56 (28.1)
Grade≥3	14 (7.1)	16 (8.0)
Serious irAEs	11 (5.6)	22 (11.1)
Leading to discontinuation	0	5 (2.5)
Leading to death	0	0

Ivonescimab exhibited similar irAEs to that of pembrolizumab.

Possible VEGF-Related AEs

Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
Possible VEGF-Related AEs (all grades)	94 (47.7)	42 (21.1)
Grade≥3	20 (10.2)	2 (1.0)

Safety Summary by Classification, n (%)	Ivonescimab (n = 197[a])		Pembrolizumab (n = 199[a])	
	All Grade	Grade≥3	All Grade	Grade≥3
Proteinuria	62 (31.5)	6 (3.1)	20 (10.1)	0
Hypertension	31 (15.7)	10 (5.1)	5 (2.5)	1 (0.5)
Haemorrhage	29 (14.7)	2 (1.0)	22 (11.1)	1 (0.5)
Arterial thromboembolism	2 (1.0)	2 (1.0)	1 (0.5)	0
Venous thromboembolism	0	0	1 (0.5)	0

- All VEGF-related AEs were grades 1-3 in both arms.
- Grade 3 haemorrhage was observed in two patients with non-SQ and was not reported in SQ patients in the ivonescimab arm.

[a] Patients who received ≥1 dose of study treatment.
Abbreviations: VEGF, vascular endothelial growth factor; irAEs, immune-related AEs; AEs, adverse events; SQ, squamous cell carcinoma.

Lancet. 2025 Mar 8;405(10481):839-849
WCLC 2024 Congress

BERLIN 2025 ESMO congress

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)

Shun Lu[1], Fang Yang[2], Zhou Jiang[3], Longhua Sun[4], Lin Wu[3], Zhengxiang Han[5], Yun Fan[6], Yanqiu Zhao[7], Xingya Li[8], Haipeng Xu[9], Xiangjiao Meng[10], Ying Cheng[11], Zhiye Zhang[12], Zhiwei Chen[1], Hui Luo[13], Qin Shi[14], Xuelei Ma[15], Xuezhen Ma[16], Zhongmin Zhang[17], Michelle Xia[18]

[1]Shanghai Chest Hospital, Shanghai, China; [2]Harbin Medical University Cancer Hospital, Harbin, China; [3]Hunan Cancer Hospital, Changsha, China; [4]The First Affiliated Hospital of Nanchang University, Nanchang, China; [5]The Affiliated Hospital of Xuzhou Medical University, Xuzhou, China; [6]Zhejiang Cancer Hospital, Hangzhou, China; [7]Henan Cancer Hospital, Zhengzhou, China; [8]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [9]Fujian Provincial Tumor Hospital, Fuzhou, China; [10]Shandong Cancer Hospital and Institute, Jinan, China; [11]Jilin Cancer Hospital, Changchun, China; [12]The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China; [13]Jiangxi Cancer Hospital, Nanchang, China; [14]Fuzhou pulmonary hospital of fujian, Fuzhou, China; [15]West China Hospital of Sichuan University, Chengdu, China; [16]Qingdao Central Hospital, Qingdao, China; [17]Linyi People's Hospital, Linyi, China; [18]Akeso Biopharma, Inc., Zhongshan, China.

19 October 2025

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

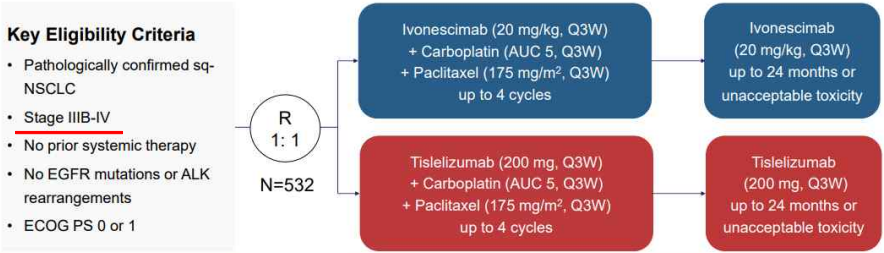
Zhiwei Chen*, Fang Yang*, Zhou Jiang*, Longhua Sun*, Lin Wu*, Zhengxiang Han, Yun Fan, Yanqiu Zhao, Xingya Li, Haipeng Xu, Xiangjiao Meng, Ying Liu, Zhiye Zhang, Hui Luo, Xuelei Ma, Xuezhen Ma, Qin Shi, Zhongmin Zhang, Xunxiang Yang, Pingli Wang, Pinhua Pan, Xiaohong Ai, Jie Li, Xingxiang Pu, Zhiwu Wang, Jian Fang, Ming He, Yong He, Shukang Gao, Juan Li, Hongbin Wang, Junqing Zhang, Qian Chu, Xunwen Liu, Shenpeng Ying, Hongsheng Wu, Hongmei Sun, Yinghua Ji, Ming Zhou, Chao Cao, Keying Tang, Zhengyu Li, Dairong Li, Zhihong Zhang, Jin Li, Jianya Zhou, Hongzhong Yang, Yingxing Du, Hui Yang, Jian Shi, Hualin Chen, Wenting Li, Dongmei Lu, Mingxiu Hu, Zhongmin Maxwell Wang, Reivona Li, Michelle Xia, Shun Lu

Lancet 2025; 406: 2078–88

ESMO EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY

Study design

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



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.

Lancet. 2025 Nov 1;406(10515):2078-2088
ESMO 2025 Congress

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.

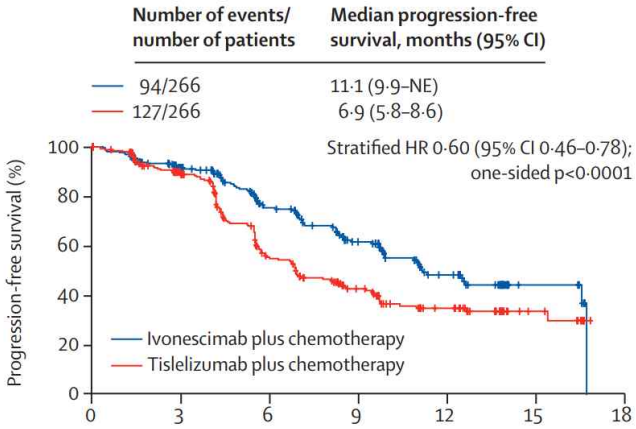
KN407

26%

7%

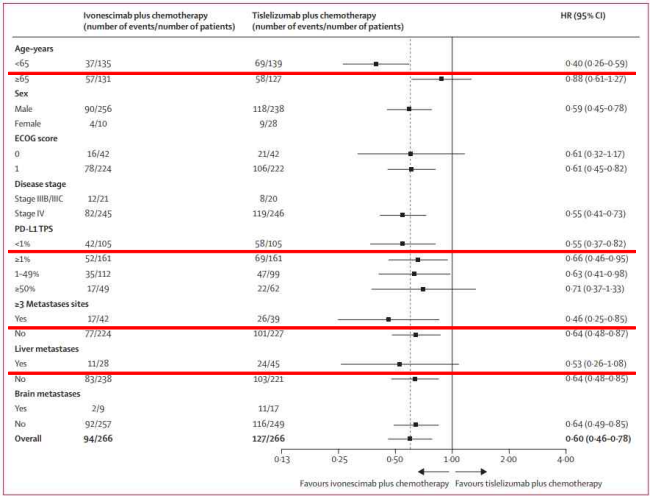
Lancet. 2025 Nov 1;406(10515):2078-2088
ESMO 2025 Congress

Primary endpoint: PFS by IRRC



Lancet. 2025 Nov 1;406(10515):2078-2088

Subgroup analysis of PFS

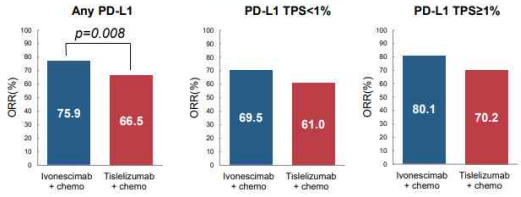


Lancet. 2025 Nov 1;406(10515):2078-2088

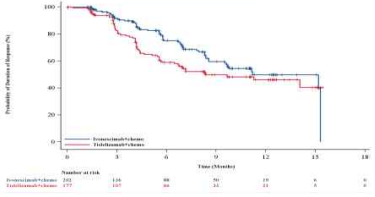
ORR and DoR by IRRC

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	

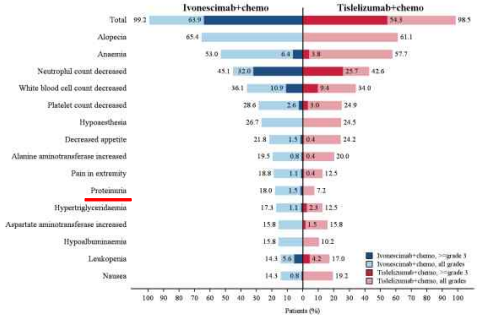
Lancet. 2025 Nov 1;406(10515):2078-2088
ESMO 2025 Congress

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%)



Lancet. 2025 Nov 1;406(10515):2078-2088
ESMO 2025 Congress

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.

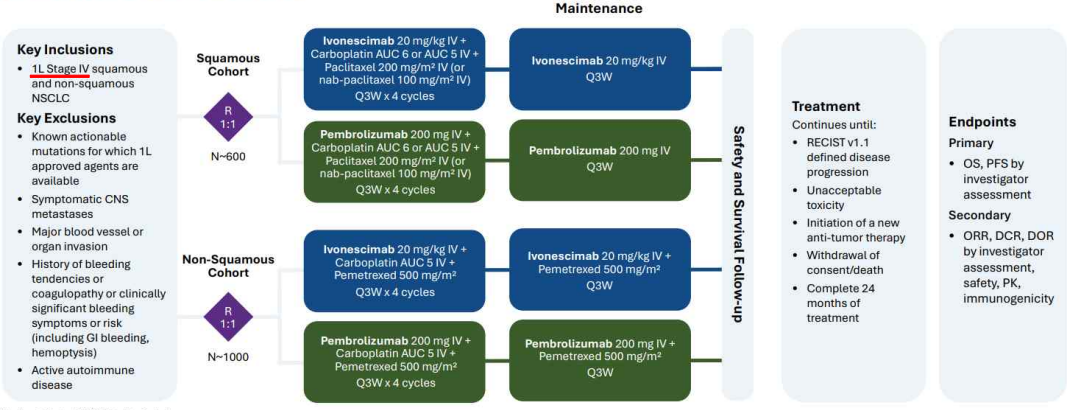
Possibly VEGF-Related AEs[#]	Ivonescimab + chemo (N=266)		Tislelizumab + chemo (N=265)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Any	123 (46.2)	20 (7.5)	60 (22.6)	6 (2.3)
Proteinuria	72 (27.1)	6 (2.3)	29 (10.9)	0
Haemorrhage	57 (21.4)	5 (1.9)	25 (9.4)	2 (0.8)
Hypertension	27 (10.2)	8 (3.0)	12 (4.5)	3 (1.1)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

Lancet. 2025 Nov 1;406(10515):2078-2088
ESMO 2025 Congress

HARMONi-3 global trials

HARMONi-3 TRIAL DESIGN



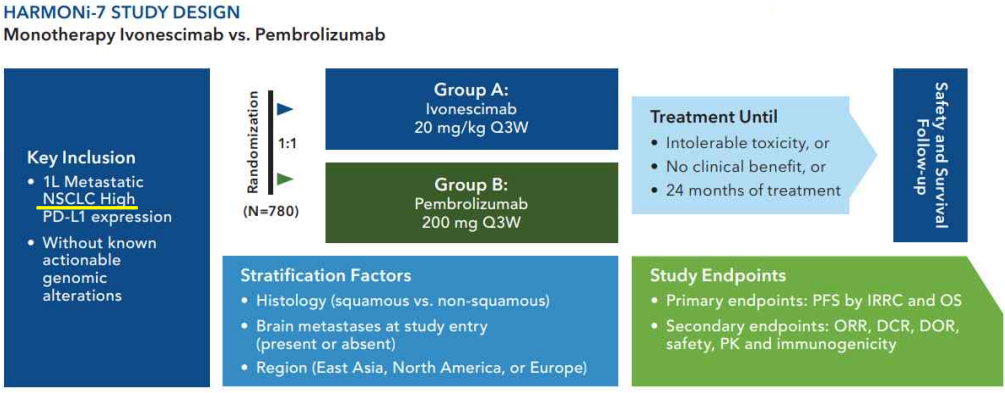
Randomization by NSCLC Histology Cohort (squamous and non-squamous)

Stratification Factors

- Sex (female vs. male)
- Age (<65 vs. >65 years)
- East Asia vs. Rest of World
- Liver or brain metastases at study entry (present vs. absent)
- Prior PD-1/L1 inhibitor containing therapy (yes vs. no)
- TPS/TC Score: PD-L1 >1% vs. <1%

Summit therapeutics homepage

HARMONi-7 global trials



2025 ASCO ANNUAL MEETING

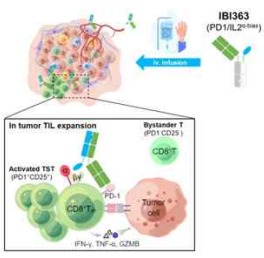
First-in-class PD-1/IL-2 bispecific antibody IBI363 in patients with advanced immunotherapy-treated non-small cell lung cancer (NSCLC)

Jianya Zhou[1], Xueli Bai[1], Yiwen Chen[1], Tingbo Liang[1], Hui Wang[2], Yuping Sun[3], Xinjun Liang[4], Qian Chu[5], Lin Wu[2], Caicun Zhou[6], Jian Fang[7], Yueyin Pan[8], Jiuwei Cui[9], Zhangzhou Huang[10], Yu Chen[10], Chengzhi Zhou[11], Xiaoqing Liu[12], Yu Yang[13], Ning Li[14], Tongmei Zhang[15]

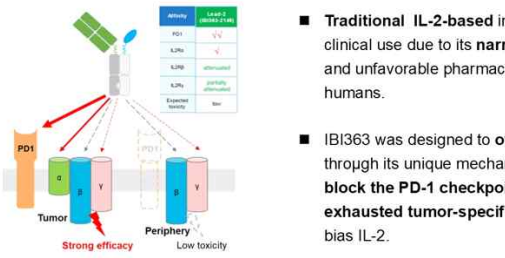
1.The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; 2.Hunan Cancer Hospital, Changsha, China; 3.Cancer Hospital of Shandong First Medical University, Jinan, China; 4.Hubei Cancer Hospital, Wuhan, China; 5.Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; 6.Shanghai East Hospital, Shanghai, China; 7.Beijing Cancer Hospital, Beijing, China; 8.Anhui Provincial Hospital, Hefei, Anhui, China; 9.The First Hospital of Jilin University, Changchun, China; 10.Fujian Cancer Hospital, Fuzhou, China; 11.The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China; 12.The Fifth Medical Center of PLA General Hospital, Beijing, China; 13.The Second Affiliated Hospital of Harbin Medical University, Harbin, China; 14.Cancer Hospital Chinese Academy of Medical Sciences, Beijing, China; 15.Beijing Chest Hospital, Capital Medical University, Beijing, China

Introduction of IBI363

MoA of IBI363



Structure of IBI363



Unique Innovation compared to traditional IL-2

- **Traditional IL-2-based** immunotherapy has limited clinical use due to its **narrow therapeutic window** and unfavorable pharmacokinetic (PK) profiles in humans.
- IBI363 was designed to **overcome these issues** through its unique mechanism of action (MOA) to **block the PD-1 checkpoint and rejuvenate exhausted tumor-specific T cells** by cis-activating α-bias IL-2.

IBI363 is a first-in-class PD-1/IL-2$^{\alpha\text{-bias}}$ bispecific antibody fusion protein with great potential to address the unmet clinical needs of patients with immune-cold and resistant tumors.

Nature cancer, 2023 Sep;4(9):1309-1325.

Baseline characteristics in sqNSCLC

- **67 patients with sqNSCLC (all *EGFR* wild-type)**
  - 28 patients treated at 1 mg/kg Q2W or 1.5 mg/kg Q3W;
  - 31 patients treated at 3 mg/kg Q3W;
  - the remaining patients treated at other dose levels*.

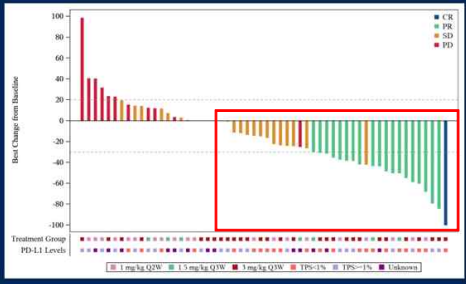
	1/1.5 mg/kg (N=28)	3 mg/kg (N=31)
Age (years), median (range)	58 (48-71)	61 (49-75)
Sex, n (%)		
Female	2 (7.1)	3 (9.7)
Male	26 (92.9)	28 (90.3)
ECOG PS, n (%)		
0	9 (32.1)	5 (16.1)
1	19 (67.9)	26 (83.9)
Smoking history, n (%)		
Current	1 (3.6)	4 (12.9)
Former	20 (71.4)	23 (74.2)
Never	7 (25.0)	4 (12.9)
Stage, n (%)		
III	3 (10.7)	7 (22.6)
IV	25 (89.3)	24 (77.4)
Metastases, n (%)		
Lung	15 (53.6)	15 (48.4)
Bone	7 (25.0)	9 (29.0)
Liver	1 (3.6)	2 (6.5)
Brain	1 (3.6)	0
PD-L1 status		
TPS<1%	10 (35.7)	13 (41.9)
TPS>=1%	12 (42.9)	11 (35.5)
Unknown	6 (21.4)	7 (22.6)
Prior lines of treatments, n (%)		
1	10 (35.7)	10 (32.3)
2	8 (28.6)	9 (29.0)
>=3	10 (35.7)	12 (38.7)
Prior Platinum-based chemotherapy, n(%)	28 (100)	30 (96.8)
Prior Taxanes chemotherapy, n(%)	27 (96.4)	31 (100)
Prior Docetaxel, n(%)	12 (42.9)	13 (41.9)
Prior anti PD-(L)1 treatment, n (%)	28 (100)	30 (96.8)

*Other dose levels included: 2 μg/kg QW (n=1), 10 μg/kg QW (n=1), 0.3 mg/kg Q2W (n=1), 0.3 mg/kg QW (n=1), 0.6 mg/kg Q2W (n=1), 2 mg/kg Q3W (n=2) or 4 mg/kg Q3W (n=1).

Efficacy in sqNSCLC

	1/1.5 mg/kg (N=27)	3 mg/kg (N=30)
Best overall response, n (%)		
Complete Response (CR)	0	1 (3.3)
Partial Response (PR)	7 (25.9)	12 (40.0)
Stable Disease (SD)	11 (40.7)	14 (46.7)
Progressive Disease (PD)	9 (33.3)	2 (6.7)
Not Evaluable (NE)	0	1 (3.3)
ORR, % (95% CI)	25.9 (11.1, 46.3)	43.3 (25.5, 62.6)
Confirmed ORR, % (95% CI)	25.9 (11.1, 46.3)	36.7 (19.9, 56.1)
DCR, % (95% CI)	66.7 (46.0, 83.5)	90.0 (73.5, 97.9)

Best overall response and change of target lesion

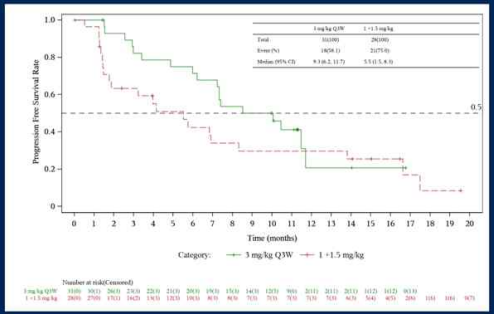


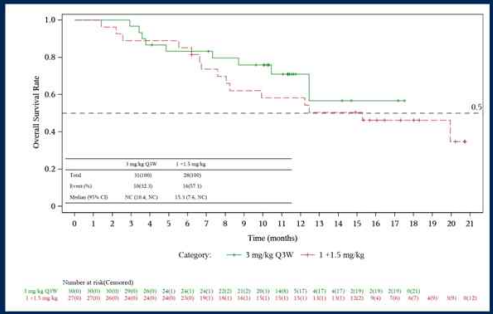
- At 1/1.5 mg/kg (n=7), median DoR was 10.2 months (95% CI: 3.1-NC) with median follow-up of 18.2 months and events of 57.1%.
- At 3 mg/kg (n=11), median DoR was not reached with median follow-up of 9.7 months and events of 36.4%.

Notes: Included patients with at least one post-baseline tumor assessment. Responses were confirmed in 18 of 20 responders including all of 7 patients treated at 1/1.5 mg/kg and 11 of 13 patients treated at 3 mg/kg.

PFS and OS in sqNSCLC

	PFS, months			OS, months			
	Median (95% CI)	Events n (%)	Follow-up Median, (95% CI)	Median (95% CI)	12-month OS rate (95% CI)	Events n (%)	Follow-up Median, (95% CI)
1/1.5 mg/kg (N=28)	5.5 (1.5, 8.3)	21 (75.0)	16.5 (14.1, 19.5)	15.3 (7.6, NC)	58.2% (37.3, 74.3)	16 (57.1)	17.3 (15.3, 20.2)
3 mg/kg (N=31)	9.3 (6.2, 11.7)	18 (58.1)	11.3 (10.1, 14.0)	NC (10.4, NC)	70.9% (49.5, 84.5)	10 (32.3)	11.3 (10.3, 11.6)





Notes: Included patients who have at least one post-baseline tumor assessment or discontinued treatment without any post-baseline tumor assessment.

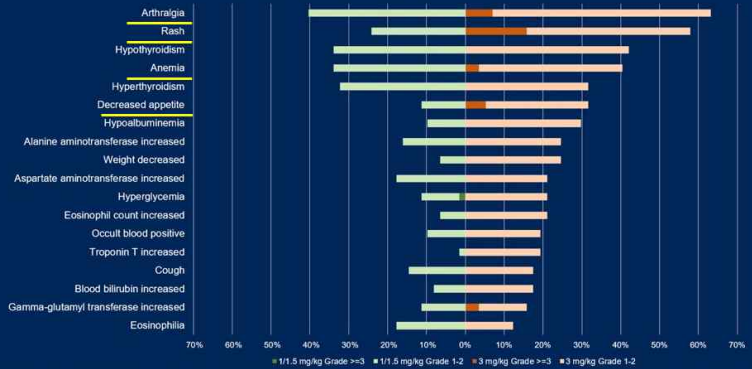
Safety overview in NSCLC

n (%)	1/1.5 mg/kg (N=62)	3 mg/kg Q3W (N=57)
Treatment Emergent Adverse Events (TEAEs)	61 (98.4)	57 (100)
>=Grade 3 TEAEs	19 (30.6)	35 (61.4)
Treatment Related Adverse Events (TRAEs)	58 (93.5)	55 (96.5)
>=Grade 3 TRAEs	11 (17.7)	25 (43.9)
Treatment Emergent Serious Adverse Events (TESAEs)	26 (41.9)	30 (52.6)
Treatment Related Emergent Serious Adverse Events (TRSAEs)	13 (21.0)	23 (40.4)
TEAEs Leading to Death	0	3 (5.3)
TRAEs Leading to Death	0	0
TEAEs Leading to Treatment Discontinuation	4 (6.5)	5 (8.8)
TRAEs Leading to Treatment Discontinuation	4 (6.5)	4 (7.0)
Participant with at least one dose delayed caused by AE (defined as >=5 days delay)	12 (19.4)	15 (26.3)

Notes: Due to limited sample size for each dose group, safety profiles were not shown for patients treated at 2 μg/kg QW (N=1), 10 μg/kg QW (N=1), 0.3 mg/kg QW (N=1), 0.3 mg/kg Q2W (N=3), 0.6 mg/kg QW (N=1), 0.6 mg/kg Q2W (N=5), 2 mg/kg Q3W (N=3), and 4 mg/kg Q3W (N=2).

Common TRAEs (>=15% in any group)

- Most of common TRAEs were grade 1-2. Grade>=3 TRAEs at 3 mg/kg were mainly rash and arthralgia.



Notes: Due to limited sample size for each dose group, safety profiles were not shown for patients treated at 2 μg/kg QW (N=1), 10 μg/kg QW (N=1), 0.3 mg/kg QW (N=1), 0.3 mg/kg Q2W (N=3), 0.6 mg/kg QW (N=1), 0.6 mg/kg Q2W (N=5), 2 mg/kg Q3W (N=3), and 4 mg/kg Q3W (N=2).

Phase 3 study: 2L/3L LUSC PD on or After PBC and Anti PD-1/PD-L1 Immunotherapy

NCT07217301

Patients with biopsy-confirmed squamous NSCLC and progression on or after platinum-based chemo and anti-PD-(L)1 IO therapy

Estimated N=600

R* 1:1

IBI363 IV (n=~300)
Priming dose: 0.1mg/kg on Cycle 1, Day 1
Intended Dose†: 3 mg/kg Q3W starting Cycle 1, Day 8
28-day cycle for Cycle 1, then 21-day cycles for Cycles 2+

Docetaxel IV (n=~300)
75 mg/m^2 Q3W, starting from Cycle 1, Day 1
21-day cycles

Primary endpoint:
Overall survival (OS)

Secondary endpoints:
PFS, ORR
DCR, DOR, TTR
Safety
PK, ADA/NAb, QoL

Key eligibility criteria

- Locally unresectable advanced or metastatic histologically or cytologically confirmed squamous NSCLC
- Radiographic progression per RECIST v1.1 during or within 6 months after discontinuation of anti-PD-1/PD-L1 monoclonal antibody treatment
- Resistant or refractory to systemic anti-tumor therapy, including platinum-based doublet chemotherapy and primary or secondary resistance to anti-PD-1/PD-L1 monoclonal antibody given in combination or sequentially
- No known actionable genomic alteration

Courtesy of Takeda Medical Affairs

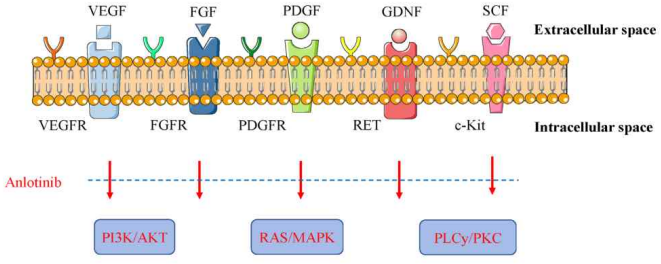
Contents

- Unmet needs in treatment of LUSC
- Bispecific antibody
- ICI combinations
- ADC
- Summary

Anlotinib

New oral multi-kinase inhibitor

Targets VEGFR1, VEGFR3, VEGFR2/KDR, PDGFR-α, c-Kit, and FGFRs 1–3



Suppress angiogenesis, survival and cell proliferation

Front Oncol. 2021 May 20:11:664853

CAMPASS Ph3 trial study design

Randomized, blind, multicenter phase 3 study (NCT04964479)

Key enrollment criteria

- Locally advanced or recurrent/metastatic NSCLC
- TPS ≥ 1%
- Age: 18-75; ECOG PS: 0-1
- Previous systemic treatment naïve
- No EGFR mutations, no ALK or ROS1 rearrangements
- No prior exposure of anti-angiogenic agents or immune checkpoint inhibitors

2:1
N = 531

- Benmelstobart 1200mg iv D1
- Anlotinib 12mg po, QD D1~D14
- 3 weeks / cycle

- Pembrolizumab 200mg iv D1
- Placebo 0mg po, QD D1~D14
- 3 weeks / cycle

Primary endpoint

Progression-free survival (PFS) per RECIST 1.1 assessed by IRC

Secondary endpoints

- Overall survival (OS)
- Objective response rate (ORR)
- PFS per RECIST 1.1 by INV
- Disease control rate (DCR)
- Safety

Stratification factors:

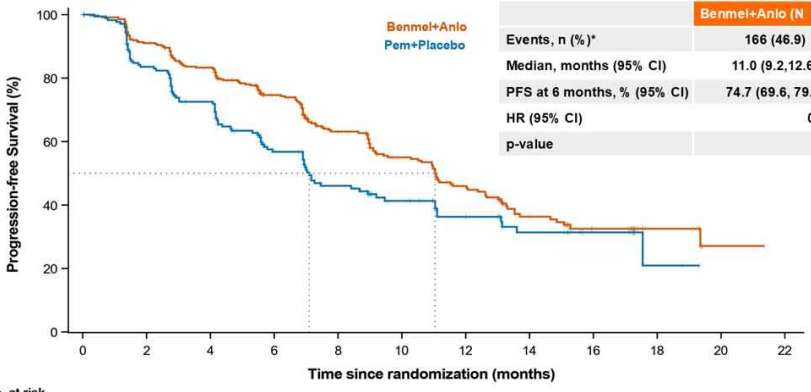
- Histology: squamous vs. non-squamous
- Brain metastases: yes vs. no
- PD-L1 expression (TPS): ≥ 50% vs. 1-49%

Abbreviation: IRC: independent review committee, INV: investigator, TPS: tumor proportion score

Baseline characteristics

Characteristics		Benmel+Anlo (N = 354)	Pem+Placebo (N = 177)
Age	Median, years (range)	65 (34-75)	65 (42-76)
	<65, n (%)	170 (48.0)	83 (46.9)
Gender	Male	300 (84.7)	149 (84.2)
Histology	Squamous	213 (60.2)	107 (60.5)
	Non-squamous	141 (39.8)	70 (39.5)
Disease stage at baseline	IIIB/C	93 (26.3)	45 (25.4)
	IV	260 (73.4)	132 (74.6)
PD-L1 tumor cell proportion score	1–49%	195 (55.1)	97 (54.8)
	≥50%	159 (44.9)	80 (45.2)
ECOG performance status	0	57 (16.1)	34 (19.2)
	1	295 (83.3)	143 (80.8)
	Unknown	2 (0.6)	0
Metastases	Bone	91 (25.7)	27 (15.3)
	Liver	30 (8.5)	9 (5.1)
	Brain	23 (6.5)	15 (8.5)
Smoking status	Former	218 (61.6)	126 (71.2)
	Current	47 (13.3)	14 (7.9)
	Never	87 (24.6)	34 (19.2)
	Unknown	2 (0.6)	3 (1.7)

Primary endpoint: PFS by IRC



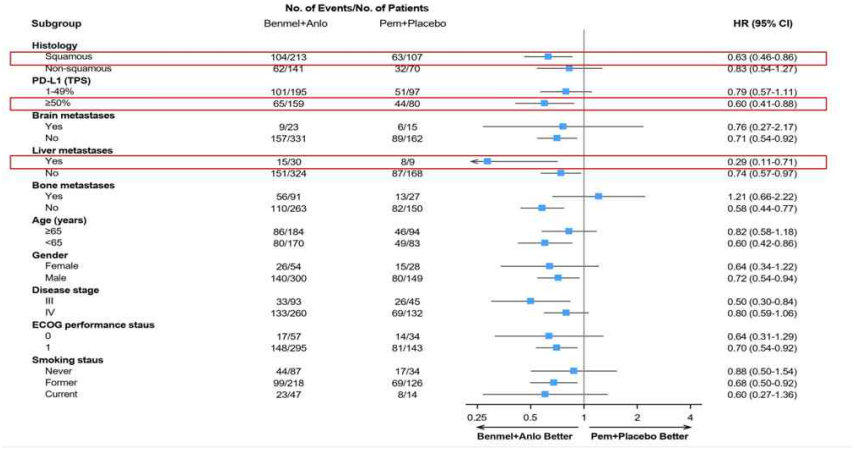
	Benmel+Anlo (N = 354)	Pem+Placebo (N = 177)
Events, n (%)*	166 (46.9)	95 (53.7)
Median, months (95% CI)	11.0 (9.2,12.6)	7.1 (5.8, 9.5)
PFS at 6 months, % (95% CI)	74.7 (69.6, 79.0)	56.8 (48.6, 64.2)
HR (95% CI)	0.70 (0.54, 0.90)	
p-value	0.0057	

No. at risk

Benmel+Anlo	354	311	276	202	142	108	78	42	24	9	1	0
Pem+Placebo	177	139	113	73	54	38	27	18	11	2	0	

*Median follow-up:
Benmel+Anlo: 11.4 months
Pem+Placebo: 10.6 months

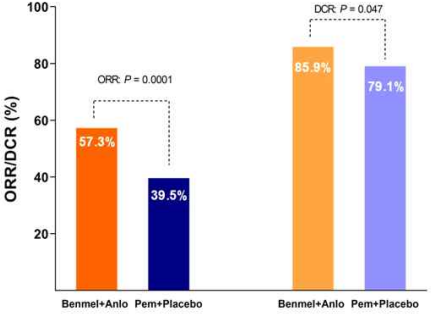
Subgroup analysis of PFS



ORR and DoR by IRC

	Benmel+Anlo (N = 354)	Pem+Placebo (N = 177)
CR*, n (%)	1 (0.3)	1 (0.6)
PR*, n (%)	202 (57.1)	69 (39.0)
SD, n (%)	101 (28.5)	70 (39.5)
PD, n (%)	36 (10.2)	27 (15.3)
NE, n (%)	14 (4.0)	10 (5.6)
ORR, n (%)	203 (57.3)	70 (39.5)
95% CI	(52.0, 62.6)	(32.3, 47.2)
Odds ratio (95% CI)	2.08 (1.43, 3.01)	
p-value†	0.0001	
DCR, n (%)	304 (85.9)	140 (79.1)
95% CI	(81.8, 89.3)	(72.4, 84.8)
p-value†	0.047	

*CR and PR were confirmed
†Analyzed using the chi-square test or Fisher's exact probability method



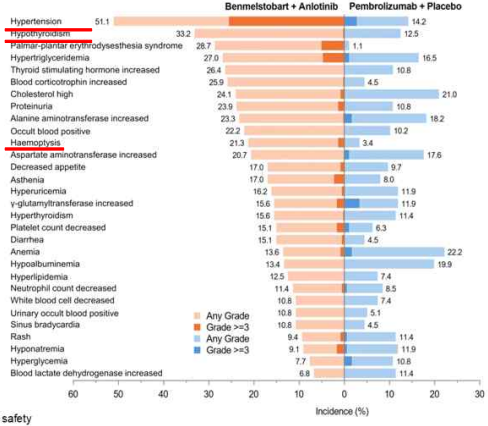
Safety Summary

Incidence of the adverse events and treatment adjustments, N (%)

	Benmel+Anlo (N = 352*)	Pem+Placebo (N = 176*)
TRAEs	346 (98.3)	155 (88.1)
≥ grade 3 TRAEs	206 (58.5)	51 (29.0)
Treatment-related SAEs	89 (25.3)	37 (21.0)
TRAE leading to death	5 (1.4)	4 (2.3)
irAEs	151 (42.9)	70 (39.8)
≥ grade 3 irAEs	38 (10.8)	22 (12.5)
Median duration of treatment, days	262.0	206.5
TRAE leading to any treatment discontinuation	25 (7.1)	14 (8.0)

- Combination treatment did not increased the incidence of treatment permanently discontinuation or death due to TRAE compared to pembrolizumab

TRAEs occurred in ≥ 10% patients of either group

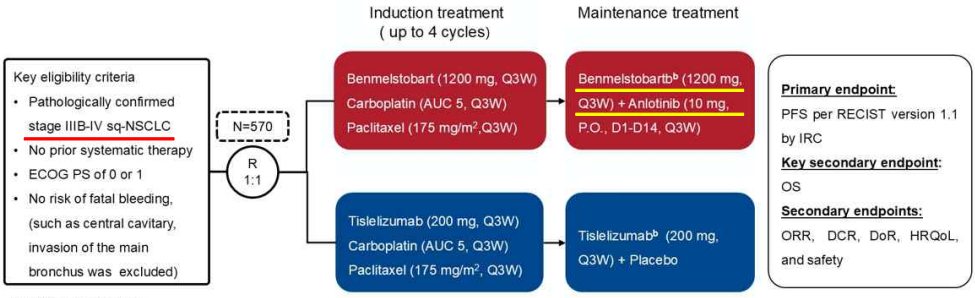


*Safety analysis was done in patients who received at least one dose of study treatment and had data of safety

Abbreviation: TRAEs: treatment-related adverse events, SAEs: serious adverse events, irAEs: immune-related adverse events

TQB2450-III-12 Ph3 study design

TQB2450-III-12 is multicenter, randomized, double-blind, parallel-controlled phase III study



Stratification factors:

- **PD-L1 TPS[a]: < 1% vs. 1-49% vs. >=50%**
- **Sites of metastases: <=3 vs. > 3**
- **ECOG PS: 0 vs. 1**

a: Assessed at a central laboratory using PD-L1 IHC E1L3N (AmoyDx PD-L1 assay); b: up to 2 years;
Data cutoff date for this interim analysis: March 1, 2024. ClinicalTrials. Gov: NCT05718167

Abbreviation: sq, squamous; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group, PS, Performance Status; PD-L1, programmed death ligand 1; TPS, , tumor proportion score; AUC, area under the curve; PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors; IRC, Independent Review Committee; OS, overall survival; ORR, objective response rate; DCR, disease control rate; DoR, duration of response; HRQoL, health related quality of life.

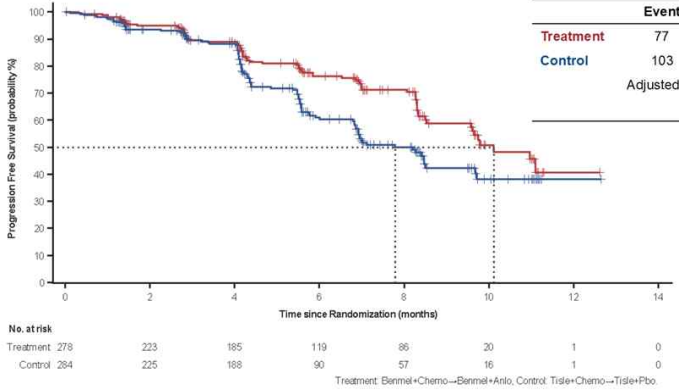
Baseline characteristics

Characteristics, n (%)		Benmelstobart+Chemotherapy→ Benmelstobart+Anlotinib (N=278)	Tislelizumab+Chemotherapy→ Tislelizumab+Placebo (N=284)
Age	Median (range), years	65 (33,75)	64 (38,75)
	<65	132 (47.48)	149 (52.46)
	>=65	146 (52.52)	135 (47.54)
Sex	Male	251 (90.29)	260 (91.55)
	Female	27 (9.71)	24 (8.45)
Smoking history	Current/Former	232 (83.45)	241 (84.86)
	Never	46 (16.55)	43 (15.14)
Clinical stage	IIIB/IIIC	110 (39.57)	86 (30.28)
	IV	168 (60.43)	198 (69.72)
ECOG PS	0	64 (23.02)	69 (24.30)
	1	213 (76.62)	215 (75.70)
	Missing	1 (0.36)	0 (0.00)
Sites of metastases	<=3	230 (82.73)	238 (83.80)
	>3	13 (4.68)	14 (4.93)
	Missing	35 (12.59)	32 (11.27)
Metastatic site	Liver	20 (7.19)	24 (8.45)
	Brain	6 (2.16)	8 (2.82)
	Bone	68 (24.46)	63 (22.18)
PD-L1 TPS	<1%	104 (37.41)	107 (37.68)
	1-49%	126 (45.32)	126 (44.37)
	>=50%	48 (17.27)	51 (17.96)

a: As of March 1, 2024, 565 patients were randomized. Three patients without recorded baseline clinical stage were excluded from the ITT population.

Abbreviation: ITT, intent to treatment; ECOG, Eastern Cooperative Oncology Group, PS, Performance Status; PD-L1, programmed death ligand 1; TPS, tumor proportion score.

Primary endpoint: PFS by IRC



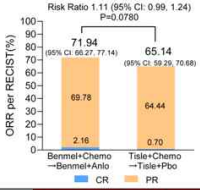
	Event	Censor (%)	Median (95 CI%)
Treatment	77	201 (72.30)	10.12 (8.54-NE)
Control	103	181 (63.73)	7.79 (6.87-9.69)
	Adjusted Hazard Ratio 0.64 (98.35% CI 0.45-0.93)		
	Stratified Log-rank P=0.0038		

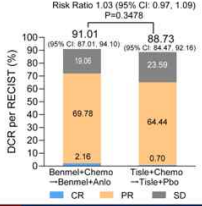
a: Superiority boundary α=0.0165; Data cutoff date for this interim analysis: March 1, 2024. Median follow-up of PFS: 6.97 months (95%CI: 5.78, 7.62) vs. 6.87 months (95%CI: 5.62, 7.29).

Abbreviation: PFS, progression free survival; RECIST, Response Evaluation Criteria in Solid Tumors; IRC, Independent Review Committee; ITT, intent to treatment; NE, not estimated.

ORR and DoR by IRRC

- Improvements in ORR, DCR, and a more durable tumor response were observed.



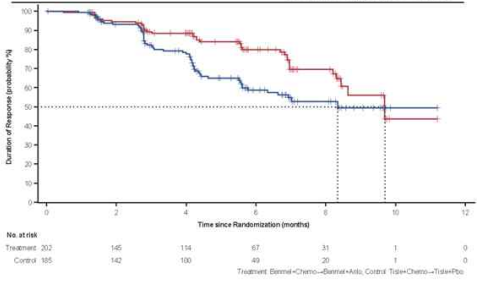


BOR n (%)	Benmelstobart+Chemotherapy →Benmelstobart+Anlotinib (N=278)	Tislelizumab+Chemotherapy →Tislelizumab+Placebo (N=284)
CR	6 (2.16)	2 (0.70)
PR	194 (69.78)	183 (64.44)
SD	53 (19.06)	67 (23.59)
PD	7 (2.52)	9 (3.17)
NE*	0 (0.00)	1 (0.35)
NA	18 (6.47)	22 (7.75)

	Event	Censor (%)	Median (95 CI%)
Treatment	40	162 (80.20)	9.69 (8.44-NE)
Control	59	126 (68.11)	8.34 (5.78-NE)

Adjusted Hazard Ratio 0.58 (95% CI 0.38-0.88)

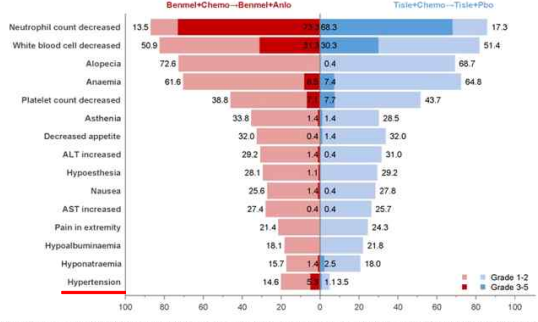
Stratified Log-rank P=0.0091



Abbreviation: DoR, duration of response; DCR, disease control rate; ORR, objective response rate; BOR, best overall response; CR, complete response; PR, partial response; SD, stable disease; NE, not estimated; NE*, not evaluable; NA, not assessable; PFS, progression free survival.

Safety Summary

Most common TRAEs (incidence ≥ 20%)



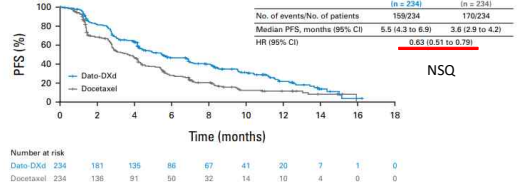
Summary of safety

TRAEs n (%)	Benmelstobart+Chemotherapy→Benmelstobart+Anlotinib (N=281)	Tislelizumab+Chemotherapy→Tislelizumab+Placebo (N=284)
Any grade	277 (98.6)	280 (98.6)
≥ Grade 3	240 (85.4)	224 (78.9)
Serious	68 (24.20)	59 (20.8)
Leading to discontinuation of any treatment	13 (4.6)	12 (4.2)
Leading to death	4 (1.4)	4 (1.4)

Abbreviation: sq, squamous; NSCLC, non-small cell lung cancer; TRAEs, treatment related adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Contents

Datopotamab Deruxtecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non–Small Cell Lung Cancer: The Randomized, Open-Label Phase III TROPION-Lung01 Study



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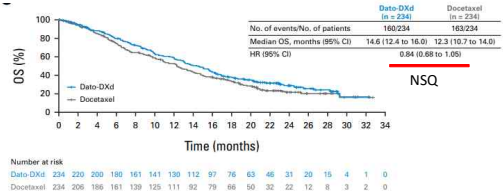

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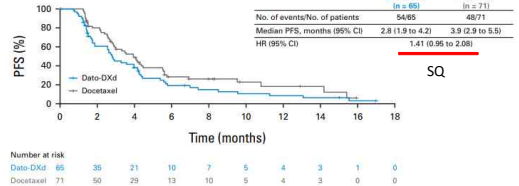
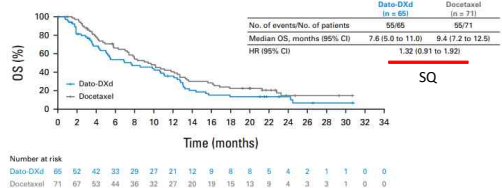


SQ



SQ

J Clin Oncol. 2025 Jan 20;43(3):260-272

Sacituzumab govitecan (SG)

Trial	Inclusion	NSCLC outcome	LUSC outcome
EVOKE-01 (ph3) (SG)	≥2L SG vs docetaxel	mOS 11.1 vs. 9.8 mo (HR 0.84, 95% CI 0.68-1.04)	mOS NSQ HR 0.87 (95% CI 0.68-1.11) SQ HR 0.83 (95% CI 0.56-1.22)
EVOKE-02 (ph2) (SG)	Cohort A (PD-L1 ≥50%) 1L mNSCLC SG w pembrolizumab	ORR 66.7%, mPFS 13.1 mo	ORR 64% (NSQ), 75% (SQ) mPFS 13.1 mo (NSQ), NR (SQ)
	Cohort B (PD-L1 <50%) 1L mNSCLC SG w pembrolizumab	ORR 29.0%, mPFS 7.0 mo	ORR 37% (NSQ), 52% (SQ) mPFS 6.6 mo (NSQ), 6.8 mo (SQ)
	Cohort C,D (All comer) 1L mNSCLC SG w pembrolizumab w carboplatin	ORR 46%, mPFS 8.1 mo	ORR 46% (NSQ), 47% (SQ) mPFS 8.1 mo (NSQ), 11.1 mo (SQ)

Ann Oncol. 2026 Mar;37(3):289-313

Sacituzumab tirumotecan (1L aNSCLC, Sac-TMT, ph2)

	Cohort 1ASac-TMT (5 mg kg^{-1} Q3W) + tagitanlimab (1,200 mg Q3W) n=40	Cohort 1BSac-TMT (5 mg kg^{-1} Q2W) + tagitanlimab (900 mg Q2W) n=63
Median follow-up[a] (95% CI), months	19.3 (18.6–21.9)	13.0 (11.3–13.3)
Median treatment duration for sac-TMT (range), months	8.1 (0–23.9)	9.9 (0–14.7)
Median treatment duration for tagitanlimab (range), months	6.7 (0–21.6)	9.7 (0–14.7)
BOR, *n* (%)		
PR	18 (45.0)	45 (71.4)
Confirmed PR	16 (40.0)	42 (66.7)
SD	16 (40.0)	13 (20.6)
PD	3 (7.5)	0
Not evaluable[b]	3 (7.5)	5 (7.9)
ORR[c], *n* (%)	18 (45.0)	45 (71.4)
(95% CI)	(29.3–61.5)	(58.7–82.1)
Confirmed ORR, *n* (%)	16 (40.0)	42 (66.7)
(95% CI)	(24.9–56.7)	(53.7–78.0)
DCR[d], *n* (%)	34 (85.0)	58 (92.1)
(95% CI)	(70.2–94.3)	(82.4–97.4)
Median DOR (95% CI), months	16.6 (8.3–N.E.)	NR (11.2–N.E.)
Median PFS (95% CI), months	15.4 (6.7–17.9)	NR (9.6–N.E.)
6-month PFS rate (95% CI), %	69.2 (51.2–81.6)	84.2 (71.8–91.4)
12-month PFS rate (95% CI), %	51.1 (33.5–66.2)	58.4 (44.2–70.1)

ORR

Cohort 1A: SQ 36.4%, NSQ 44.4%

Cohort 1B: SQ 69.0%, NSQ: 64.7%

12M mPFS rate

Cohort 1A: SQ 44.1%, NSQ: 60.3%

Cohort 1B: SQ 48.0%, NSQ: 65.8%

Nat Med. 2025 Nov;31(11):3654-3661

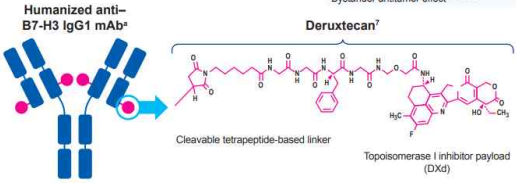
B7-H3 ADC, I-DXd (Ifinatamab Deruxtecan)

- B7-H3 (CD276) is a transmembrane immune checkpoint molecule expressed in a wide range of cancer types, including LUSC
- B7-H3 expression is associated with disease progression and shorter OS in most tumor types studied
- B7-H3 expression is low or absent in normal tissues, making B7-H3 a promising target for ADCs
- I-DXd (DS-7300) is a novel B7-H3–directed ADC that leverages DXd to enhance selective tumor cell death and reduce systemic exposure

Figure 1: I-DXd was Designed with 7 Key Attributes

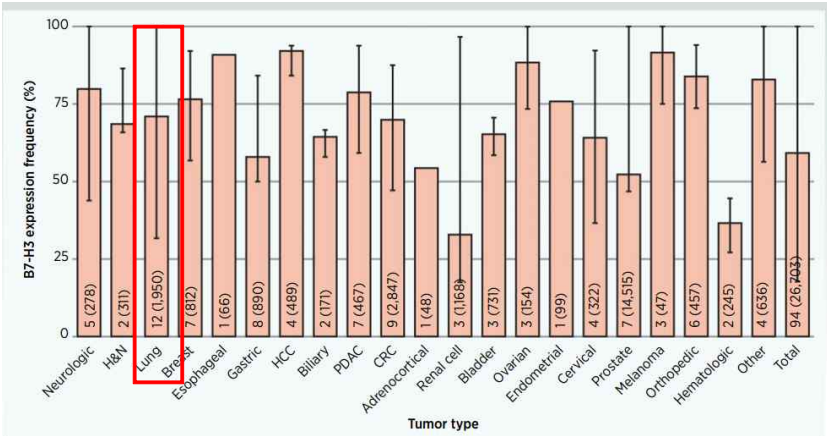
- I-DXd is a B7-H3–directed ADC composed of three parts[7–11]:
  - A humanized anti–B7-H3 IgG1 mAb
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other two components

Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[7,11,b]
Optimized drug-to-antibody ratio ≈4[7–10,12,b]
Payload with short systemic half-life[7,11,b,c]
Stable linker-payload[7,11,b]
Tumor-selective cleavable linker[7,11,b]
Bystander antitumor effect[7,9,11,12,b]



ESMO Annual Meeting 2023
Clin Cancer Res. 2021 Mar 1;27(5):1227-1235

B7-H3 expression in all the cancer types



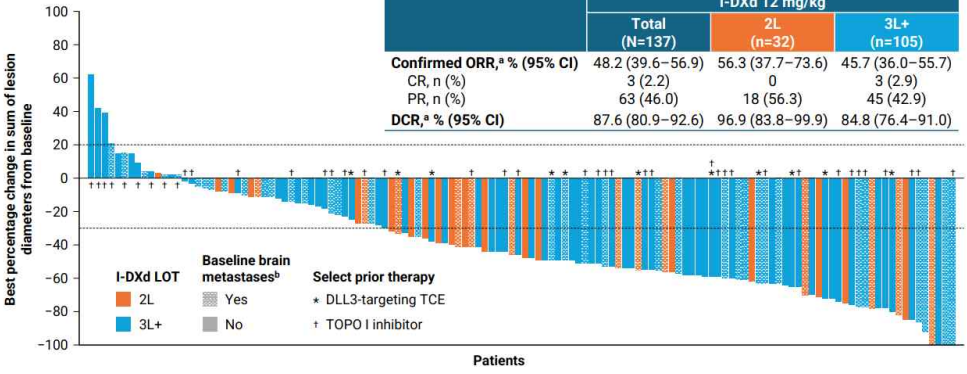
Clin Cancer Res. 2021 Mar 1;27(5):1227-1235

IDeate-Lung01 Study (ph2, ≥2L SCLC-ES)

I-DXd 12 mg/kg demonstrated promising antitumor activity

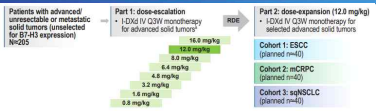
mPFS 4.9 months, mOS 10.3 months

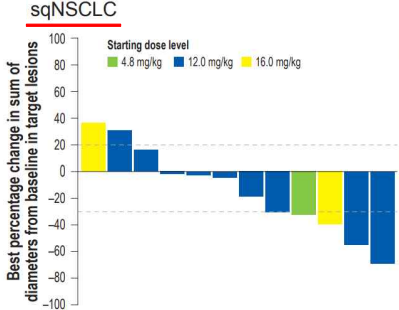
	I-DXd 12 mg/kg		
	Total (N=137)	2L (n=32)	3L+ (n=105)
Confirmed ORR,[a] % (95% CI)	48.2 (39.6–56.9)	56.3 (37.7–73.6)	45.7 (36.0–55.7)
CR, n (%)	3 (2.2)	0	3 (2.9)
PR, n (%)	63 (46.0)	18 (56.3)	45 (42.9)
DCR,[a] % (95% CI)	87.6 (80.9–92.6)	96.9 (83.8–99.9)	84.8 (76.4–91.0)



Ifinatamab Deruxtecan (I-DXd; DS-7300) in patients with advanced solid tumors: Updated clinical and biomarker results from a phase 1/2 study

Ideate-Pantumor 01





	sqNSCLC
Efficacy population (≥4.8 mg/kg)	**n=13**
Confirmed ORR, n (%; 95% CI)	4 (30.8, 9.1–61.4)
Confirmed PR, n (%)	4 (30.8)
TTR, median (95% CI), months	1.3 (0.7–NE)
DOR, median (95% CI), months	4.1 (2.8–NE)
Follow-up, median (95% CI), months	5.2 (1.7–NE)
Safety population (all doses)	**n=18**
Number of prior systemic regimens, median (range)	3 (1–12)
Platinum-based chemotherapy, n (%)	18 (100)
Immunotherapy, n (%)	18 (100)
Taxane, n (%)	16 (88.9)

Change from baseline in target lesions was assessed per RECIST v1.1. One patient did not have any post-baseline tumor assessments and was not included in the waterfall plot. Since enrollment in the sqNSCLC cohort is ongoing, analyses of PFS and OS in this cohort are not yet mature.

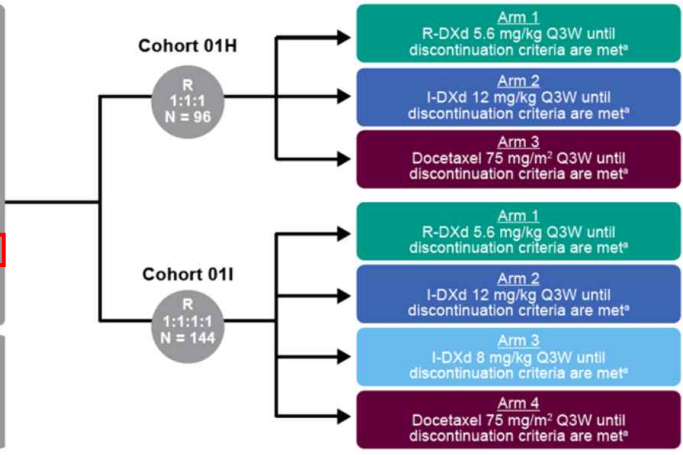
Phase 2 KEYMAKER-U01I

Key Eligibility Criteria

- Age ≥18 y
- Previously treated stage IV NSCLC with PD on anti–PD-(L)1 treatment and platinum-based chemotherapy given together or in sequence
  - Cohort 01H: nonsquamous histology and not eligible for *EGFR*-, *ROS1*-, or *ALK*-directed primary therapy
  - Cohort 01I: squamous histology
- ECOG PS 0 or 1
- No pneumonitis or ILD

Stratification Factors

- Best response to prior anti–PD-(L)1 treatment (CR/PR vs non-CR/PR)
- ECOG PS (0 vs 1)



Summary

- Higher tumor heterogeneity than LUAD, Cold TIME
- **Breakthrough with Bispecific antibody**
  - Ivonescimab (PD-1/VEGF), IBI363 (PD-1/IL-2)
- **Synergistic ICI Combination**
  - Novel combinations, with anlotinib (oral multi-kinase inhibitor)
- **Emerging ADCs**
  - Next-generation ADCs targeting TROP2 (SG, Sac-TMT) and B7-H3 (I-DXd)