oncology exchange
fall 2024

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cencora

Fall Oncology Exchange Meeting – Recent Advances in Lung Cancer

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PD-1 and VEGF Blockade

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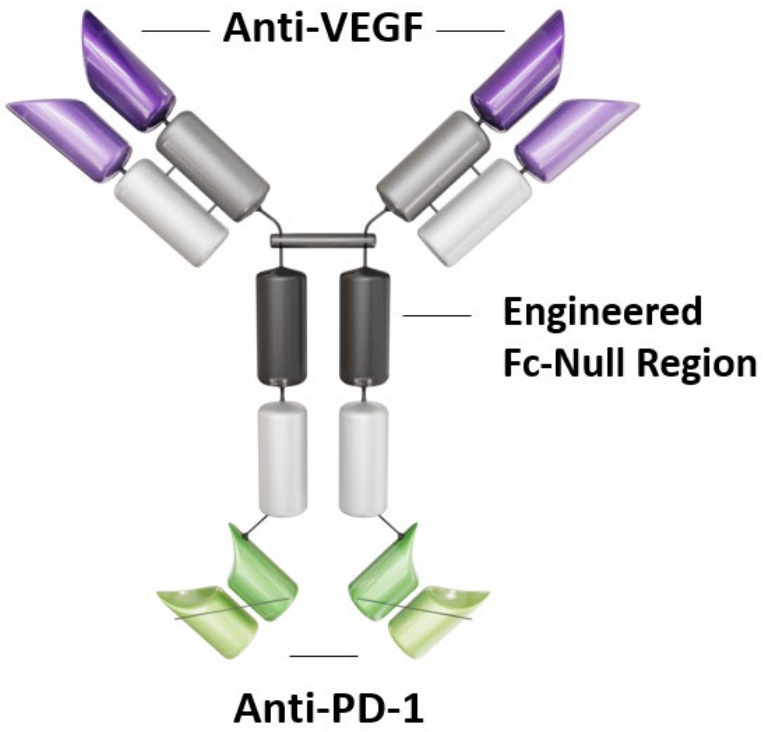
Background



- For patients with EGFR-mutant NSCLC, upfront treatment with tyrosine kinase inhibitors is standard. However, drug resistance remains a challenge, and an effective therapy after progression is needed.
- Ivonescimab (AK112/SMT112) is an anti-PD-1/VEGF bispecific antibody displaying cooperative binding characteristics.
- Phase II clinical studies have shown potential efficacy of Ivonescimab plus chemotherapy in NSCLC patients with EGFR mutations who progressed on prior EGFR-TKIs therapies[1-2].
- This phase 3 study aimed to evaluate and confirm the efficacy and safety of ivonescimab combined with chemotherapy compared to chemotherapy alone in this population (NCT05184712).

1. L Zhang et al: ASCO 2023; 2. YY Zhao et al: eClinicalMedicine 2023;62: 102106.

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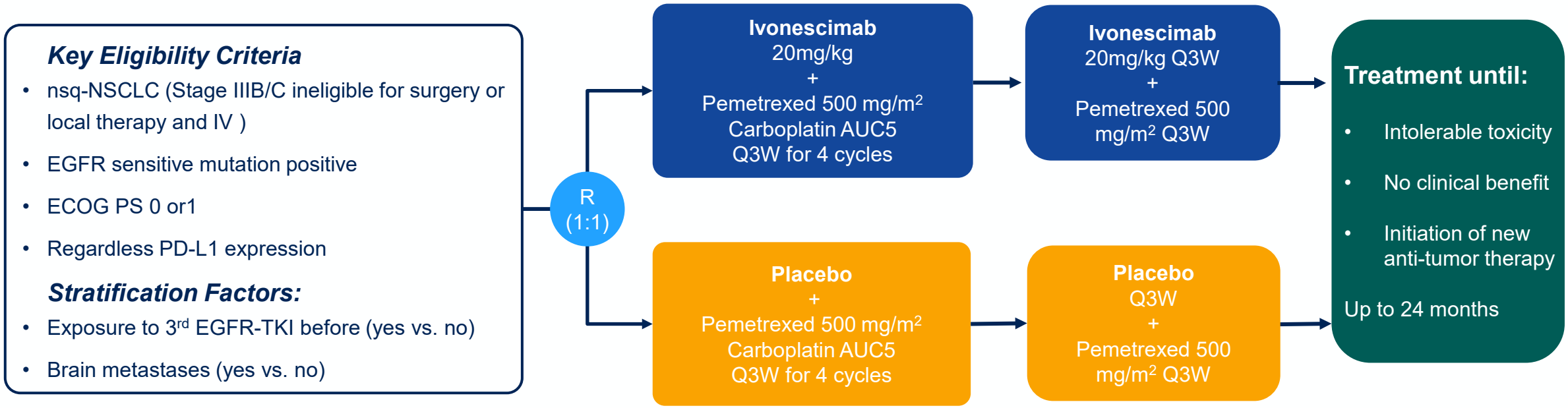
HARMONi-A Study Design



Endpoints

- Primary: Progression-free survival by independent radiologic review committee (IRRC)
- Secondary: Overall survival, Response rate, Duration of response, Time to response and Safety

ClinicalTrials.gov, NCT05184712; NSCLC, non-small cell lung carcinoma; EGFR, epidermal growth factor receptor; ECOG, eastern copperative oncology group; TKI, tyrosine-kinase inhibitor; Q3W, every 3 weeks.

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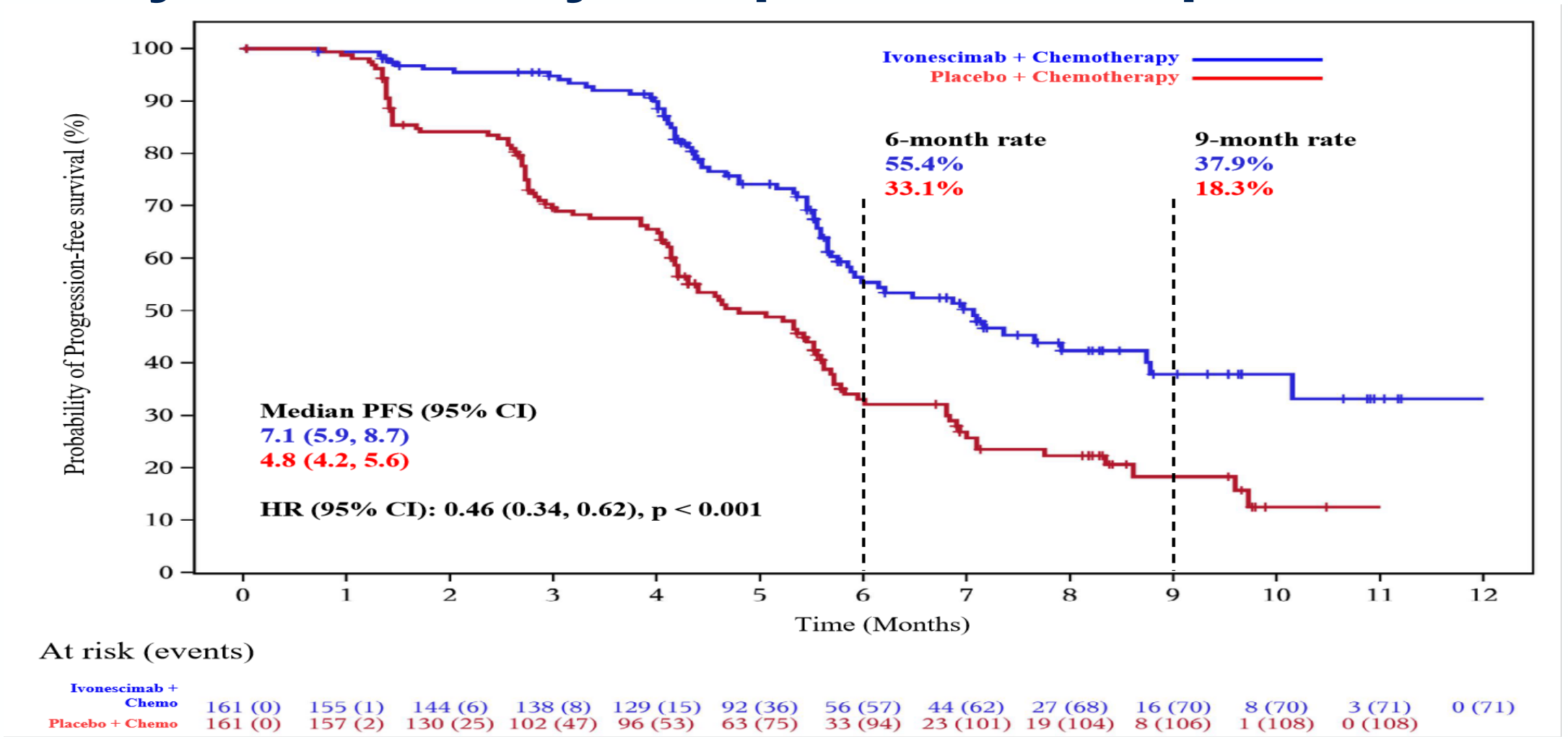
Study Met Primary Endpoint of PFS per IRRC



HR and P-value were stratified by previous 3rd Gen EGFR-TKI ues (yes vs. no) and presence of brain metastases (yes vs. no), and were calculated with stratified Cox model and log rank test. The two-sided P-value boundary is 0.024 as calculated using Lan-Demets spending function with O'Brien-Fleming approximation.
HR, hazard ratio; CI, confidence interval; IRRC, independent radiology review committee.

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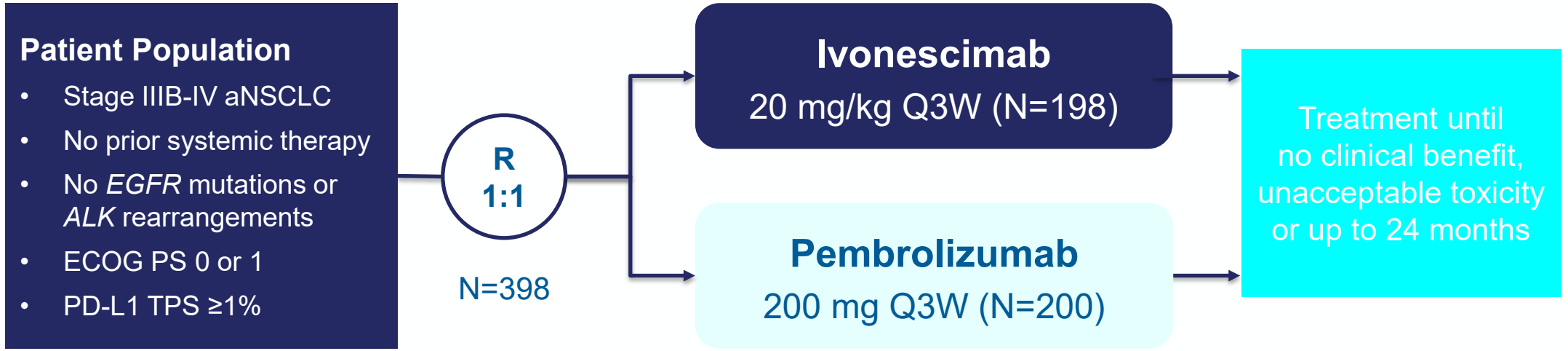
HARMONi-2 (AK112-303) Study Design

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.

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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)

[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 cell carcinoma.

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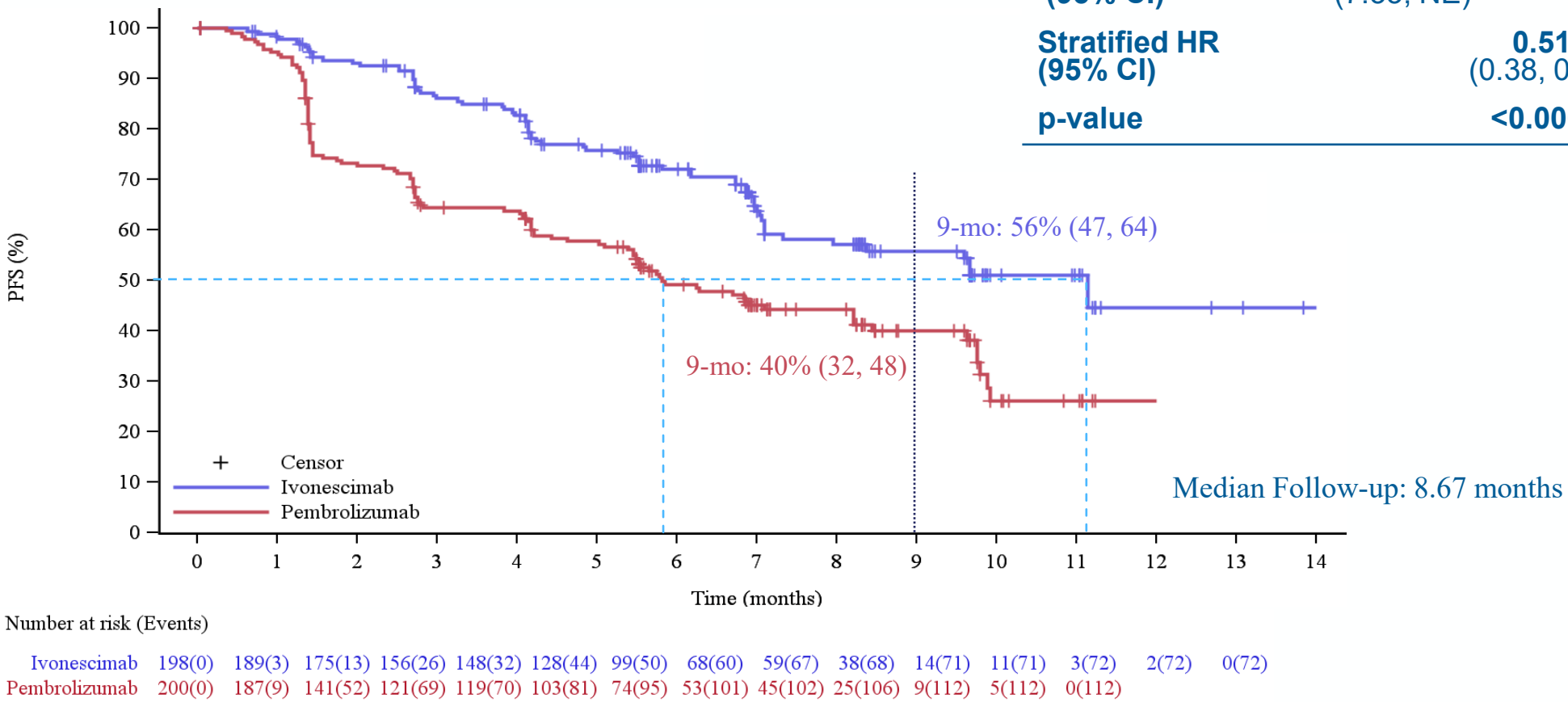
Primary endpoint: PFS per IRRC

	Ivonescimab (n = 198)	Pembrolizumab (n = 200)
mPFS, mos (95% CI)	**11.14** (7.33, NE)	5.82 (5.03, 8.21)
Stratified HR (95% CI)	**0.51** (0.38, 0.69)	
p-value	**<0.0001**	



Number at risk (Events)

Ivonescimab	198(0)	189(3)	175(13)	156(26)	148(32)	128(44)	99(50)	68(60)	59(67)	38(68)	14(71)	11(71)	3(72)	2(72)	0(72)
Pembrolizumab	200(0)	187(9)	141(52)	121(69)	119(70)	103(81)	74(95)	53(101)	45(102)	25(106)	9(112)	5(112)	0(112)		

Ivonescimab demonstrated a statistically significant improvement in PFS vs. pembrolizumab with HR = 0.51, and a 5.3 months improvement in mPFS.

Abbreviations: mPFS, median progression-free survival; IRRC, independent radiology review committee; mo, month; NE, not estimable; HR: hazard ratio; CI, confidence interval.

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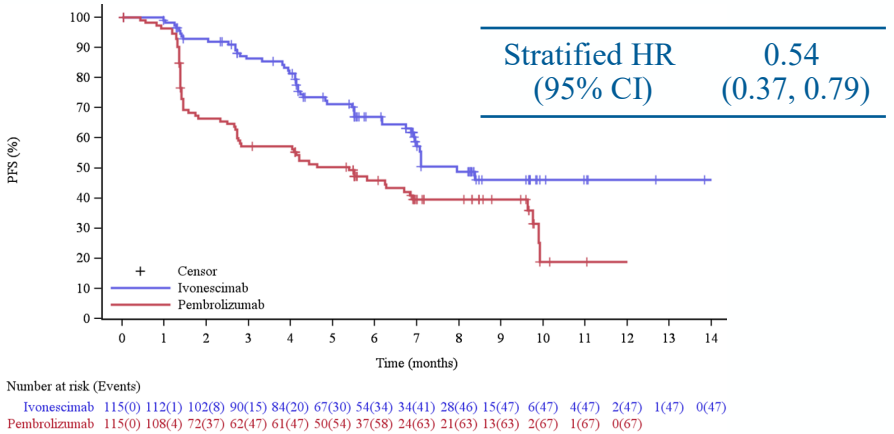
Key PFS Subgroup Analyses

PD-L1 expression

PD-L1 Low (TPS 1-49%)

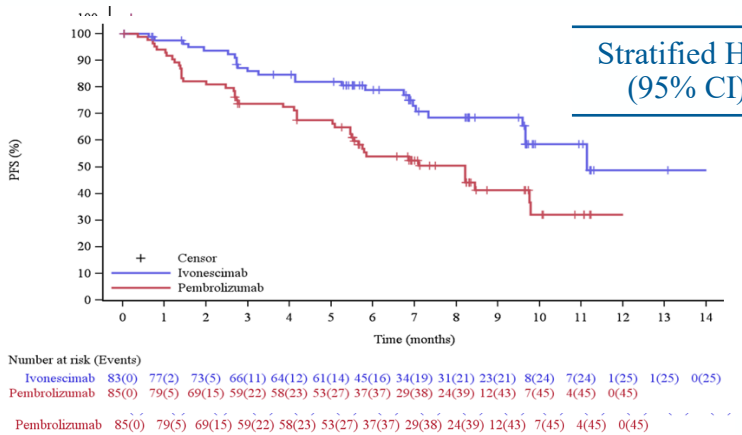


Stratified HR (95% CI)	0.54 (0.37, 0.79)

Number at risk (Events)

Ivonescimab	115(0)	112(1)	102(8)	90(15)	84(20)	67(30)	54(34)	34(41)	28(46)	15(47)	6(47)	4(47)	2(47)	1(47)	0(47)
Pembrolizumab	115(0)	108(4)	72(37)	62(47)	61(47)	50(54)	37(58)	24(63)	21(63)	13(63)	2(67)	1(67)	0(67)		

PD-L1 High (TPS ≥50%)



Stratified HR (95% CI)	0.46 (0.28, 0.75)

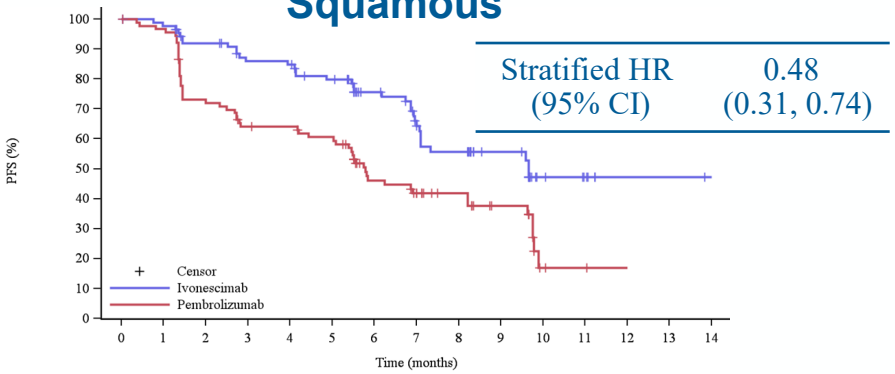
Number at risk (Events)

Ivonescimab	83(0)	77(2)	73(5)	66(11)	64(12)	61(14)	45(16)	34(19)	31(21)	23(21)	8(24)	7(24)	1(25)	1(25)	0(25)
Pembrolizumab	85(0)	79(5)	69(15)	59(22)	58(23)	53(27)	37(37)	29(38)	24(39)	12(43)	7(45)	4(45)	0(45)		

Pembrolizumab 85(0) 79(5) 69(15) 59(22) 58(23) 53(27) 37(37) 29(38) 24(39) 12(43) 7(45) 4(45) 0(45)

NSCLC Histology

Squamous

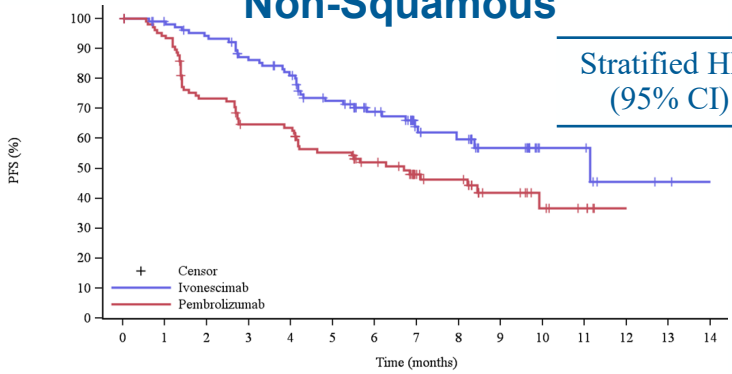


Stratified HR (95% CI)	0.48 (0.31, 0.74)

Number at risk (Events)

Ivonescimab	90(0)	87(2)	79(7)	71(12)	70(13)	63(17)	49(20)	37(27)	32(32)	21(32)	8(35)	5(35)	1(35)	1(35)	0(35)
Pembrolizumab	91(0)	87(3)	65(24)	56(32)	55(32)	51(35)	32(46)	25(49)	20(49)	13(51)	2(56)	1(56)	0(56)		

Non-Squamous



Stratified HR (95% CI)	0.54 (0.36, 0.82)

Number at risk (Events)

Ivonescimab	108(0)	102(1)	96(6)	85(14)	78(19)	65(27)	50(30)	31(33)	27(35)	17(36)	6(36)	6(36)	2(37)	1(37)	0(37)
Pembrolizumab	109(0)	100(6)	76(28)	65(37)	64(38)	52(46)	42(49)	28(52)	25(53)	12(55)	7(56)	4(56)	0(56)		

Ivonescimab showed meaningful improvement in PFS vs. pembrolizumab in patients with both low and high PD-L1, with squamous or non-squamous advanced NSCLC.

Abbreviations: PFS, progression-free survival; PD-L1, programmed death ligand 1; TPS, tumor proportion score; HR: hazard ratio; CI, confidence interval; NSCLC, non-small cell lung cancer.

2024 World Conference on Lung Cancer
Presidential Symposium, 9/8/24, San Diego, CA

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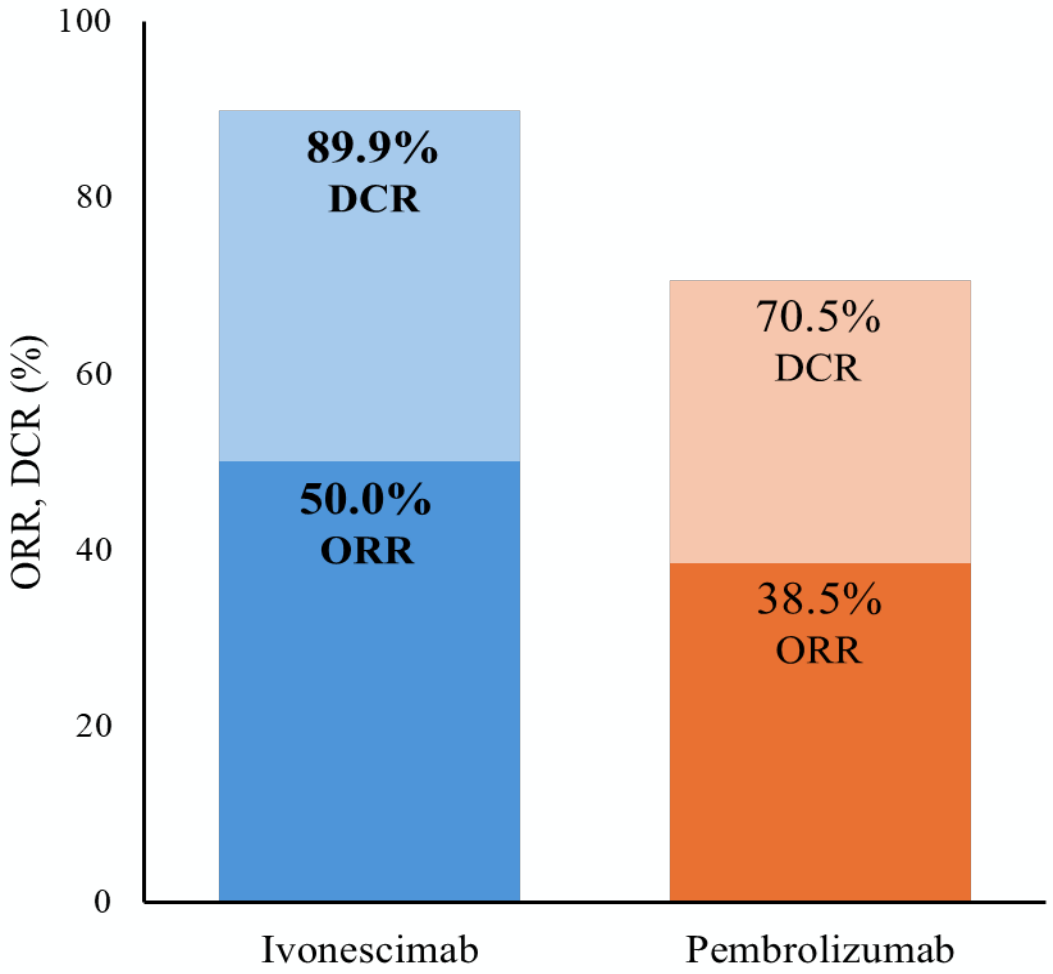
ORR, DCR and DoR per IRRC



	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

Data cut off: January 29, 2024.
Abbreviations: ORR, overall response rate; DCR, disease control rate; DoR, duration of response; IRRC, independent radiology review committee; CI, confidence interval; mo, month; NR, not reached; NE, not estimable.

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Safety Summary

TRAEs

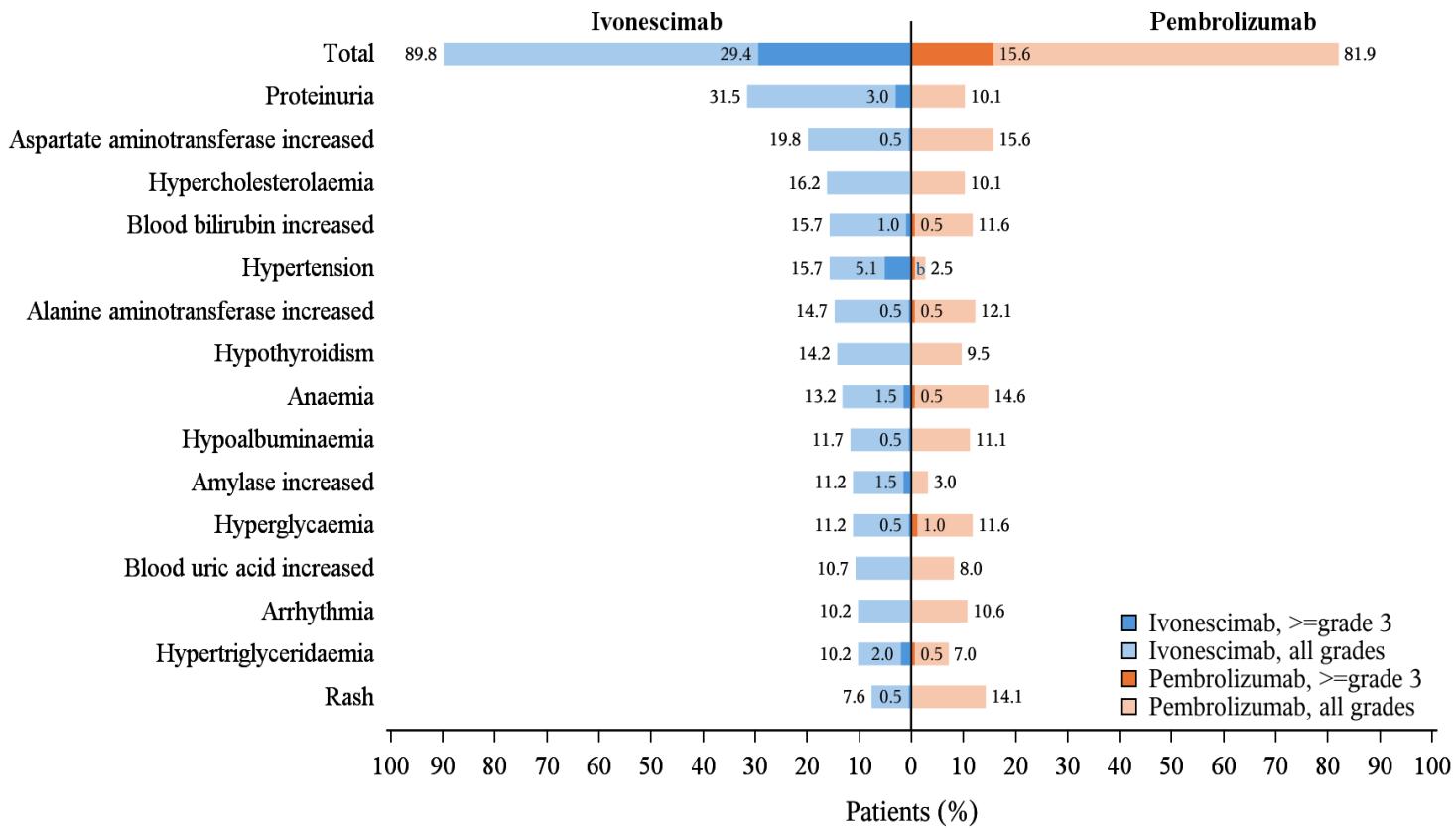
Safety Summary, n (%)	Ivonescimab (n = 197[a])	Pembrolizumab (n = 199[a])
TRAEs (all grades)	177 (89.8)	163 (81.9)
Grade≥3	58 (29.4)	31 (15.6)
Serious TRAEs	41 (20.8)	32 (16.1)
Leading to discontinuation	3 (1.5)	6 (3.0)
Leading to death	1 (0.5)	2 (1.0)

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 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.

[a] Patients who received ≥1 dose of study treatment. [b] The incidence of ≥grade 3 Hypertension was 0.5%.
Abbreviations: AEs, adverse events; TRAEs, treatment-related adverse events; SQ, squamous cell carcinoma.

Immune-Related and Possible 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

- 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.

Conclusions

- First-line ivonescimab significantly improve IRRC-assessed PFS in patients with aNSCLC and PD-L1 TPS ≥1%, compared with pembrolizumab (**median PFS (mos), 11.14 vs. 5.82; HR, 0.51; *p*<0.0001**).
- PFS benefit with ivonescimab were consistent across major clinical subgroups:
  - TPS ≥50%, HR = 0.46 (0.28, 0.75); TPS 1-49%, HR = 0.54 (0.37, 0.79)
  - SQ, HR = 0.48 (0.31, 0.74); non-SQ, HR = 0.54 (0.36, 0.82)
- Higher ORR (50.0% vs. 38.5%) and DCR (89.9% vs. 70.5%) were observed with ivonescimab vs. pembrolizumab.
- OS was not matured at this time; the OS analysis is event-driven and will be reported in the future.
- The safety profile of ivonescimab was consistent with prior studies and well tolerated, including in patients with SQ-NSCLC.
- HRQoL with ivonescimab was comparable to pembrolizumab.

First randomized phase 3 study to demonstrate a clinically significant improvement in efficacy with a novel drug compared to pembrolizumab in aNSCLC

Ivonescimab is an investigational therapy in this setting worldwide; ivonescimab is approved in 2L EGFRm NSCLC in China.
Abbreviations: IRRC, independent radiology review committee; PFS, progression-free survival; aNSCLC, advanced non-small cell lung cancer; PD-L1, programmed death ligand 1; TPS, tumor proportion score; mo, month; HR: hazard ratio; CI, confidence interval; SQ, squamous cell carcinoma; ORR, overall response rate; DCR, disease control rate; OS, overall survival.

Ongoing/Planned Ivonescimab Multi-regional Trials in NSCLC

Indication	Study	Treatment Population	Regimen	Phase	Status
NSCLC		2L EGFRm+	+ Chemo vs. chemo	III	Enrollment Complete
		1L Squamous	+ Chemo vs. pembrolizumab (PD-1) + chemo	III	Ongoing
		1L PD-L1 High	Monotherapy vs. pembrolizumab (PD-1)	III	Planned

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EGFR Mutations

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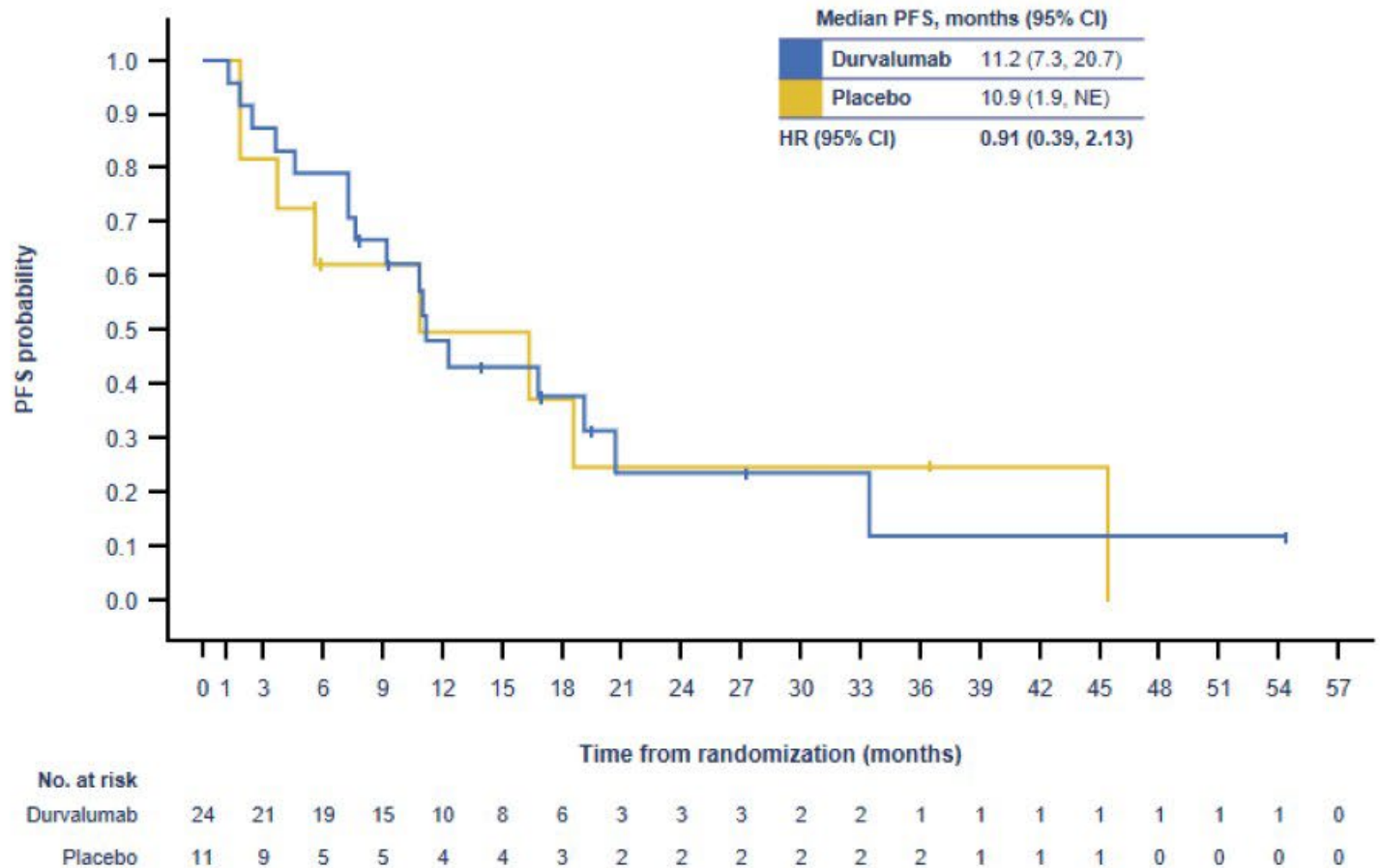
Unmet need in unresectable stage III EGFRm NSCLC

- In unresectable stage III NSCLC following CRT without progression, standard of care is consolidation durvalumab
- Benefit of consolidation durvalumab in EGFRm NSCLC is uncertain based on PACIFIC *post-hoc* subgroup analysis
- Efficacy of EGFR-TKIs is supported by the Phase 2 RECEL study and real-world data but prospective Phase 3 data are needed
- No approved targeted therapies for unresectable stage III EGFRm NSCLC

PACIFIC EGFRm *post-hoc* subgroup analysis



Daly et al. J Clin Oncol 2022;40:1356–1384; Remon et al. Ann Oncol 2021;32:1637–1642; Naidoo et al. J Thorac Oncol 2023;18:657–663; Xing et al. Int J Rad Oncol Biol Phys 2021;109:1349–1358; Sun et al. BMC Cancer 2020;20:646; Aredo et al. J Thorac Oncol 2021;16:1994–1998; Nassar et al. J Thorac Oncol 2024; S1556-0864(24)00032-7.

Figure reprinted from J Thorac Oncol, Vol 18, Naidoo et al., Brief report: Durvalumab after chemoradiotherapy in unresectable Stage III EGFR-mutant NSCLC: A post hoc subgroup analysis from PACIFIC, Pages 657–663, Copyright (2023), with permission from Elsevier.

CI, confidence interval; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; HR, hazard ratio; NSCLC, non-small cell lung cancer; NE, not evaluable; PFS progression-free survival; TKI, tyrosine kinase inhibitor

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LAURA Phase 3 double-blind study design

Patients with locally advanced, unresectable stage III* EGFRm NSCLC with no progression during / following definitive CRT† treatment

Key inclusion criteria:
- ≥18 years (Japan: ≥20)
- WHO PS 0 / 1
- Confirmed locally advanced, unresectable stage III* NSCLC
- Ex19del / L858R‡
- Maximum interval between last dose of CRT and randomization: 6 weeks

Osimertinib 80 mg, once daily

Randomization 2:1 (N=216)

Stratification by:
Concurrent vs sequential CRT
Stage IIIA vs stage IIIB/IIIC
China vs non-China

Placebo, once daily

Treatment duration until BICR-assessed progression (per RECIST v1.1), toxicity, or other discontinuation criteria

Open-label osimertinib after BICR-confirmed progression offered to both treatment arms§

Tumor assessments:
- Chest CT / MRI and brain MRI
- At baseline, every 8 weeks to Week 48, then every 12 weeks until BICR-assessed progression

Endpoints
- **Primary endpoint:** PFS assessed by BICR per RECIST v1.1 (sensitivity analysis: PFS by investigator assessment)
- **Secondary endpoints included:** OS, CNS PFS, safety

*According to AJCC / UICC staging (8th edition);
†Concurrent or sequential CRT comprising ≥2 cycles of platinum-based chemotherapy (or 5 doses of weekly platinum-based chemotherapy) and a total dose of radiation of 60 Gy ±10%;
‡Central or FDA-approved local testing (from a CLIA-approved laboratory, or accredited local laboratory for sites outside of USA) based on tissue;
§If deriving clinical benefit (osimertinib arm); by the judgement of treating physician (placebo arm).

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CLIA, Clinical Laboratory Improvement Amendments; CNS, central nervous system; CRT, chemoradiotherapy; CT, computed tomography; EGFRm, epidermal growth factor receptor-mutated; Ex19del, exon 19 deletion; FDA, Food and Drug Administration; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; UICC, Union for International Cancer Control; WHO PS, World Health Organization performance status

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Baseline characteristics

Characteristics, %	Osimertinib (n=143)	Placebo (n=73)
Sex: male / female	37 / 63	42 / 58
Age: median (range), years	62 (36–84)	64 (37–83)
Smoking history: formerly / currently / never	26 / 3 / 71	32 / 1 / 67
Race: Asian / non-Asian	81 / 19	85 / 15
WHO PS: 0 / 1	56 / 44	42 / 58
AJCC / UICC staging (8th edition) at diagnosis: IIIA / IIIB / IIIC	36 / 47 / 17	33 / 52 / 15
Histology: adenocarcinoma / other	97 / 3	95 / 5
EGFR mutation at randomization:* Ex19del / L858R	52 / 48†	59 / 41
Type of CRT: concurrent CRT / sequential CRT	92 / 8	85 / 15
Response to prior CRT: CR / PR / SD / PD / NE	3 / 47 / 43 / 0 / 8	4 / 37 / 51 / 0 / 8
Target lesion size by BICR:‡ mean (SD), mm	33 (18)	36 (17)

Data cut-off: January 5, 2024.
*Tissue tested by central or FDA-approved local test from a CLIA-approved laboratory, or accredited local laboratory for sites outside the USA;
†One patient in the osimertinib arm had missing EGFR mutation;
‡Post-CRT.

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CLIA, Clinical Laboratory Improvement Amendments; CR, complete response; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; FDA, Food and Drug Administration; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; UICC, Union for International Cancer Control; WHO PS, World Health Organization performance status

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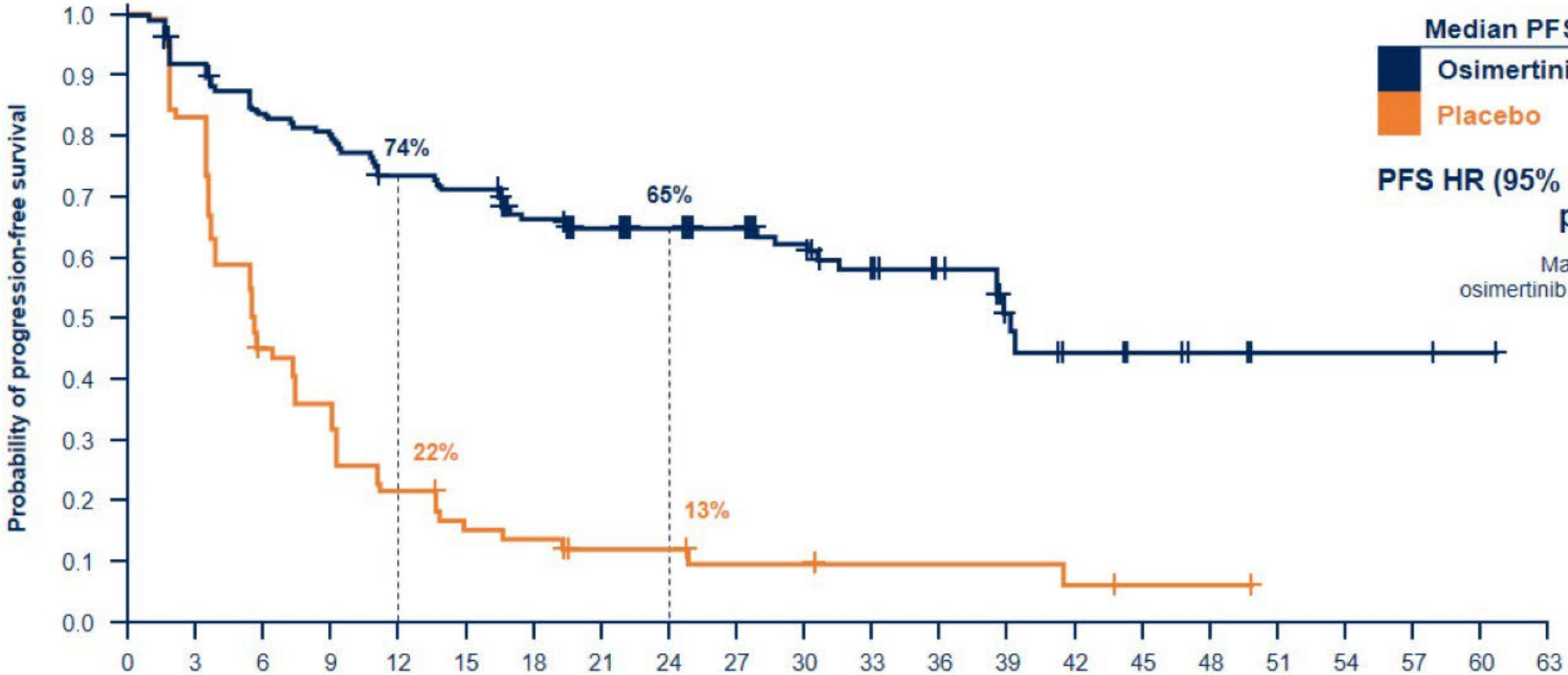
Progression-free survival by BICR



Median PFS, months (95% CI)

Osimertinib	39.1 (31.5, NC)
Placebo	5.6 (3.7, 7.4)

PFS HR (95% CI): 0.16 (0.10, 0.24), p<0.001

Maturity 56%:
osimertinib 40%, placebo 86%

No. at risk

Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Data cut-off: January 5, 2024.

Tick marks indicate censored data. Median follow-up for PFS (all patients): osimertinib 22.0 months, placebo 5.6 months. Median follow-up for PFS (censored patients): osimertinib 27.7 months, placebo 19.5 months.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

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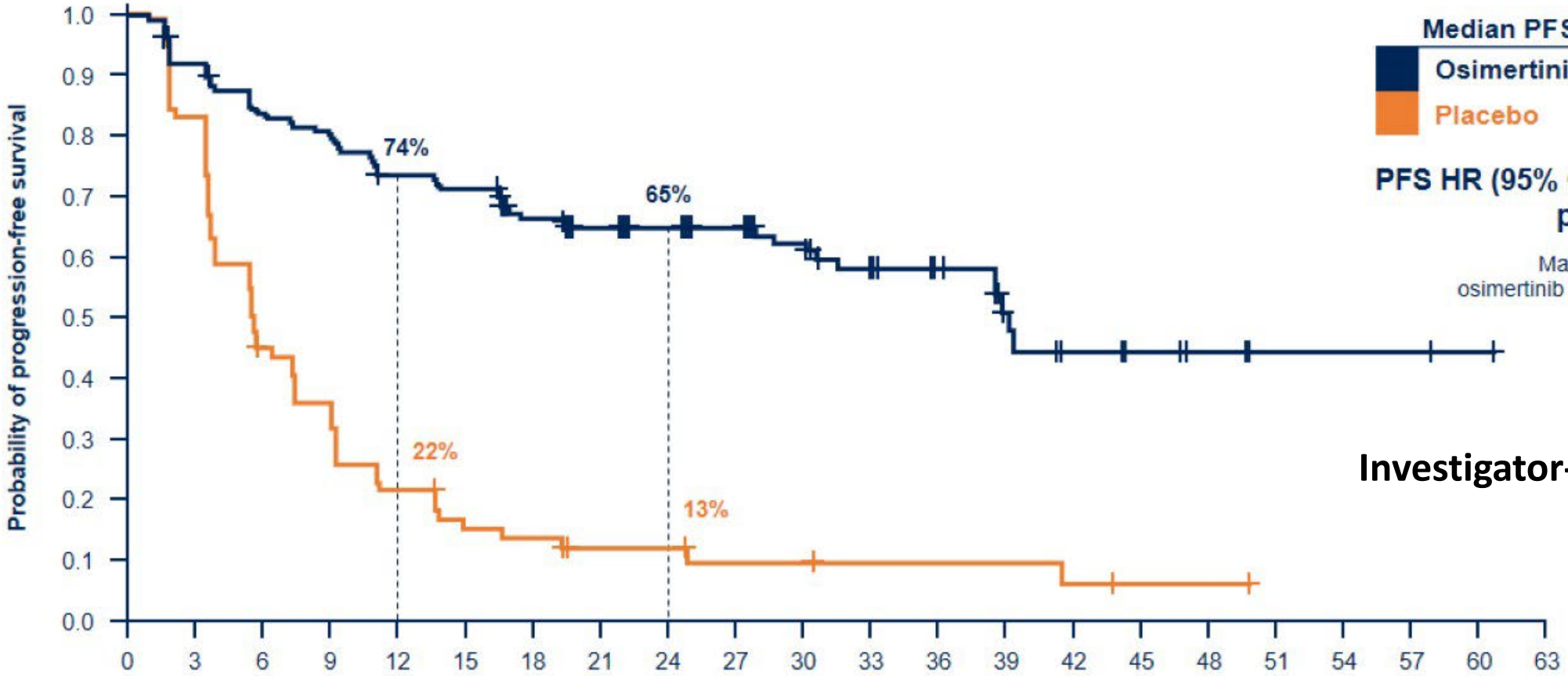
Progression-free survival by BICR



Median PFS, months (95% CI)

Osimertinib	39.1 (31.5, NC)
Placebo	5.6 (3.7, 7.4)

PFS HR (95% CI): 0.16 (0.10, 0.24), p<0.001

Maturity 56%:
osimertinib 40%, placebo 86%

Investigator-assessed HR 0.19

No. at risk

Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Tick marks indicate censored data. Median follow-up for PFS (all patients): osimertinib 22.0 months, placebo 5.6 months. Median follow-up for PFS (censored patients): osimertinib 27.7 months, placebo 19.5 months.

Data cut-off: January 5, 2024.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; PFS, progression-free survival

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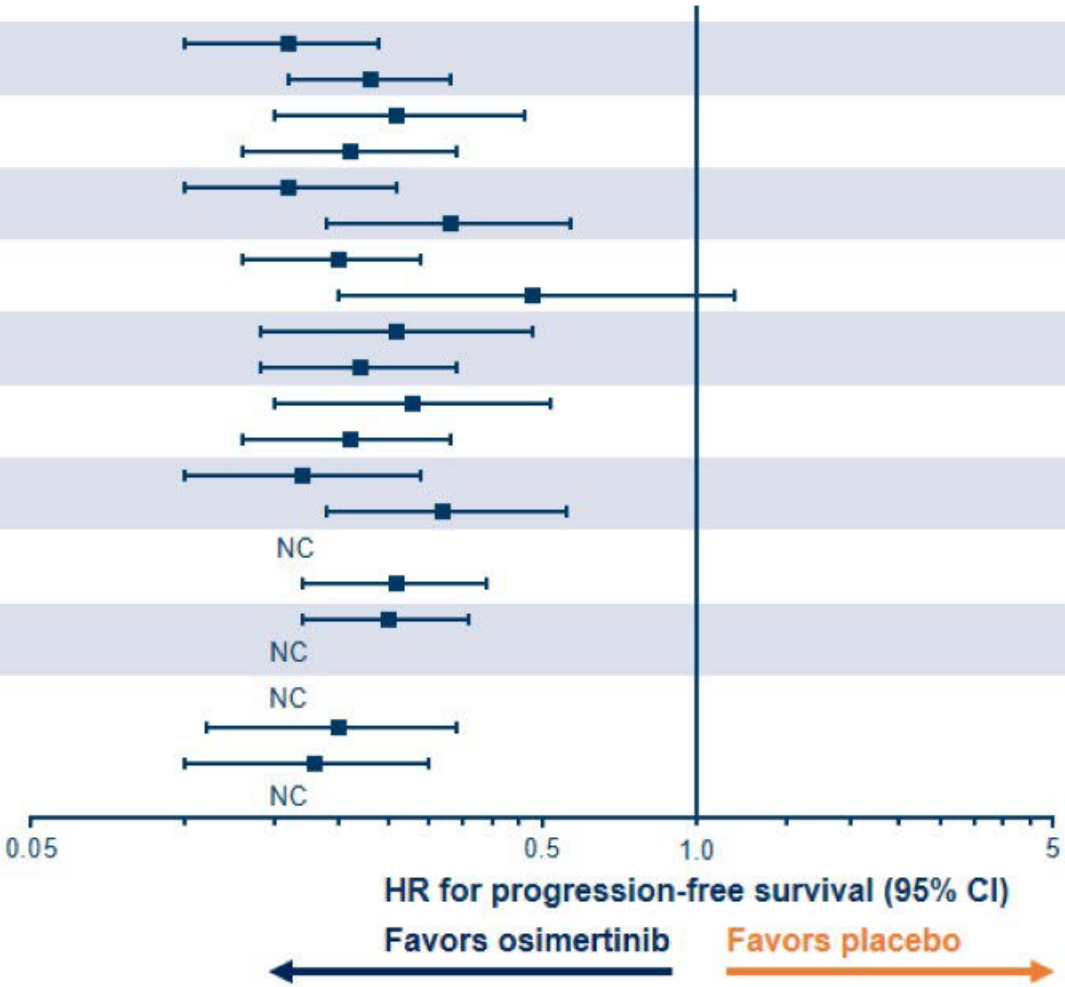
Progression-free survival by BICR across subgroups

Subgroup		No. of events / patients	HR	95% CI
Overall (N=216)	Stratified log-rank	120 / 216	0.16	0.10, 0.24
	Unadjusted Cox PH	120 / 216	0.23	0.16, 0.33
Sex	Male	50 / 84	0.26	0.15, 0.46
	Female	70 / 132	0.21	0.13, 0.34
Age	<65 years	67 / 120	0.16	0.10, 0.26
	≥65 years	53 / 96	0.33	0.19, 0.57
Race	Asian	98 / 178	0.20	0.13, 0.29
	Non-Asian	22 / 38	0.48	0.20, 1.19
Smoking history	Current / former (yes)	42 / 65	0.26	0.14, 0.48
	Never (no)	78 / 151	0.22	0.14, 0.34
Stage*	IIIA	42 / 76	0.28	0.15, 0.52
	IIIB / IIIC	78 / 140	0.21	0.13, 0.33
EGFR mutation†	Ex19del	65 / 117	0.17	0.10, 0.29
	L858R	55 / 98	0.32	0.19, 0.56
China cohort	Chinese	18 / 40	NC	NC, NC
	Non-Chinese	102 / 176	0.26	0.17, 0.39
Chemoradiotherapy	Concurrent	107 / 193	0.25	0.17, 0.36
	Sequential	13 / 23	NC	NC, NC
Response to prior CRT	Complete response	3 / 7	NC	NC, NC
	Partial response	53 / 94	0.20	0.11, 0.34
	Stable disease	58 / 98	0.18	0.10, 0.30
	Non-evaluable	6 / 17	NC	NC, NC



Data cut-off: January 5, 2024.

Note: HRs were calculated only for subgroups with >20 events across both arms to allow for meaningful analysis. Subgroup (not prespecified) of WHO PS: PS=0 HR 0.17 (95% CI 0.10, 0.28); PS=1 HR 0.34 (95% CI 0.20, 0.56);
*Stage prior to CRT by AJCC / UICC staging (8th edition);
†Central test of tumor tissue at screening, or local pre-existing test result; one patient in the osimertinib arm had missing EGFR mutation information.

AJCC, American Joint Committee on Cancer; BICR, blinded independent central review; CI, confidence interval; CRT, chemoradiotherapy; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; NC, not calculable; PFS, progression-free survival; PH, proportional-hazards model; UICC, Union for International Cancer Control; WHO PS, World Health Organization performance status

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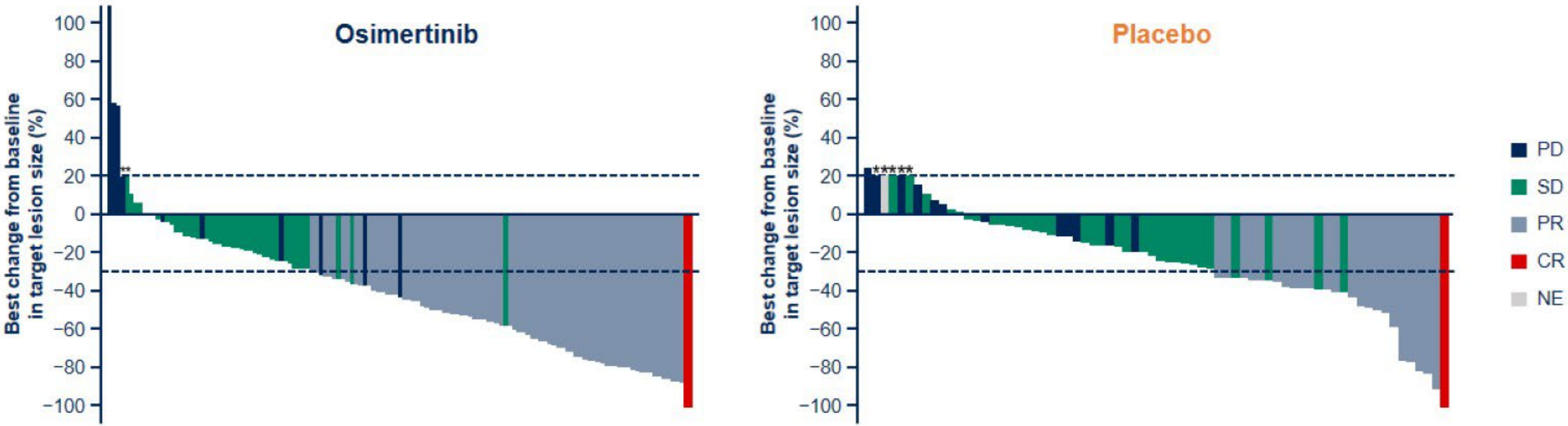
Tumor response by BICR



	Osimertinib (n=143)	Placebo (n=73)
Objective response rate, % (95% CI)	57 (49, 66)	33 (22, 45)
Disease control rate, % (95% CI)	89 (83, 94)	79 (68, 88)
Median duration of response, months (95% CI)	36.9 (30.1, NC)	6.5 (3.6, 8.3)

Data cut-off: January 5, 2024.
*Missing data imputed as +20% according to predefined rules.

BICR, blinded independent central review; CI, confidence interval; CR, complete response; NC, not calculable; NE, not evaluable PD, progressive disease; PR, partial response; SD, stable disease

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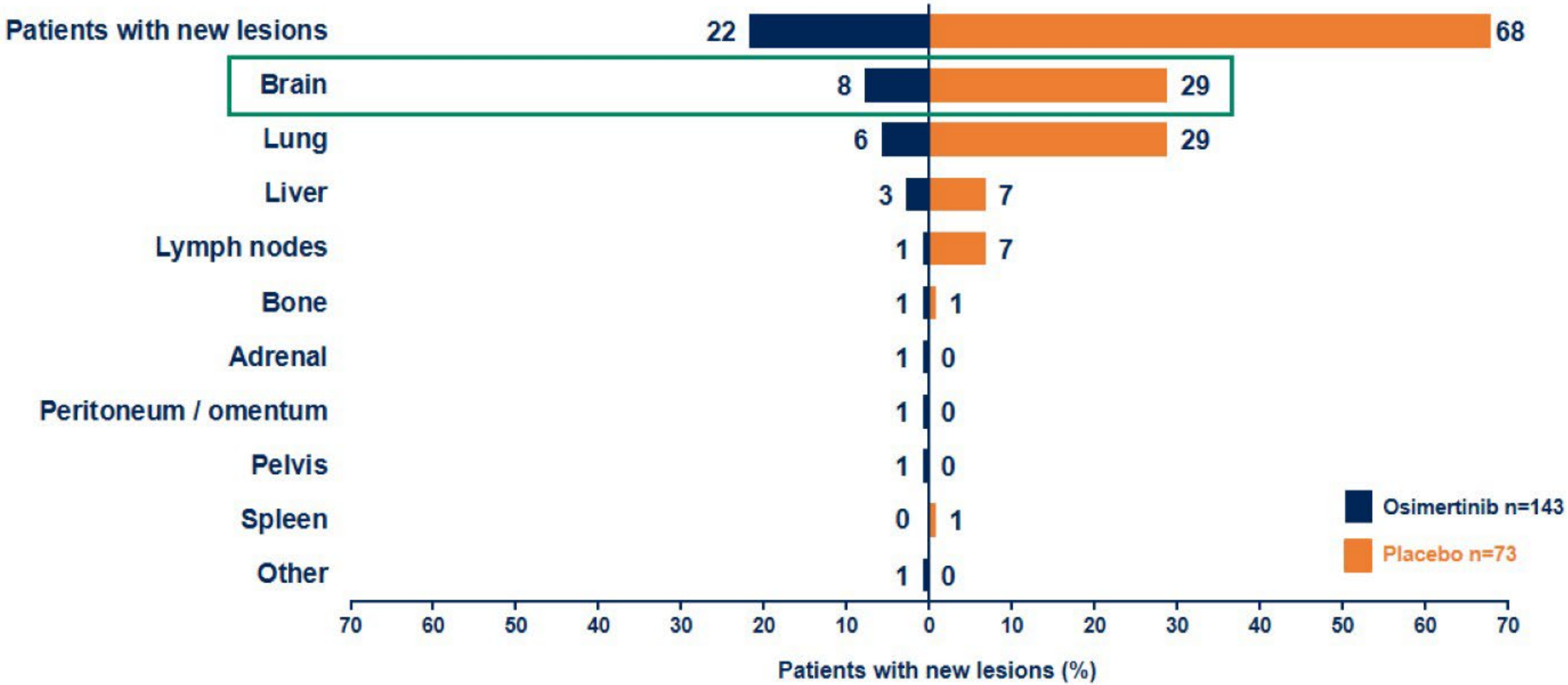
Sites of new lesions by BICR



Data cut-off: January 5, 2024.

Percentages based on number of patients in each treatment arm. Patients can have more than one new lesion site. Based on BICR assessments according to RECIST v1.1 and includes all new lesions at any time (including those whose RECIST progression event had been censored).

BICR, blinded independent central review

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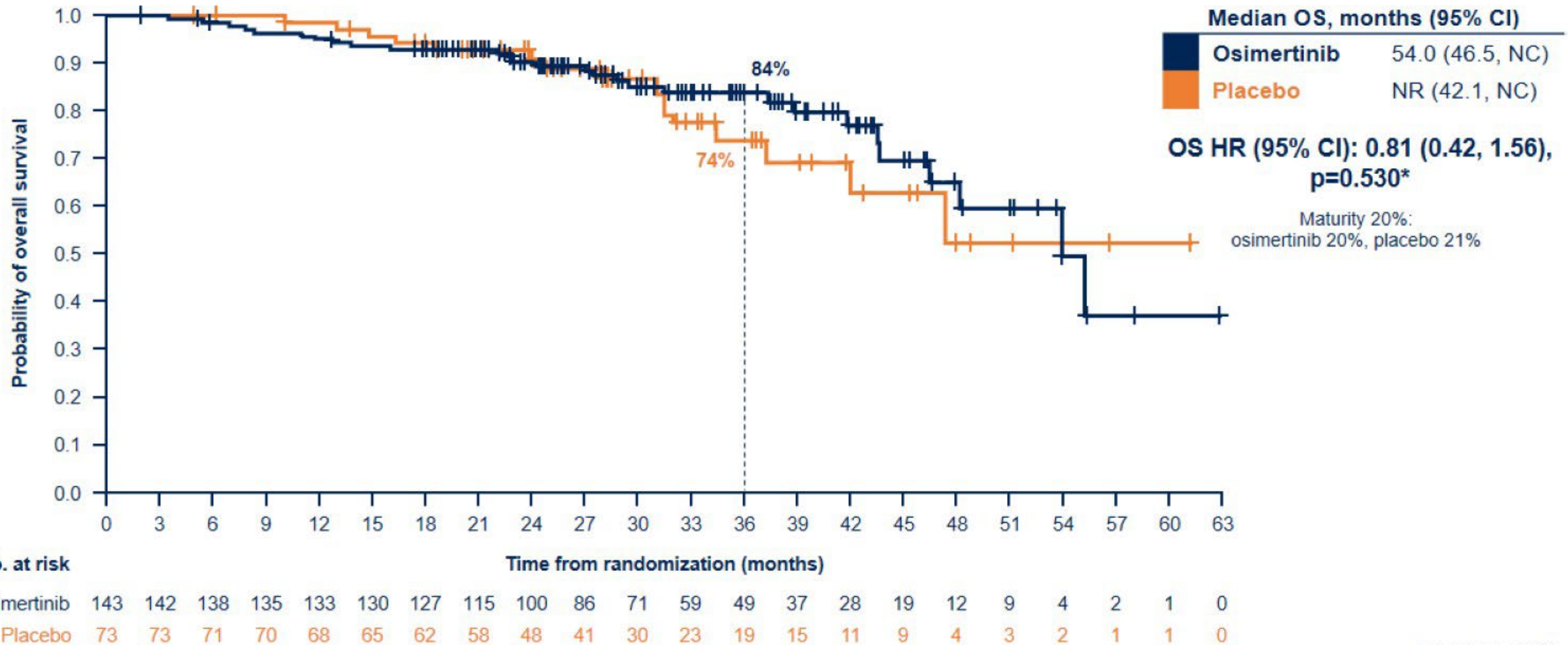
Interim analysis of overall survival

- In the placebo arm, 81% of patients with BICR-confirmed progression crossed over to osimertinib



No. at risk																						
Osimertinib	143	142	138	135	133	130	127	115	100	86	71	59	49	37	28	19	12	9	4	2	1	0
Placebo	73	73	71	70	68	65	62	58	48	41	30	23	19	15	11	9	4	3	2	1	1	0

Data cut-off: January 5, 2024.
Tick marks indicate censored data. *For statistical significance at this interim analysis, a p-value of <0.00036 was required; Median follow-up for OS (all patients): osimertinib 29.5 months, placebo 28.1 months. Median follow-up for OS (censored patients): osimertinib 30.9 months, placebo 28.1 months.

BICR, blinded independent central review; CI, confidence interval; HR, hazard ratio; NC, not calculable; NR, not reached; OS, overall survival

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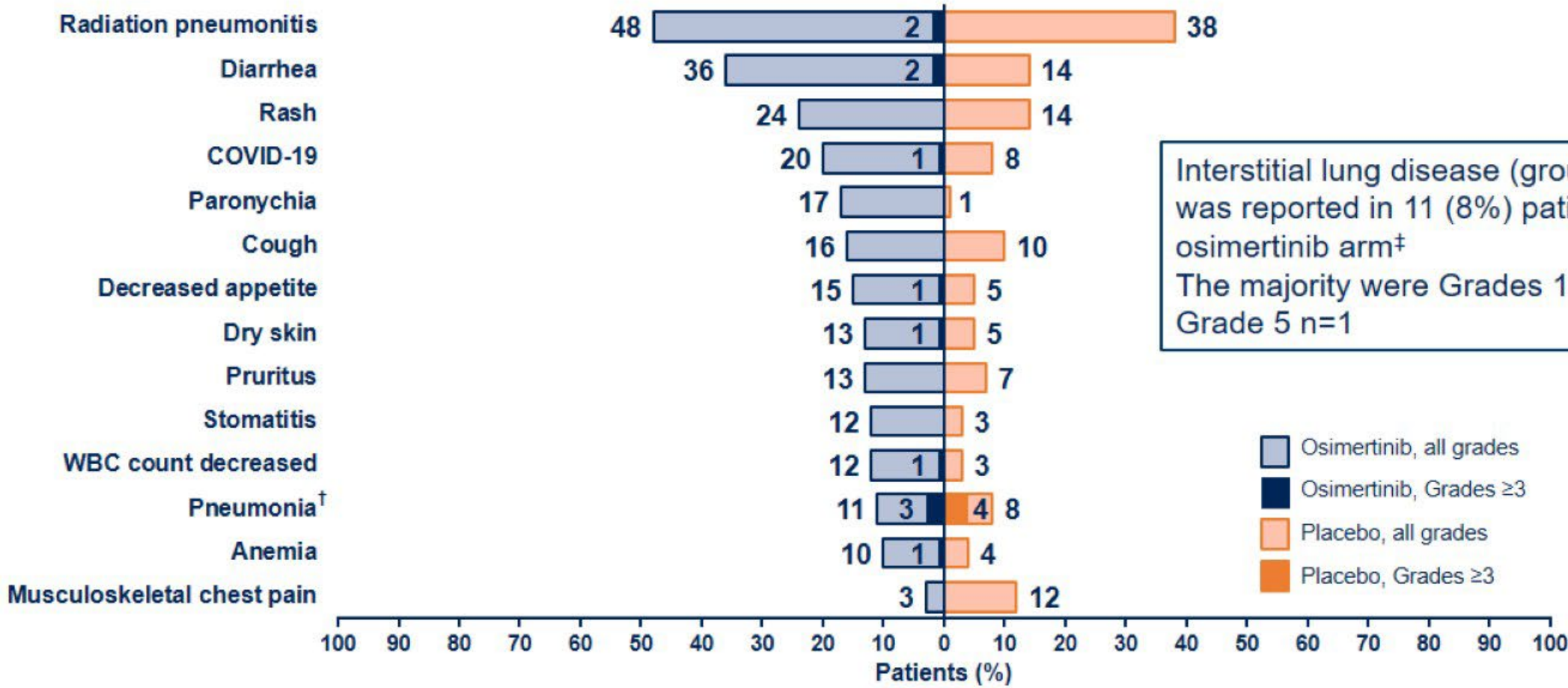
All-causality adverse events (≥10%)*

- The most common AE in both arms was radiation pneumonitis; the majority were low grade (no Grade 4 / 5), non-serious and manageable



Interstitial lung disease (grouped term) was reported in 11 (8%) patients in the osimertinib arm‡
The majority were Grades 1 / 2; Grade 5 n=1

Data cut-off: January 5, 2024.

*AEs with incidence of 10% or more in either treatment arm are shown. Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the discontinuation of study treatment and before starting subsequent cancer therapy; †One grade 5 AE of pneumonia was reported in the osimertinib arm; ‡Interstitial lung disease (grouped term) was reported in 1 patient (1%) in placebo arm; AE was pneumonitis, Grade 1.

AE, adverse event; WBC, white blood cells

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Conclusions

- In LAURA, osimertinib demonstrated a statistically significant and clinically meaningful improvement in PFS vs placebo by BICR in unresectable stage III EGFRm NSCLC following definitive chemoradiotherapy
  - **Median PFS** was **39.1 months** (95% CI 31.5, NC) with osimertinib, **5.6 months** (95% CI 3.7, 7.4) with placebo; **HR 0.16** (95% CI 0.10, 0.24), p<0.001
  - PFS benefit was consistent across subgroups
- Interim OS data showed a positive trend in favor of osimertinib, despite a high proportion of patients crossing over to osimertinib in the placebo arm (81%)
- Safety profile of osimertinib post-chemoradiotherapy was as expected and manageable
- EGFR mutation testing is critical in stage III disease to ensure optimal outcomes for patients with EGFRm NSCLC

Osimertinib will become the new standard of care for patients with unresectable stage III EGFRm NSCLC who have not progressed after definitive chemoradiotherapy

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BICR, blinded independent central review; CI, confidence interval; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; HR, hazard ratio; NC, not calculable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival

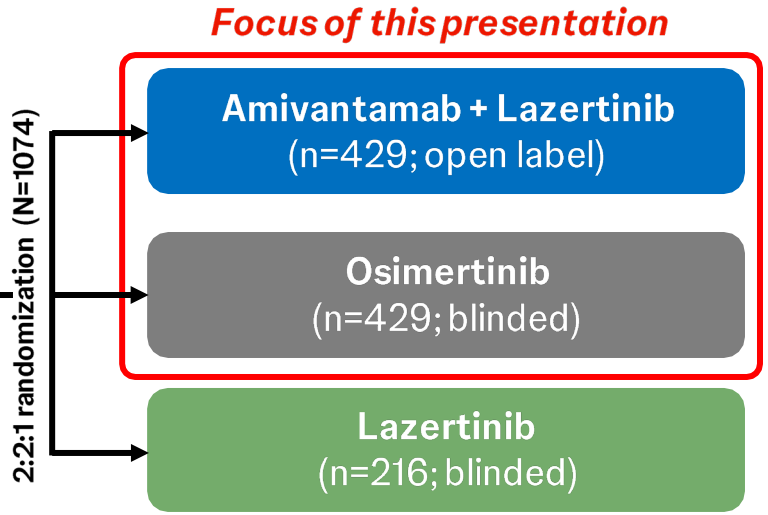
Data cut-off: January 5, 2024.

MARIPOSA Study Design and Methods

- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity[1-3]
- Lazertinib is a CNS-penetrant, 3rd-generation EGFR TKI[4,5]

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Treatment naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1
- Asymptomatic brain metastases did not require definitive treatment



Primary endpoint of PFS[a] by BICR per RECIST v1.1:

- Amivantamab + Lazertinib vs Osimertinib

High-risk subgroups analyzed:

- Brain metastases
- Liver metastases
- *TP53* co-mutation
- Detectable *EGFR*m ctDNA at baseline
- Without *EGFR*m ctDNA clearance at Week 9 (C3D1)

Diagnostic tests:

- ctDNA NGS[b]: baseline co-mutations
- ctDNA ddPCR[c]: detection and clearance of Ex19del and L858R

MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080). [a]Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS. The lazertinib arm was included to assess contribution of components. [b]Guardant Health G360® panel (Redwood City, CA). [c]Biodesix (Louisville, CO) ddPCR. C3D1 is Cycle 3 Day 1. Each cycle was 28 days.

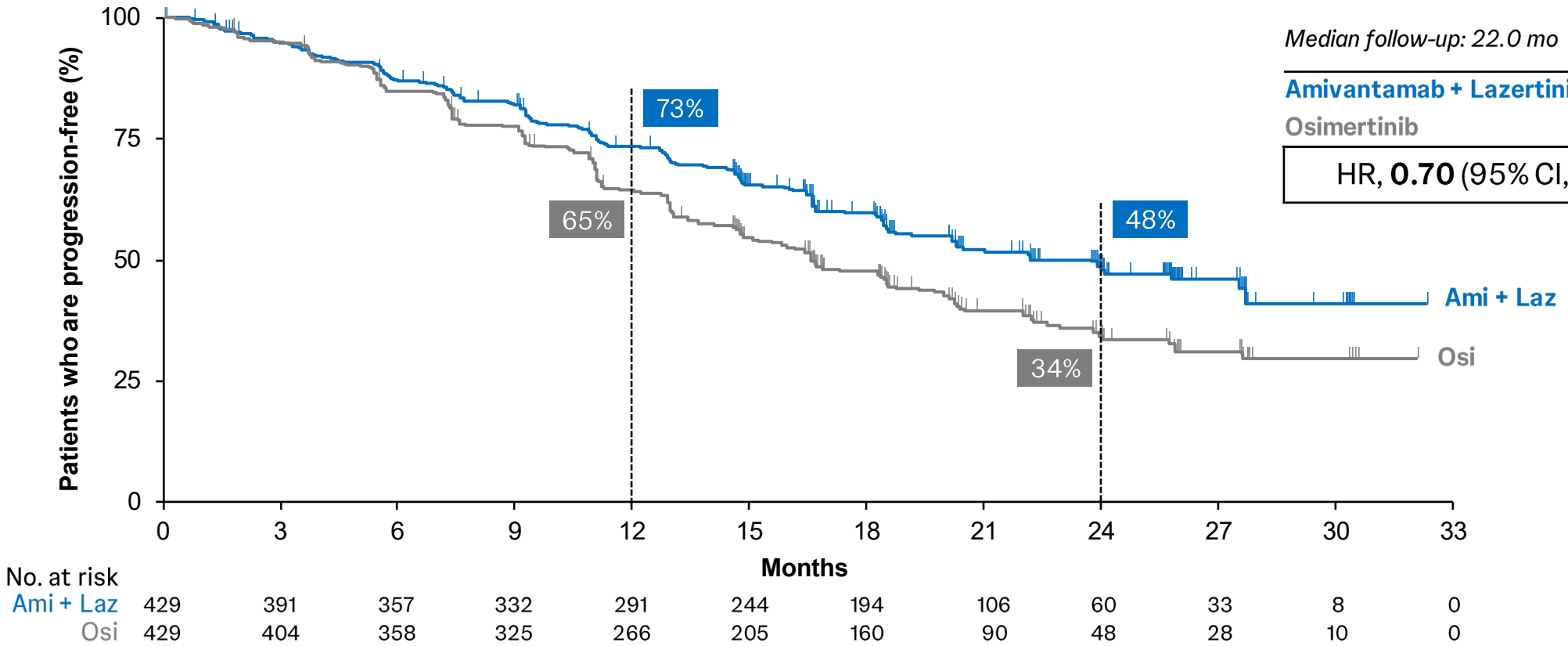
ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; NGS, next-generation sequencing.

1. Moores SL, et al. *Cancer Res.* 2016;76(13):3942-3953. 2. Vijayaraghavan S, et al. *Mol Cancer Ther.* 2020;19(10):2044-2056. 3. Yun J, et al. *Cancer Discov.* 2020;10(8):1194-1209. 4. Ahn MJ, et al. *Lancet Oncol.* 2019;20(12):1681-1690. 5. Cho BC, et al. *J Thorac Oncol.* 2022;17(4):558-567.

Presented by E Felip at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

Primary Endpoint: PFS by BICR

Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



Median follow-up: 22.0 mo	Median PFS (95% CI)
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

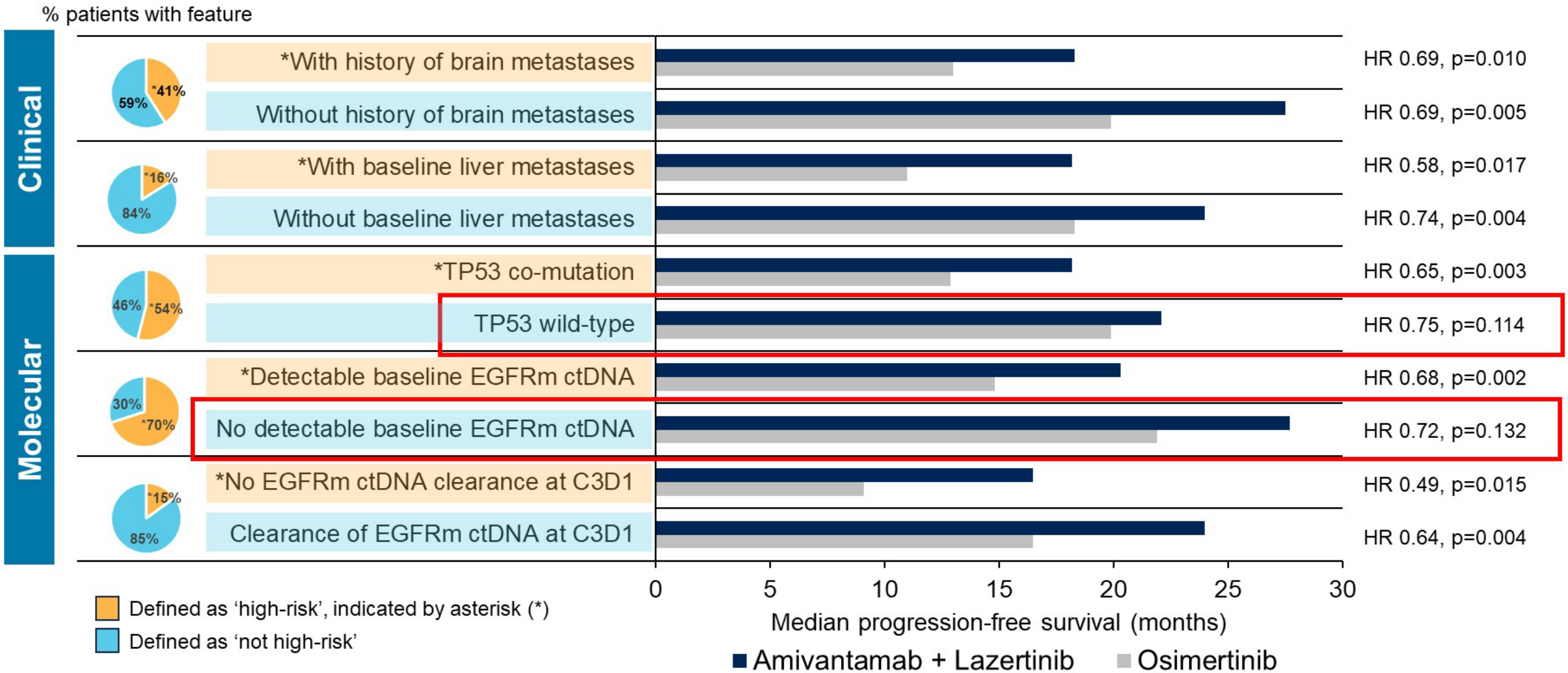
Amivantamab + lazertinib also meaningfully improved PFS2 and DoR vs osimertinib in MARIPOSA

Data cutoff: August 11, 2023.

Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

1. Cho BC, et al. Presented at: the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

MARIPOSA Subgroup Analysis Findings



TP53 co-mutation status identification by Guardant Health G360 panel; EGFRm ctDNA detection by Biodesix ddPCR

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Pros/Cons of "Intensified" 1st Line Therapy

Osimertinib

- Once daily oral therapy
- Gr 1-2 tox – 0-44%
- Gr ≥ 3 tox – 1-2%
- Less financial toxicity

FLAURA-2/MARIPOSA

- Multiple infusion center visits
- Once daily oral therapy
- Gr 1-2 tox – 20-57% Ami/lazer
  13-42% FLAURA-2
- Gr ≥ 3 tox – 1-15% AMI/lazer
  0-23% FLAURA-2
- Added met-related and chemo tox
- DVT prophylaxis (Ami/Lazer)
- More financial toxicity
- PFS benefit, uncertain OS benefit

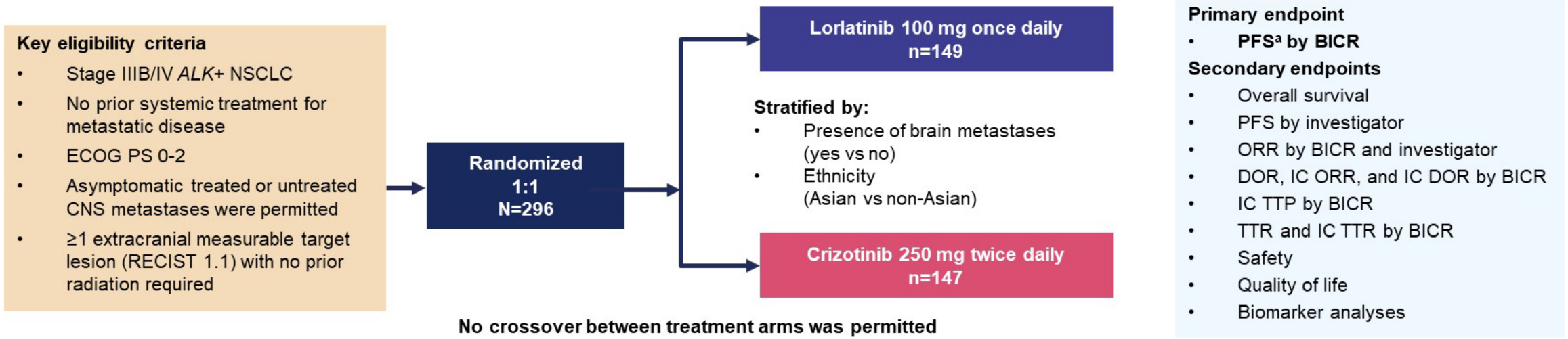
AdventHealth

ALK Fusions

AdventHealth

CROWN: A Randomized Global Phase 3 Study

- Lorlatinib is a brain-penetrant, third-generation ALK TKI that has broader coverage of *ALK* resistance mutations than second-generation ALK TKIs[1,2]



- At the planned interim analysis, at 18.3 months of median follow-up in the lorlatinib arm, median PFS by BICR was not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib, with an HR of 0.28 (95% CI, 0.19-0.41) and P<0.001[3]
- In a subsequent post hoc analysis, at 3 years of follow-up, median PFS by BICR was still not reached (95% CI, NR-NR) with lorlatinib and 9.3 months (95% CI, 7.6-11.1 months) with crizotinib (HR, 0.27; 95% CI, 0.18-0.39)[4]

ALK, anaplastic lymphoma kinase; BICR, blinded independent central review; CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; IC, intracranial; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor; TTP, time to tumor progression; TTR, time to tumor response.
[a] Defined as the time from randomization to RECIST-defined progression or death due to any cause.
1. Johnson TW, et al. *J Med Chem*. 2014;57:4720-4744. 2. Shaw AT, et al. *Lancet Oncol*. 2017;18:1590-1599. 3. Shaw AT, et al. *N Engl J Med*. 2020;383:2018-2029. 4. Solomon BJ, et al. *Lancet Respir Med*. 2023;11:354-366.

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Current Post Hoc Analyses at 5 Years

Endpoint evaluation by BICR stopped after the 3-year analysis

Key eligibility criteria

- Stage IIIB/IV *ALK*+ NSCLC
- No prior systemic treatment for metastatic disease
- ECOG PS 0-2
- Asymptomatic treated or untreated CNS metastases were permitted
- ≥1 extracranial measurable target lesion (RECIST 1.1) with no prior radiation required

Randomized 1:1 N=296

Lorlatinib 100 mg once daily n=149

Stratified by:

- Presence of brain metastases (yes vs no)
- Ethnicity (Asian vs non-Asian)

Crizotinib 250 mg twice daily n=147

No crossover between treatment arms was permitted

Current analyses

Data cutoff: October 31, 2023

- **Investigator Assessed**
  - PFS[a]
  - ORR and IC ORR
  - DOR and IC DOR
  - IC TTP
- Safety
- Biomarker analyses

- The median duration of follow-up for PFS was 60.2 months (95% CI, 57.4-61.6) in the lorlatinib arm and 55.1 months (95% CI, 36.8-62.5) in the crizotinib arm

CNS, central nervous system; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; IC, intracranial; ORR, objective response rate; NSCLC, non-small cell lung cancer; PFS, progression-free survival; PS, performance status; RECIST, Response Evaluation Criteria in Solid Tumors; TTP, time to tumor progression.

[a] Defined as the time from randomization to RECIST-defined progression or death due to any cause.

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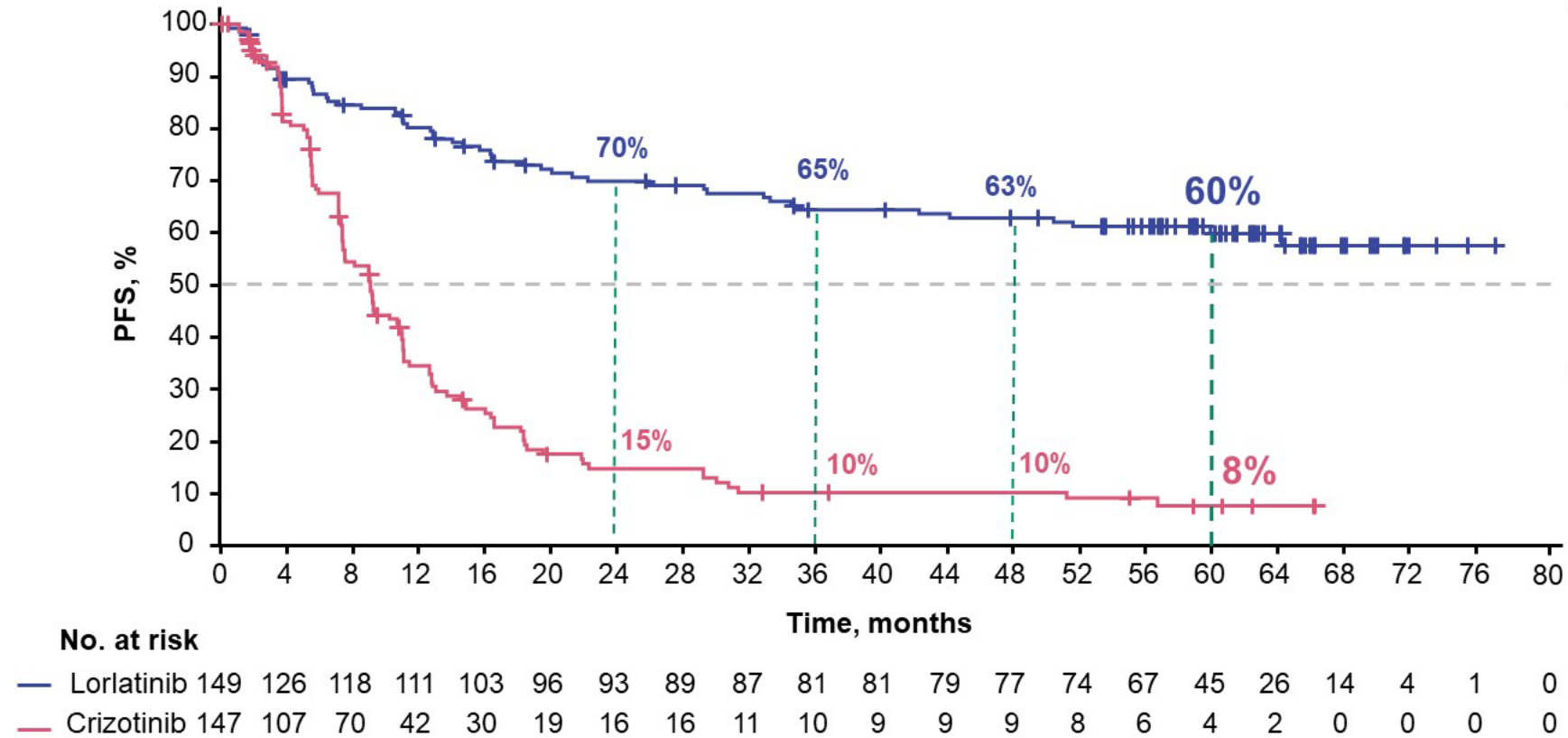
At 60.2 Months of Median Follow-Up, Median PFS by Investigator Was Still Not Reached With Lorlatinib



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	55	115
PFS, median (95% CI), months	NR (64.3-NR)	9.1 (7.4-10.9)
HR (95% CI)	**0.19 (0.13-0.27)**	

At the time of this analysis, the required number of OS events for a protocol-specified second interim analysis **has not been reached**. OS follow up is ongoing

HR, hazard ratio; NR, not reached; OS, overall survival; PFS, progression-free survival.

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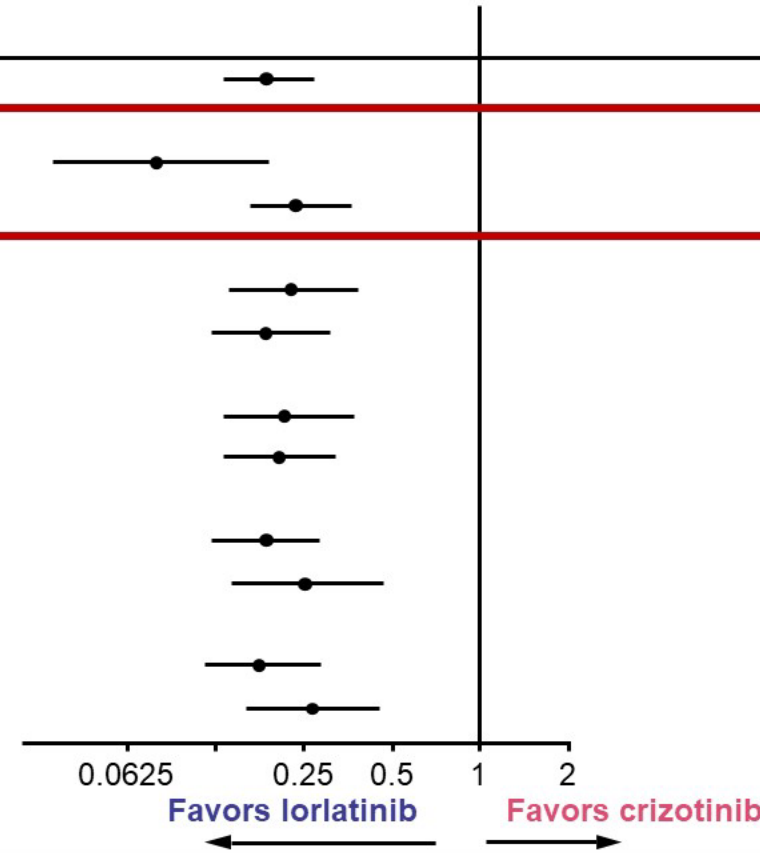
PFS Benefit With Lorlatinib Was Observed Across Patient Subgroups

Subgroup	Patients, n (%)		Events, n		HR (95% CI)
	Lorlatinib	Crizotinib	Lorlatinib	Crizotinib	
All patients (stratified)	149 (100)	147 (100)	55	115	0.19 (0.13-0.27)
Presence of brain metastases					
Yes	35 (23)	38 (26)	16	34	0.08 (0.04-0.19)
No	114 (77)	109 (74)	39	81	0.24 (0.16-0.36)
Ethnic origin					
Asian	66 (44)	65 (44)	25	50	0.23 (0.14-0.38)
Non-Asian	83 (56)	82 (56)	30	65	0.19 (0.12-0.31)
Sex					
Male	65 (44)	56 (38)	24	48	0.22 (0.13-0.37)
Female	84 (56)	91 (62)	31	67	0.21 (0.13-0.32)
Age					
<65 years	96 (64)	110 (75)	33	88	0.19 (0.12-0.28)
≥65 years	53 (36)	37 (25)	22	27	0.26 (0.14-0.47)
Smoking status					
Never	81 (54)	94 (64)	30	75	0.18 (0.12-0.29)
Current/former	68 (46)	52 (35)	25	39	0.27 (0.16-0.45)



PFS, progression-free survival.

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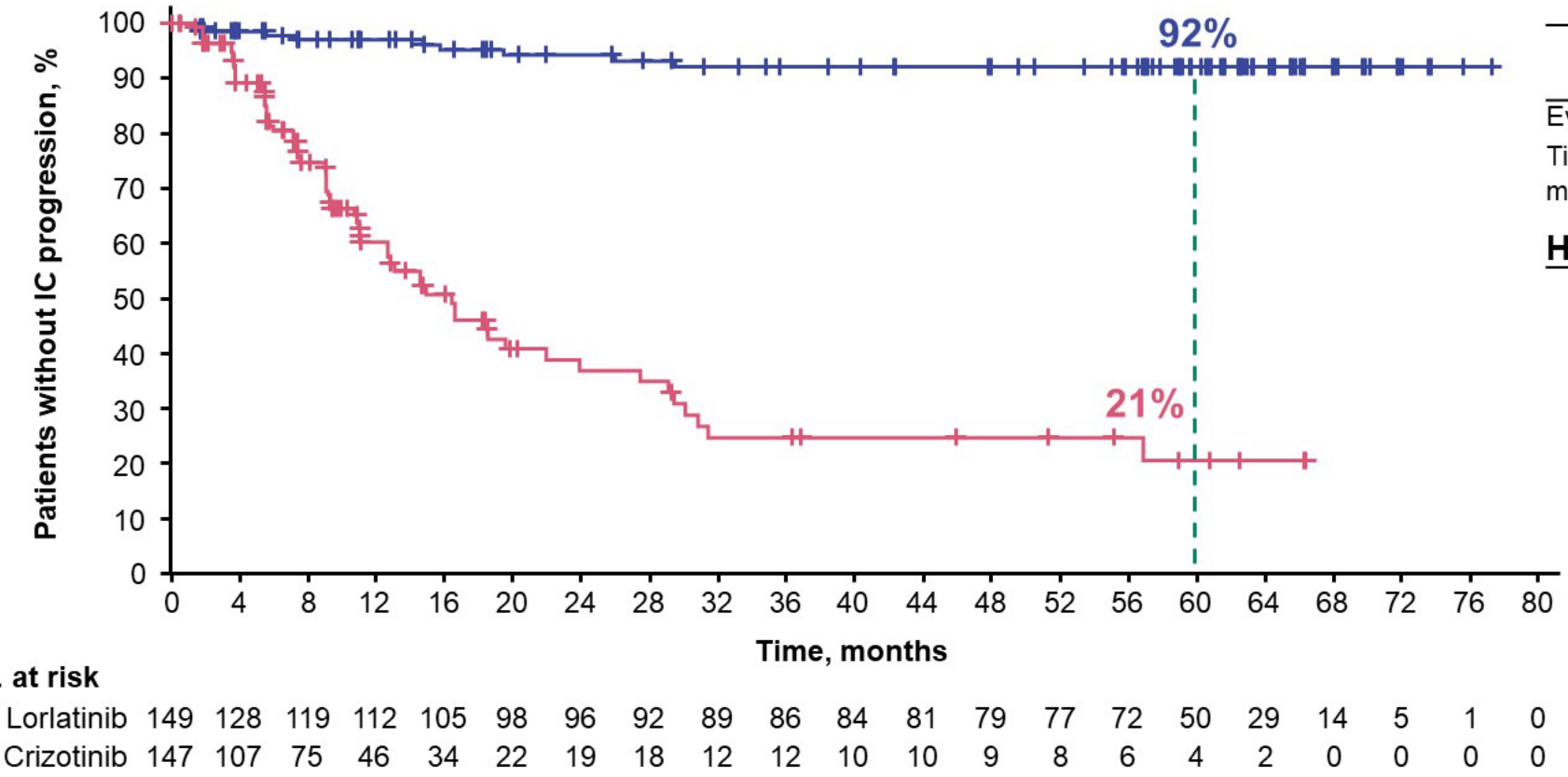
Time to IC Progression by Investigator Assessment Was Longer With Lorlatinib (ITT Population)



	Lorlatinib (n=149)	Crizotinib (n=147)
Events, n	9	65
Time to IC progression, median (95% CI), months	NR (NR-NR)	16.4 (12.7-21.9)
HR (95% CI)	**0.06 (0.03-0.12)**	

Tumor assessments, including brain MRI, have been performed every 8 weeks in all patients throughout the study

HR, hazard ratio; IC, intracranial; ITT, intention to treat; NR, not reached. MRI, magnetic resonance imaging

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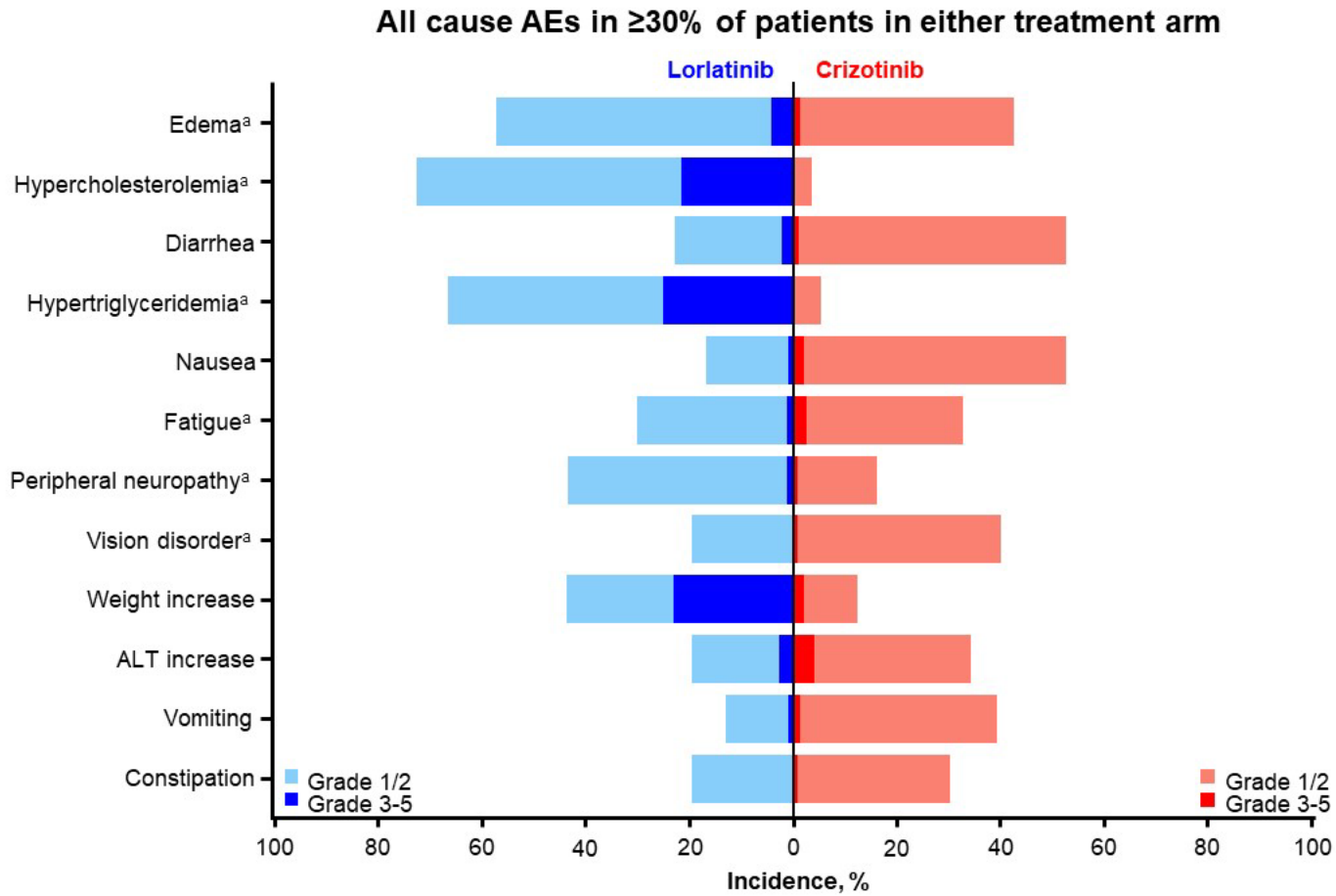
Safety Profile of Lorlatinib Was Consistent With That Observed in Prior Analyses

All-causality AEs observed in the lorlatinib arm:

- AEs of any-grade, grade 3/4, and serious occurred in 100%, 77%, and 44% of patients
- The higher incidence of grade 3/4 AEs was largely due to hypertriglyceridemia (25%), weight increase (23%), hypercholesterolemia (21%), and hypertension (12%)
- CNS AEs[b] occurred in 42% of patients in the lorlatinib arm, 86% of which were grade 1/2
- AEs led to dose reduction in 23% of patients, temporary treatment discontinuation in 62%, and permanent discontinuation in 11%; of which 5% were due to treatment-related AEs, all reported during the first 26 months



AE, adverse event; CNS, central nervous system.
[a]This category comprised a cluster of AEs that may represent similar clinical symptoms or syndromes. [b]Includes cognitive effects (28%), mood effects (21%), speech effects (6%), and psychotic effects (5%),

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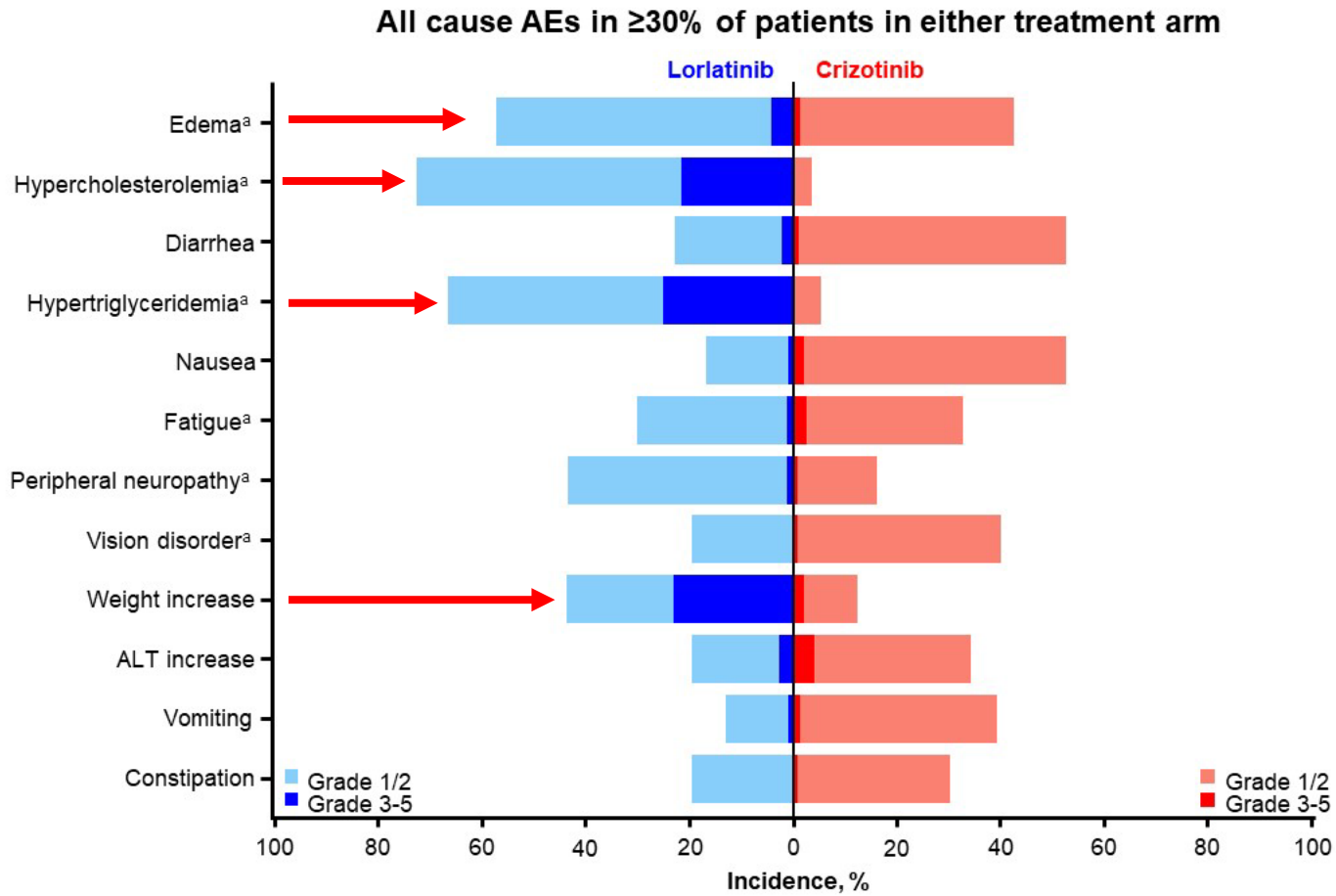

AE, adverse event; CNS, central nervous system.
[a]This category comprised a cluster of AEs that may represent similar clinical symptoms or syndromes. [b]Includes cognitive effects (28%), mood effects (21%), speech effects (6%), and psychotic effects (5%),

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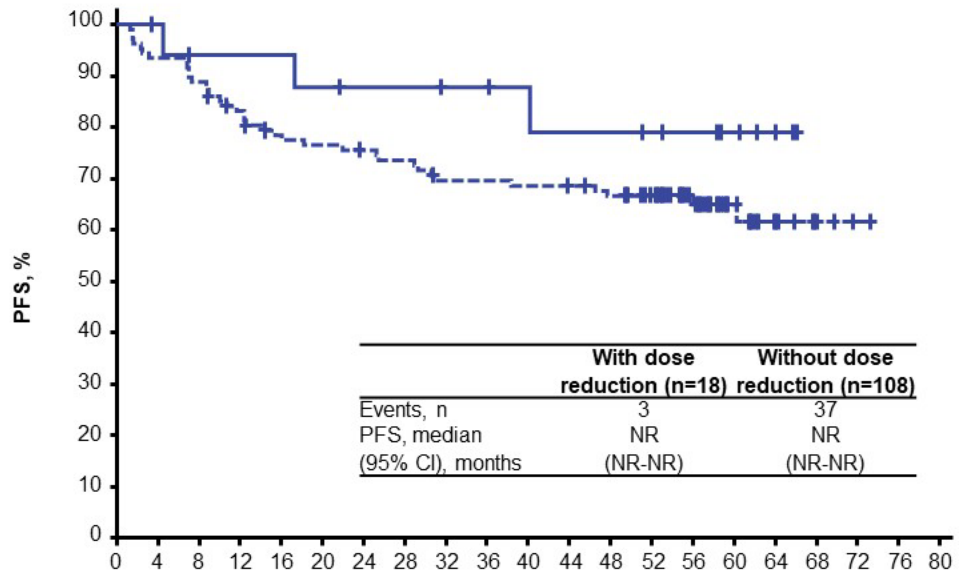
Dose Reduction Did Not Impact Efficacy of Lorlatinib in Patients Who Had Dose Reduction in the First 16 Weeks

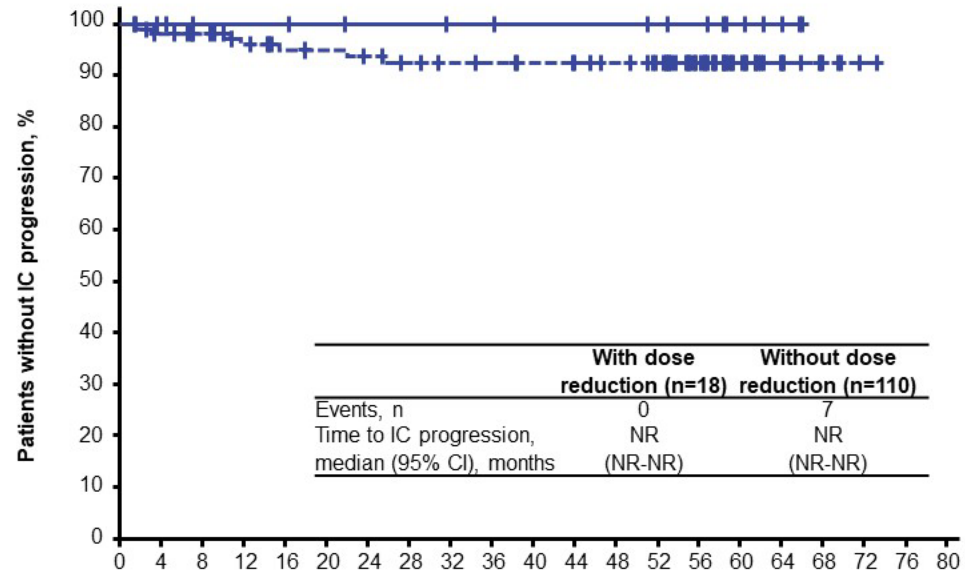
PFS



	With dose reduction (n=18)	Without dose reduction (n=108)
Events, n	3	37
PFS, median (95% CI), months	NR (NR-NR)	NR (NR-NR)

No. at risk																					
With dose reduction	18	17	15	15	15	14	12	12	11	11	10	9	9	8	7	5	3	0	0	0	-
Without dose reduction	108	101	96	88	81	79	77	75	70	70	69	68	65	59	38	21	11	4	1	0	-

Time to IC Progression



	With dose reduction (n=18)	Without dose reduction (n=110)
Events, n	0	7
Time to IC progression, median (95% CI), months	NR (NR-NR)	NR (NR-NR)

No. at risk																					
With dose reduction	18	17	15	15	15	14	12	12	11	11	10	10	10	9	8	5	3	0	0	0	-
Without dose reduction	110	102	97	90	83	82	80	77	75	73	71	69	67	63	42	24	11	5	1	0	-

IC, intracranial; NR, not reached; PFS, progression-free survival.

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Conclusions

- After 5 years of follow-up in the CROWN study, with lorlatinib treatment:
  - Median PFS has still not been reached and PFS was 60%
  - The probability of being free of intracranial progression was 92%
  - No new safety signals emerged
  - Efficacy benefit was seen across all subgroups, including patients with poor prognostic biomarkers
- The PFS observed with lorlatinib corresponds to the longest PFS reported in advanced NSCLC
- These systemic efficacy results coupled with protection from intracranial progression and absence of new safety signals, indicates that first-line lorlatinib provides an unprecedented improvement in outcomes for patients with advanced *ALK*+ NSCLC

NSCLC, non-small cell lung cancer; PFS, progression-free survival.

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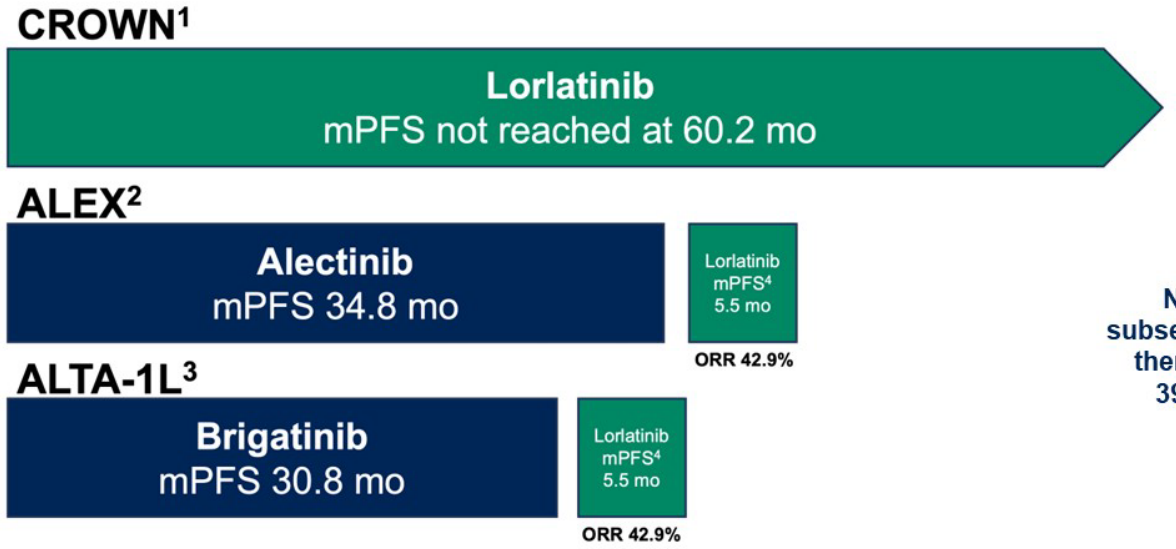
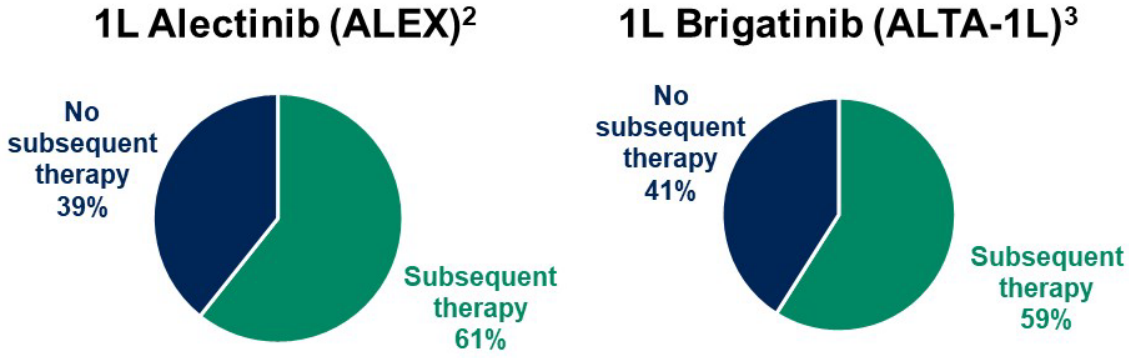
CROWN: Conclusions and Implications for Practice

The 5-year updated analyses of CROWN (re)affirm lorlatinib as standard-of-care first-line treatment for patients with metastatic ALK+ NSCLC



1L ALK TKI PFS from indicated trials, per investigator assessment

Attrition Following 1L ALK TKI



1. Solomon BJ et al., Lancet Respir Med 2023;11(4):354-66; 2. Mok T et al., Ann Oncol 2020;31(8):1056-64
3. Camidge DR et al., J Thorac Oncol 2021;16(12):2091-108; 4. Felip E et al., Ann Oncol 2021;32(5):620-30

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KRAS Mutations

AdventHealth

KRYSTAL-12[a] study design

Key eligibility criteria

- Locally advanced or metastatic NSCLC with *KRAS*^{G12C} mutation[b]
- Prior treatment with platinum-based chemotherapy and anti-PD-(L)1 therapy[c]
- ECOG PS 0–1
- Stable brain metastases allowed

Stratified by:

- **Region (non-Asia-Pacific vs Asia-Pacific)**
- **Prior treatment (sequential vs concurrent chemotherapy and immunotherapy)**

N = 453

R 2:1

ADA 600 mg BID PO[d]

DOCE 75 mg/m^2 Q3W IV

Crossover from DOCE to ADA was allowed in cases where disease progression per RECIST v1.1 was confirmed by real-time BICR[e]

Primary endpoint

- PFS by BICR (RECIST v1.1)

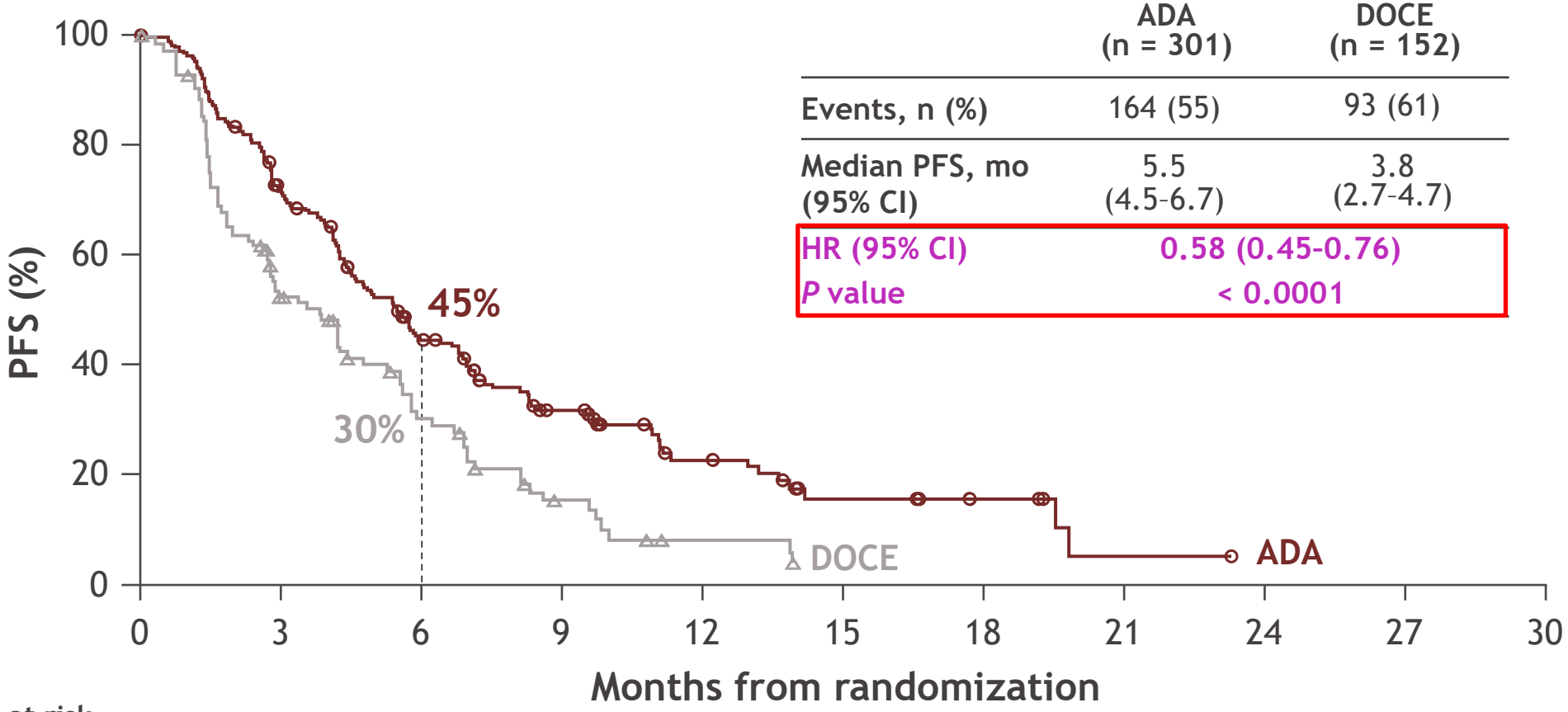
Secondary endpoints

- ORR by BICR (RECIST v1.1)
- DOR
- OS
- Safety
- Patient-reported outcomes

Database lock: March 19, 2024. Data cut-off: December 31, 2023.

[a]NCT04685135. [b]Detected in tumor tissue using sponsor-approved local or central testing. [c]No washout period was required between prior therapy and study treatment. [d]Tablet formulation, except for four patients who initially received the capsule formulation. [e]Other crossover criteria: ECOG PS 0–2, recovery from DOCE-related AEs to grade 1 or baseline (except peripheral neuropathy and alopecia for which grade 2 is acceptable).

Primary endpoint: PFS[a] per BICR



	ADA (n = 301)	DOCE (n = 152)
Events, n (%)	164 (55)	93 (61)
Median PFS, mo (95% CI)	5.5 (4.5-6.7)	3.8 (2.7-4.7)
HR (95% CI)	0.58 (0.45-0.76)	
P value	< 0.0001	

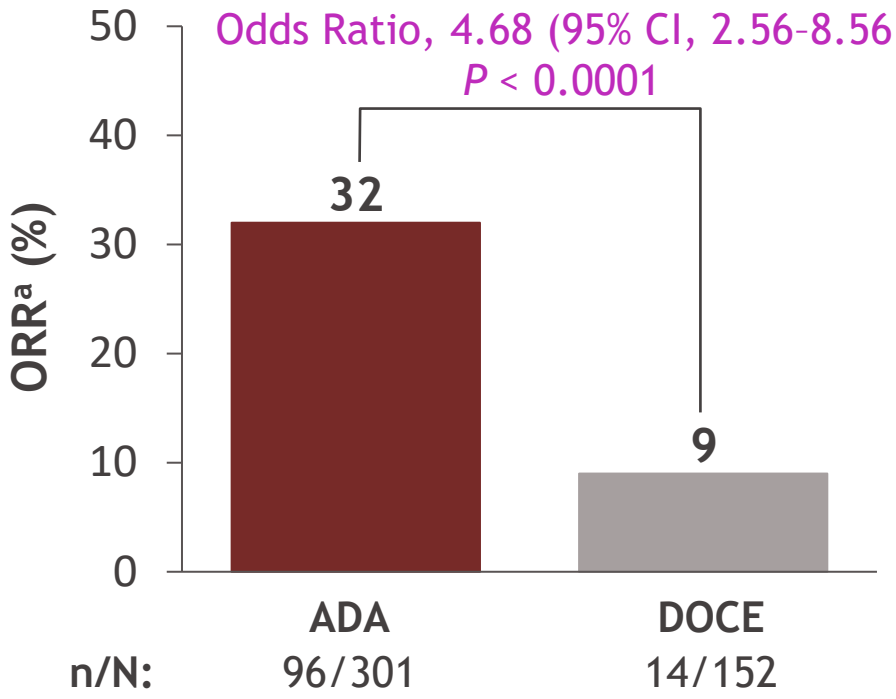
No. at risk

ADA	301	160	77	41	19	8	5	1	0	0	0
DOCE	152	51	24	9	2	0	0	0	0	0	0

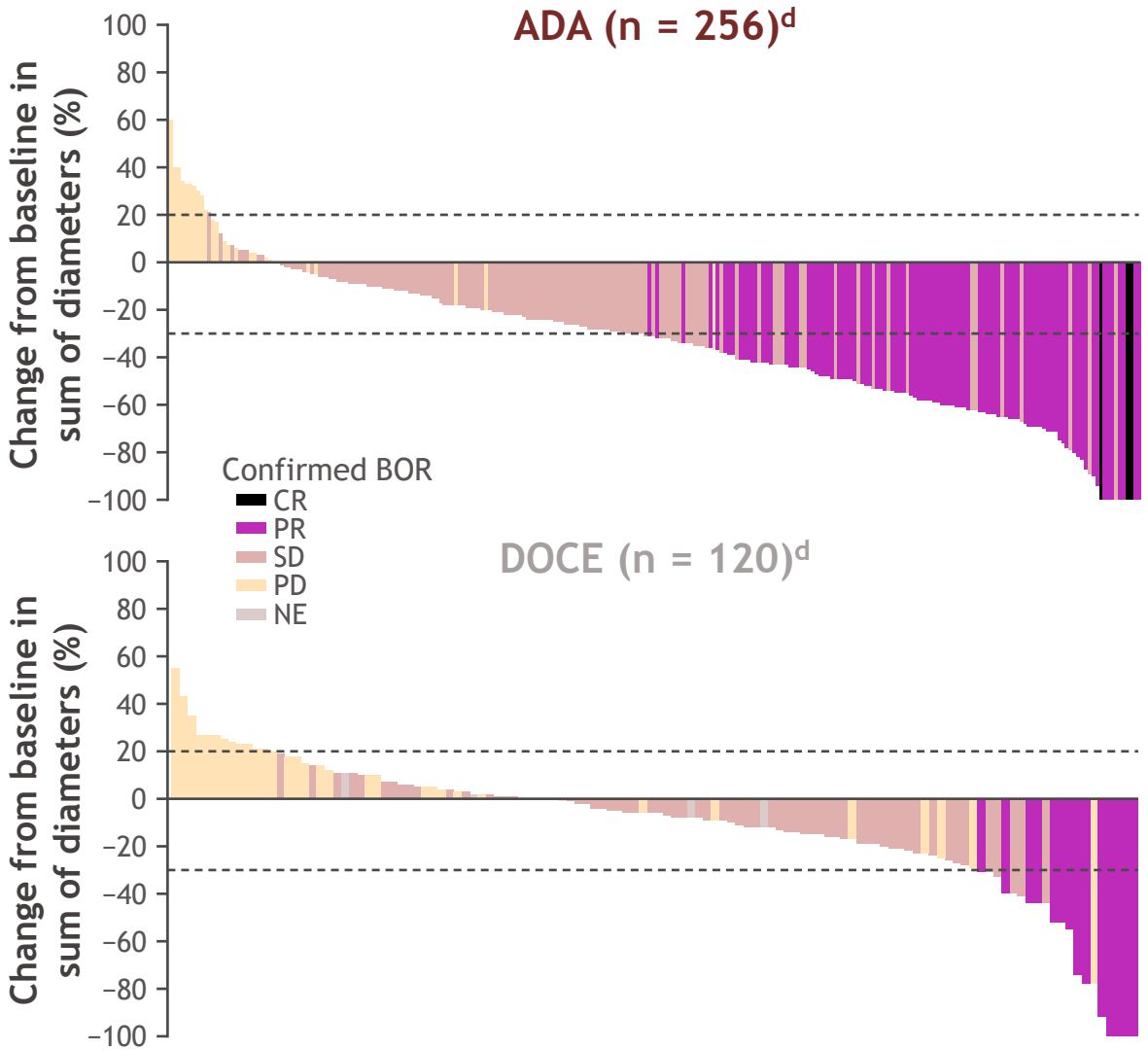
Median follow-up: 7.2 months.

[a]Time from randomization to the date of disease progression per BICR or death due to any cause, whichever occurs first. For patients who started a subsequent anticancer therapy prior to disease progression or death, PFS was censored at the date of the last tumor assessment prior to the start of the new therapy.

Tumor response per BICR



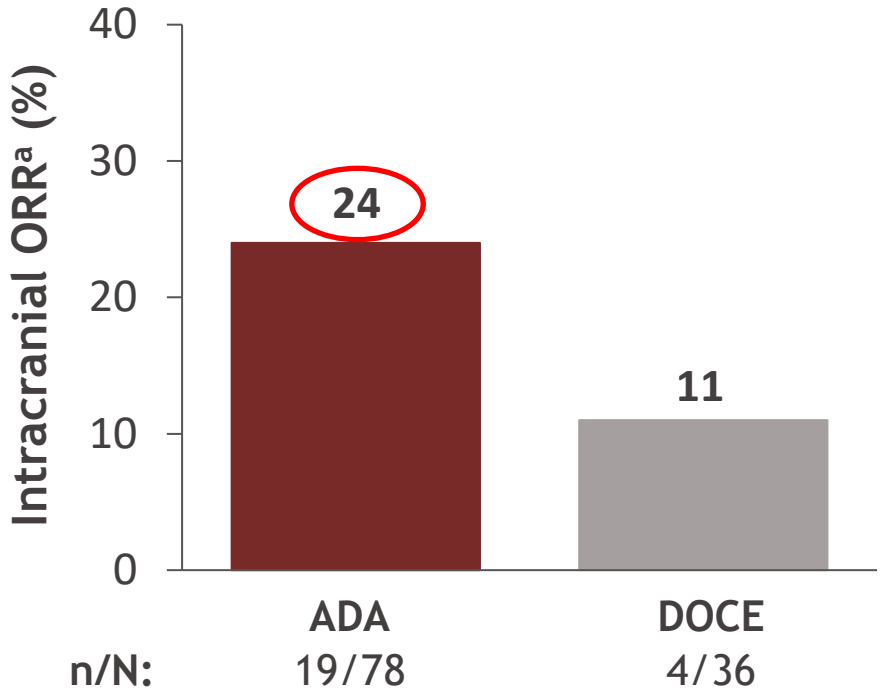
Tumor response	ADA (n = 301)	DOCE (n = 152)
DCR,[b] n (%)	236 (78)	89 (59)
Median DOR,[c] mo (95% CI)	8.3 (6.1-10.4)	5.4 (2.9-8.5)
Remaining in response at 6 mo, %	64	39



[a]ORR is defined as the percent of patients documented to have a confirmed CR/PR by BICR (per RECIST v1.1). [b]Disease control rate (DCR) is defined as the percent of patients documented to have a confirmed CR/PR/SD by BICR (per RECIST v1.1). [c]DOR is defined as the time from the date of first documentation of CR/PR to the first documentation of PD or death due to any cause in the absence of documented PD. DOR is only calculated for patients with confirmed CR/PR. [d]Waterfall plots include patients with at least one target lesion at baseline and at least one post-baseline tumor assessment.

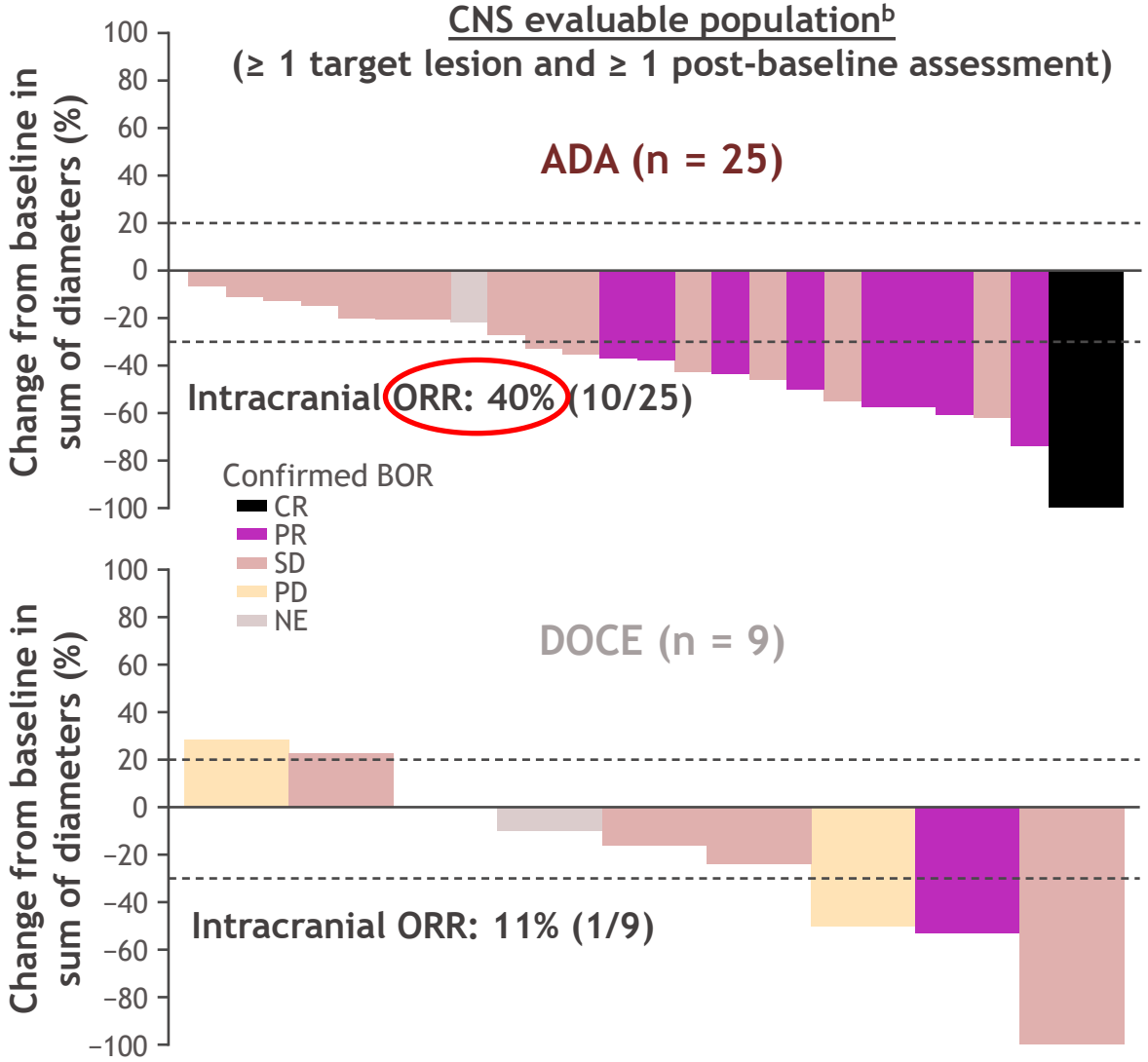
Intracranial response per BICR[a]

All patients with baseline CNS metastases[a]



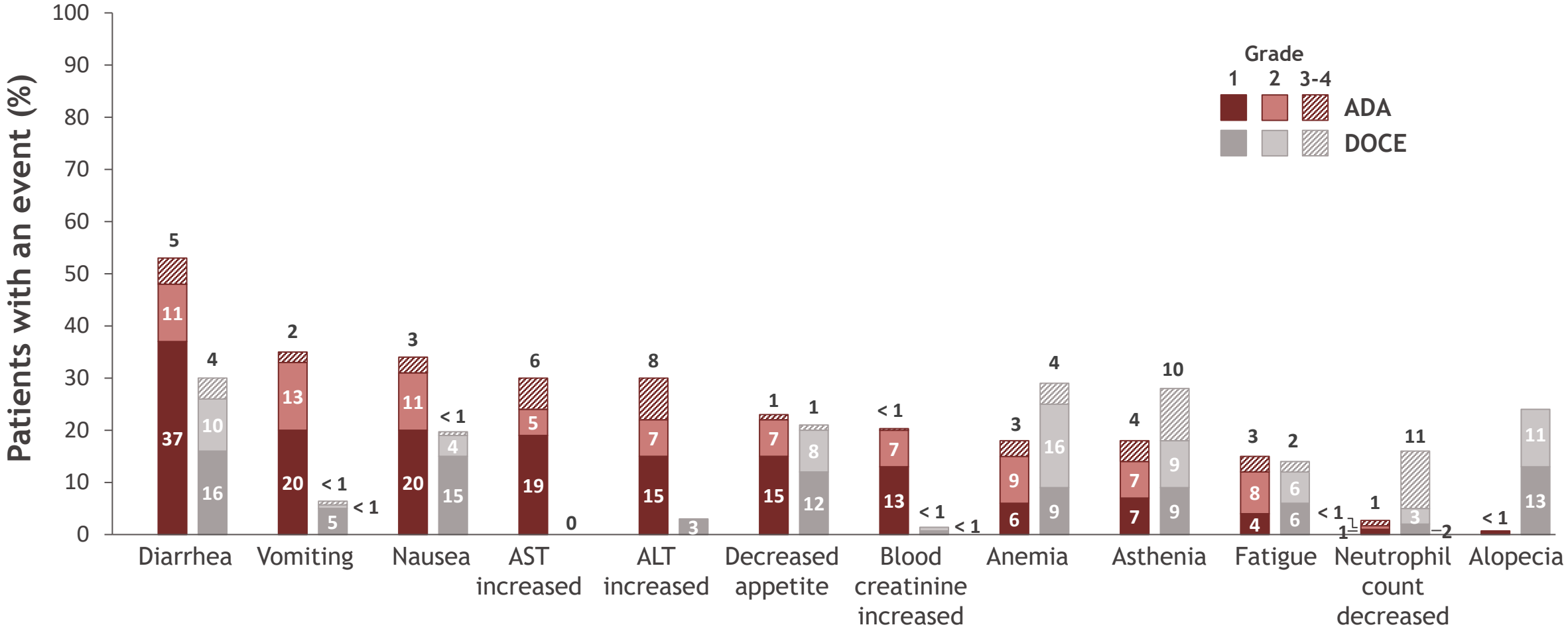
Intracranial response[a]	ADA (n = 78)	DOCE (n = 36)
Intracranial DCR, n (%)	64 (82)	20 (56)

CNS evaluable population[b]
(≥ 1 target lesion and ≥ 1 post-baseline assessment)



[a]In accordance with CNS-adapted RECIST v1.1. CNS RECIST data (including identification of patients with baseline CNS metastases) were based on a separate CNS imaging charter and neuroradiologist review. [b]Waterfall plots show CNS evaluable population including patients with at least one CNS target lesion at baseline and at least one post-baseline CNS tumor assessment. For lesions to be considered target lesions, they must have been measurable and either not previously treated with CNS-directed therapy or must have progressed after prior CNS-directed therapy.

Most frequent TRAEs (> 15% in either treatment arm[a])



[a]For each TRAE, patients are included only once at the maximum severity.

Summary

- In the phase 3 KRYSTAL-12 trial, ADA demonstrated a statistically significant and clinically meaningful improvement in PFS over DOCE in patients with previously treated *KRAS*^{G12C}-mutated NSCLC (median PFS, 5.5 vs 3.8 mo, respectively; HR, 0.58; $P < 0.0001$)
  - PFS benefit was observed across key subgroups
- ORR was also significantly higher with ADA vs DOCE (32% vs 9%; odds ratio, 4.68; $P < 0.0001$); overall, the responses were deep and appear to be durable
- ADA showed intracranial efficacy among patients with brain metastases at baseline, with a response rate that was more than double that observed with DOCE (intracranial ORR, 24% vs 11%)
- The safety profiles of ADA and DOCE were consistent with previous reports, with no new safety signals
- **These results reinforce ADA as an efficacious treatment option for patients with *KRAS*^{G12C}-mutated NSCLC after disease progression on prior chemotherapy and immunotherapy**
- A phase 3 trial comparing first-line ADA plus pembrolizumab vs pembrolizumab alone is currently enrolling patients with advanced *KRAS*^{G12C}-mutated NSCLC and PD-L1 TPS ≥ 50% (KRYSTAL-7; NCT04613596)

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ADCs

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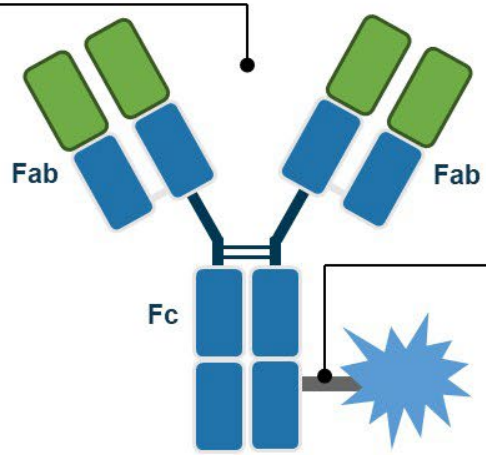
Antibody-Drug Conjugates: New kids on the block

Important Properties of the ADC Components and Target Antigen

Antigen
- High homogeneous expression on tumor
- Low or no expression on healthy tissues
- High affinity and avidity for antibody recognition

Antibody
- High affinity and avidity for tumor antigen
- Chimeric or humanized to decrease immunogenicity
- Long half-life and high molecular weight

Cytotoxic Payload
- Highly potent agents:
  - Calicheamicin
  - Maytansine derivative (DM1 or DM4)
  - Auristatin (MMAE or MMAF)
  - SN-38
  - DXd topoisomerase I inhibitor
- Optimal DAR (range: 2 to 8)



Linker
- Stable in circulation
- Efficient release of payload at target site
- Prevents premature release of payload at nontarget tissue
- Efficient linker technology **(cleavable vs noncleavable)**
- Site of conjugation
- DAR affects drug distribution and pharmacokinetics

Cleavable Linkers
Depend on physiological conditions: pH, proteolysis, or high intracellular glutathione
Noncleavable Linkers
Depend on lysosomal degradation

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Chau CH, et al. Lancet. 2019;394:793-804.

ADCs in Clinical Development for Lung Cancer[1]

Target	Drug	Payload	Linker	RP2D and Schedule	DAR
HER2	Trastuzumab-DM1 Trastuzumab-DXd	DM1 Deruxtecan	Noncleavable (thioether) Cleavable (tetrapeptide)	3.6 mg/kg, once every 3 weeks 6.4 mg/kg, once every 3 weeks	3.1 8
HER3	Patritumab-DXd	Deruxtecan	Cleavable (tetrapeptide)	5.5 mg/kg, once every 3 weeks	8
TROP2	Datopotamab-DXd Sacituzumab govitecan	Deruxtecan SN-38	Cleavable (tetrapeptide) Cleavable (carbonate)	6.0 mg/kg, once every 3 weeks 10 mg/kg on day 1 and 8, once every 3 weeks	4 7.6
CEACAM5	Tusamitamab ravtansine	DM4	Cleavable (SPDB)	100 mg/m^2, once every 2 weeks	3.8
c-MET	Telisotuzumab vedotin	MMAE	Cleavable (valine–citrulline)	2.7 mg/kg, once every 3 weeks	3.1
B7-H3	Ifinatamab-DXd (DS-7300a) MGC018	Deruxtecan DUBA	Cleavable (tetrapeptide) Cleavable (valine–citrulline)	TBD TBD	4 2.7
CD56	Lorvotuzumab mertansine	DM1	Cleavable (disulfide)	TBD	–
AXL	Enapotamab vedotin Mecbotamab vedotin	MMAE MMAE	Cleavable (protease) Cleavable (valine–citrulline)	2.2 mg/kg, once every 3 weeks TBD	– –
PK7	Cofetuzumab pelidotin	Auristatin-0101	Cleavable (valine–citrulline)	TBD	4
PVRL4	Enfortumab vedotin	MMAE	Cleavable (valine–citrulline)	TBD	4
TF	Tisotumab vedotin	MMAE	Cleavable (valine–citrulline)	TBD	4
EGFR	MRG003	MMAE	Cleavable (valine–citrulline)	2.0 mg/kg, once every 3 weeks	4
ROR2	Ozuriftamab vedotin	MMAE	Cleavable (valine–citrulline)	TBD	4
NaPi2b	Upifitamab rilsodotin Lifastuzumab vedotin	AF-HPA MMAE	Cleavable (protease) Cleavable (valine–citrulline)	TBD TBD	12-15 3-4

Passaro, Janne, Peters, *J Clin Oncol*. 2023;JCO2300013.

AdventHealth

DESTINY-Lung02

Blinded, randomized, multicenter, international, noncomparative, phase 2 trial (NCT04644237)

Background

- T-DXd 5.4 mg/kg and 6.4 mg/kg showed robust antitumor activity in multiple cancer types; however, T-DXd 5.4 mg/kg has not been evaluated in patients with previously treated *HER2*-mutant (*HER2*m) mNSCLC
- DESTINY-Lung02 assessed the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg in patients with *HER2*m mNSCLC
  - In the interim analysis, T-DXd showed deep and durable responses and an acceptable and generally manageable safety profile[1]
- Herein, we report the **primary analysis results** of DESTINY-Lung02

Statistical considerations

- Statistical hypothesis testing for the primary analysis was performed by comparing the lower limit of the 95% Clopper-Pearson CI of confirmed ORR of a T-DXd dose with the benchmark ORR of 26.4% (upper limit of the ORR 95% CI in the ramucirumab plus docetaxel arm of the REVEL trial)[2]
- The study was not powered to statistically compare between arms

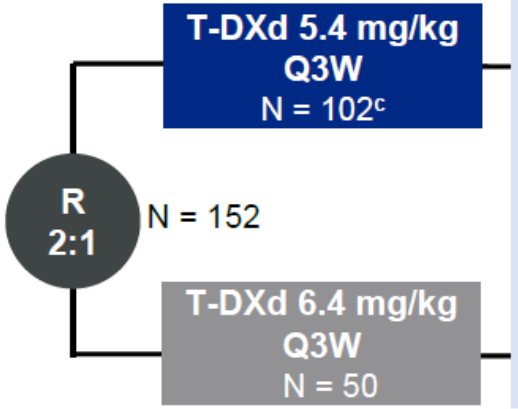
Key Eligibility Criteria[a]

- Metastatic *HER2*m[b] NSCLC
- ≥1 prior anticancer therapy (2L+), including platinum-based chemotherapy
- Measurable disease per RECIST v1.1
- ECOG PS of 0 or 1

Stratification Factor:

- Prior anti–PD-(L)1 treatment

Study Design



Primary Endpoint

- Confirmed ORR by BICR

Secondary Endpoints

- Confirmed ORR by INV
- DoR by BICR and INV
- DCR by BICR and INV
- PFS by BICR and INV
- OS
- Safety

Patients and investigators were blinded to the dose level

Primary analysis data cutoff: 23 December 2022

BICR, blinded independent central review; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator assessment; NSCLC, non–small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; T-DXd, trastuzumab deruxtecan.
[a]Patients with stable baseline brain metastases (asymptomatic; not requiring corticosteroid or anticonvulsant treatment) were eligible. [b]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment. [c]1 patient randomly assigned to the T-DXd 5.4 mg/kg arm did not receive treatment as the patient discontinued due to COVID-19 before cycle 1 day 1.

1. Goto K et al. *Annals of Oncol*. 2022;33 (suppl_7): S808-S869 2. Garon EB et al. *Lancet*. 2014;384:665-73.

Baseline Characteristics and Efficacy Summary

Baseline Characteristics

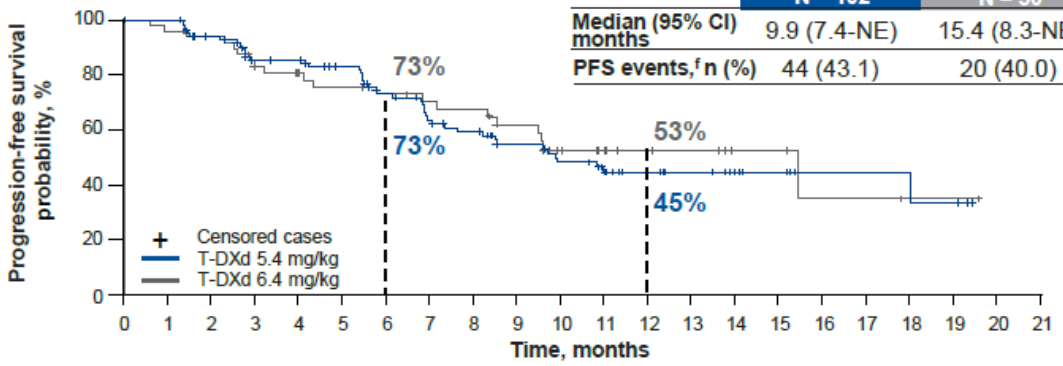
In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively:

- **Median age** was 59.4 years (range, 31-84) and 61.3 years (range, 28-86)
- Most patients were **female** (63.7% and 68.0%), **from Asia** (61.8% and 60.0%), had **never smoked** (53.9% and 58.0%), and **received prior anti–PD-(L)1 therapy** (73.5% and 78.0%)
- *HER2* mutations were primarily in the **kinase domain** (97.1% and 100%)
- **Baseline CNS metastasis** was present in 34.3% and 44.0% of patients
- **Median prior lines of treatment** was 2 (range, 1-12) and 2 (range, 1-7)

Efficacy summary	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Confirmed ORR,[a] n (%) [95% CI]	**50 (49.0)** [39.0-59.1]	**28 (56.0)** [41.3-70.0]
CR | PR	1 (1.0) | 49 (48.0)	2 (4.0) | 26 (52.0)
SD | PD	45 (44.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable[b]	3 (2.9)	2 (4.0)
DCR,[c] n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0) [80.8-97.8]
Median DoR,[d,e] months (95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median TTIR,[d] months (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median follow-up, months (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)

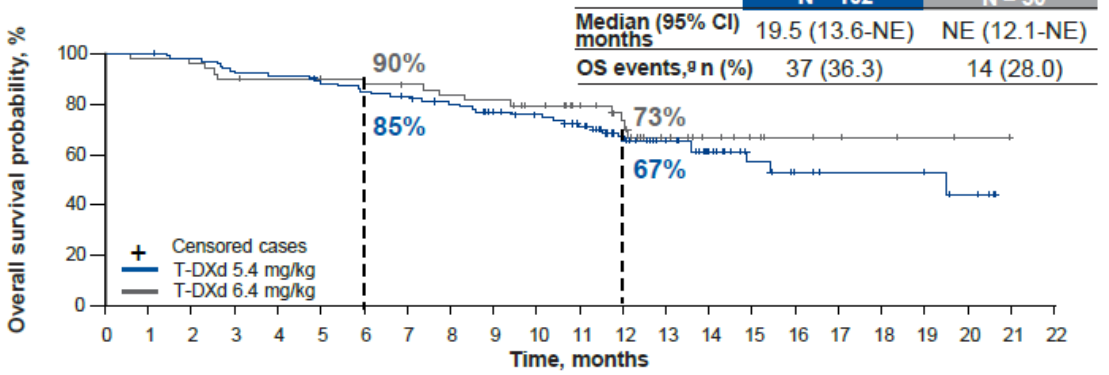
PFS

	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Median (95% CI) months	9.9 (7.4-NE)	15.4 (8.3-NE)
PFS events,[f] n (%)	44 (43.1)	20 (40.0)



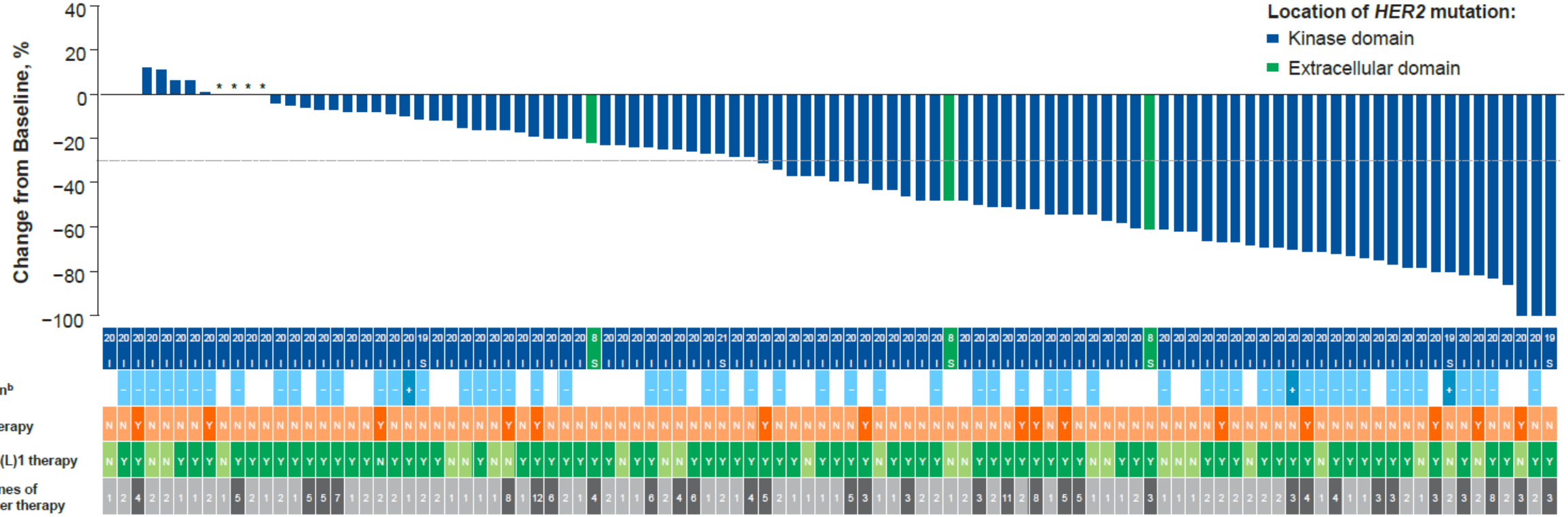
OS

	T-DXd 5.4 mg/kg N = 102	T-DXd 6.4 mg/kg N = 50
Median (95% CI) months	19.5 (13.6-NE)	NE (12.1-NE)
OS events,[g] n (%)	37 (36.3)	14 (28.0)



BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTIR, time to initial response. [a]Proportion of patients with confirmed CR or PR assessed by BICR per RECIST v1.1. [b]3 patients were non-evaluable at 5.4 mg/kg (1 patient never received treatment due to COVID-19; 2 patients discontinued before first tumor assessment); 2 patients were non-evaluable at 6.4 mg/kg (discontinued due to adverse event before first tumor assessment). [c]Proportion of patients with confirmed CR, PR, or SD assessed by BICR. [d]Assessed by BICR. [e]60.0% and 75.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored. [f]56.9% and 60.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored. [g]63.7% and 72.0% of patients in the 5.4 mg/kg and 6.4 mg/kg arms were censored.

Best Percentage Change in Tumor Size by BICR With T-DXd 5.4 mg/kg (N = 102)



Responses were observed regardless of *HER2* mutation type, *HER2* amplification status, and number or type of prior therapies

BICR, blinded independent central review; I, insertion; HER2, human epidermal growth factor receptor 2; N, no; PD-(L)1, programmed death (ligand)1; S, substitution; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Y, yes. The line at −30% indicates a partial response. *Indicates the patient had 0 best percentage change from baseline in the sum of diameters for all target lesions. Numbers in the *HER2* mutation row indicate in which exon the mutation occurred (8, 19, or 20). *HER2* amplification was only assessed in patients who received T-DXd 5.4 mg/kg. [a]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment. [b]*HER2* amplification status was evaluated using an exploratory Oncomine DX Target test copy number algorithm on NSCLC formalin-fixed paraffin-embedded tissue samples.

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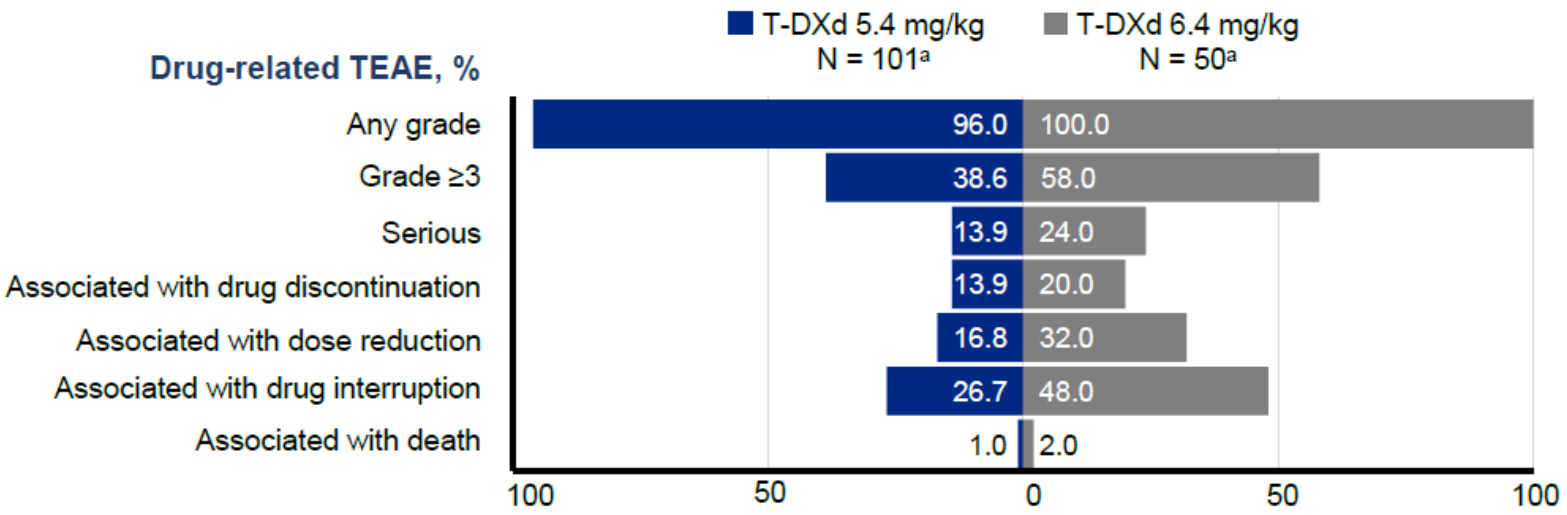
Overall Safety Summary

Overall Safety



Adjudicated Drug-Related ILD

Adjudicated as drug-related ILD	T-DXd 5.4 mg/kg N = 101[a]	T-DXd 6.4 mg/kg N = 50[a]
Any grade, n (%)	**13 (12.9)**	**14 (28.0)**
Grade 1	4 (4.0)	4 (8.0)
Grade 2	7 (6.9)	9 (18.0)
Grade 3	1 (1.0)	0
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

- **Median treatment duration** was 7.7 months (range, 0.7-20.8) with T-DXd 5.4 mg/kg and 8.3 months (range, 0.7-20.3) with T-DXd 6.4 mg/kg
- The **most common any-grade TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **nausea** (67.3% and 82.0%), **neutropenia** (42.6% and 56.0%), and **fatigue** (44.6% and 50.0%)
- The **most common grade ≥3 TEAEs** in the T-DXd 5.4 mg/kg and 6.4 mg/kg arms included **neutropenia** (18.8% and 36.0%) and **anemia** (10.9% and 16.0%)

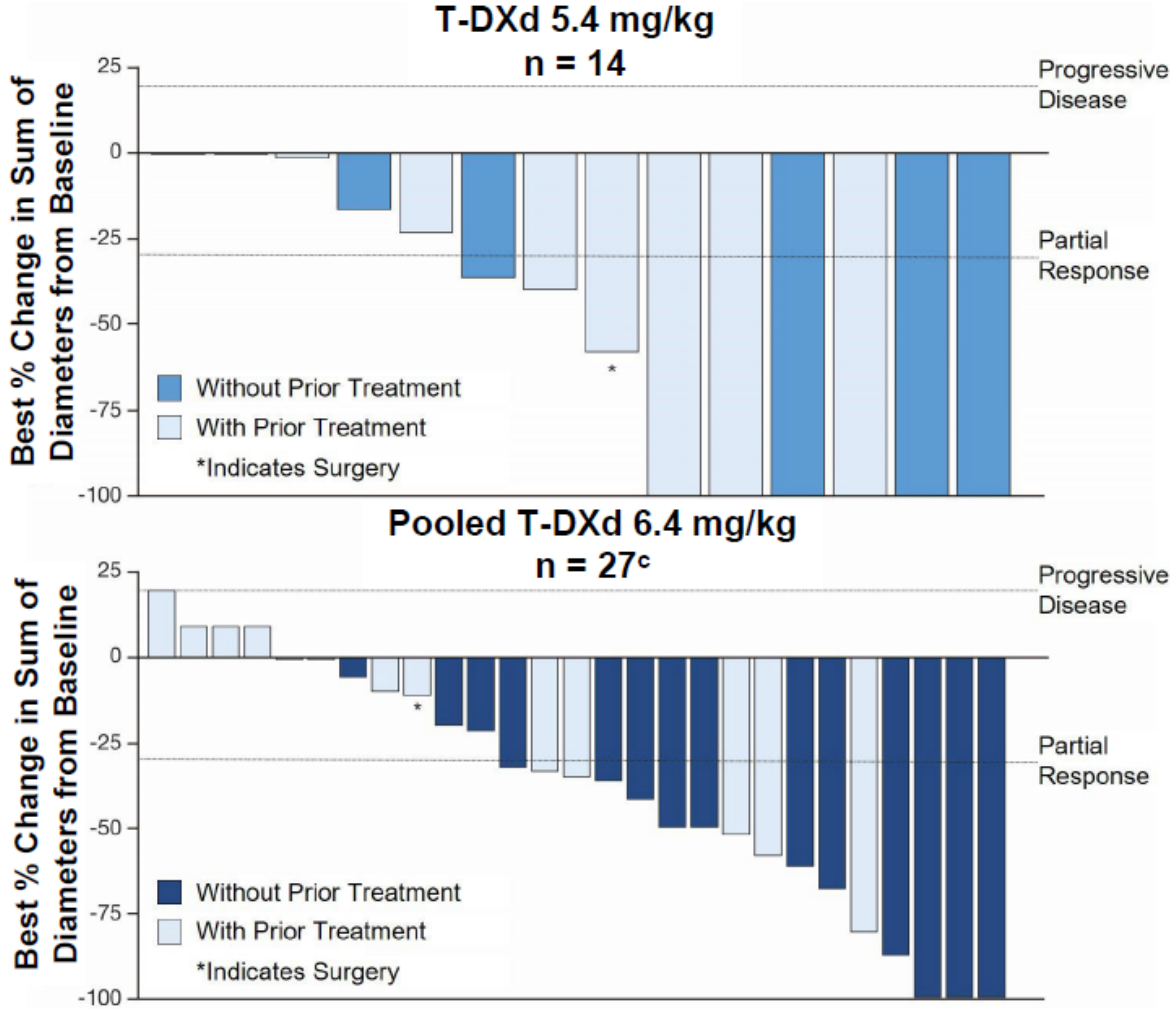
ILD, interstitial lung disease; TEAE, treatment emergent adverse event; T-DXd, trastuzumab deruxtecan.
[a]The safety analysis set included all randomly assigned patients who received ≥1 dose of study drug.

IC Objective Response Rates & Best Overall Response (BICR)

Measurable BM at Baseline

	T-DXd 5.4 mg/kg DL-02 BM n = 14	Pooled T-DXd 6.4 mg/kg DL-01 *HER2m*/DL-02 BM n = 30
IC-cORR, n (%)[a]	**7 (50.0)**	**9 (30.0)**
95% CI[b]	23.0-77.0	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30.0)
SD	6 (42.9)	13 (43.3)
PD	1 (7.1)	4 (13.3)
NE[c]	0	2 (6.7)
Missing	0	2 (6.7)
IC-DCR, n (%)[a]	**13 (92.9)**	**22 (73.3)**
95% CI[b]	66.1-99.8	54.1-87.7
IC-DoR, months[d]		
Median, (95% CI)[e]	9.5 (3.6-NE)	4.4 (2.9-10.2)

12/14 (86%) patients with measurable BM receiving T-DXd 5.4 mg/kg and 21/27 (78%) in the pooled 6.4 mg/kg group experienced a reduction in brain lesion size from baseline as their best overall response



BICR, blinded independent central review; BM, brain metastases; CR, complete response; DCR, disease control rate; DL, DESTINY-Lung; DoR, duration of response; *HER*2m, human epidermal growth factor receptor 2-mutant; IC, intracranial; IC-cORR, intracranial confirmed objective response rate; IC-DCR, intracranial disease control rate; IC-DoR, intracranial duration of response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan. [a]Denominator for percentage is the number of patients in the full analysis set who have at least 1 target lesion at baseline, per BICR. [b]Based on Clopper-Pearson method for single proportion. [c]For one patient deemed NE in the 6.4 mg/kg group, it was not possible to derive objective response due to missing data of 1 target lesion; the patient's best overall response however was calculated from available target lesion assessments and included the waterfall plot. [d]Calculated as time from first response in brain until progression in brain. [e]Based on Kaplan-Meier analysis and computed with the Brookmeyer-Crowley method.

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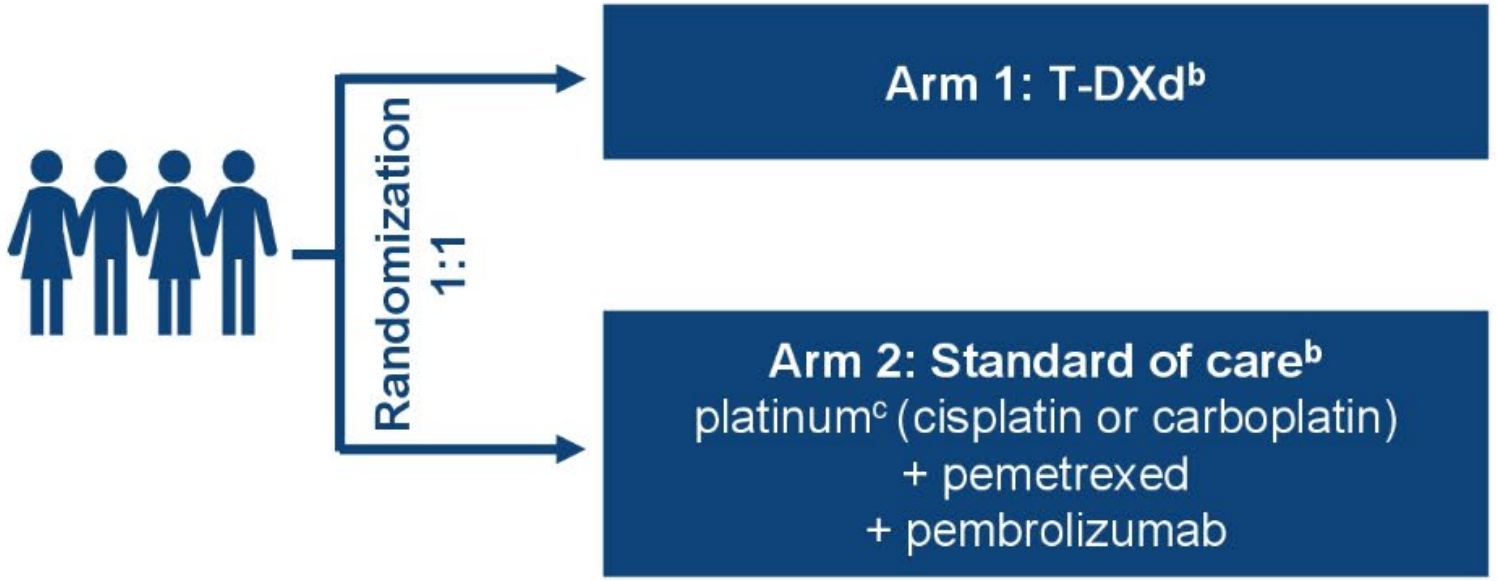
DESTINY-Lung04

Patient population (N≈264)

- Unresectable, locally advanced (not amenable to curative therapy), or metastatic nonsquamous NSCLC with *HER2* exon 19 or 20 mutations[a]
- Naive to systemic therapy in the locally advanced or metastatic setting
- No known other targetable oncogenic mutations/alterations



[a] *HER2* mutations may be detected in tissue or ctDNA.
[b] Crossover is not permitted.
[c] Investigator's choice of cisplatin or carboplatin.

Li B et al. ASCO 2022. Abstract TPS9137.

April 5, 2024 - FDA grants accelerated approval for traztuzumab deruxtecan in HER2- positive (IHC 3+) solid tumors

- 192 HER2-positive (IHC 3+) previously treated, metastatic solid tumors enrolled in 3 multi-center trials
- DESTINY-PanTumor02 – ORR – 51.4%, DoR – 19.4 mos
- DESTINY-Lung01 – ORR – 52.9%, DoR – 6.9 mos
- DESTINY-CRC02 – ORR – 46.9%, DoR – 5.5 mos

References

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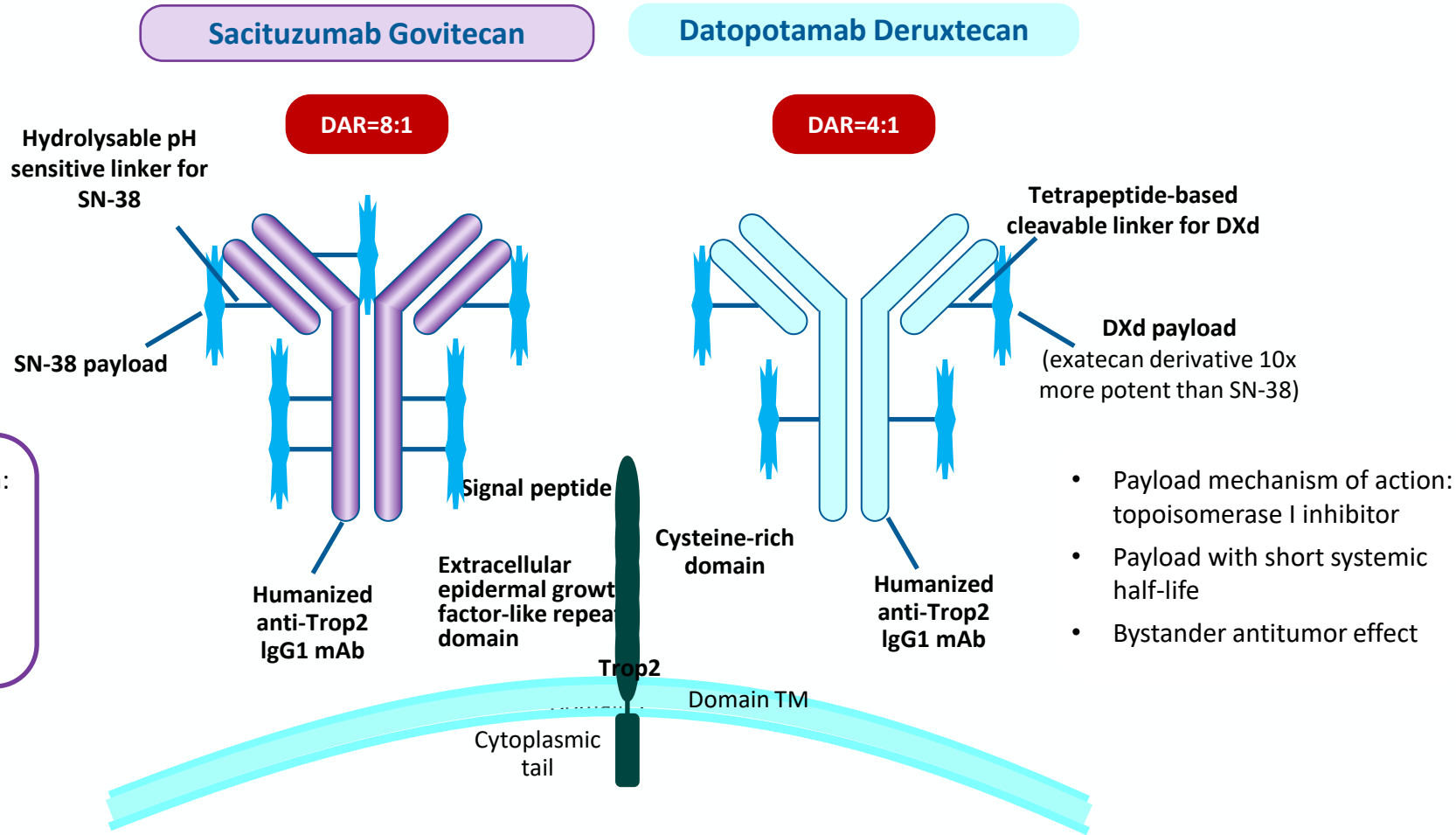
ADCs Targeting Trop-2 in NSCLC



- Payload mechanism of action: topoisomerase I inhibitor
- Payload with long systemic half-life
- Bystander antitumor effect

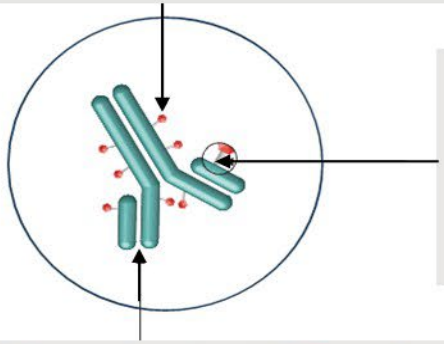
- Payload mechanism of action: topoisomerase I inhibitor
- Payload with short systemic half-life
- Bystander antitumor effect

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio; DXd, deruxtecan; mAb, monoclonal antibody; SN-38, 7-ethyl-10-hydroxycamptothecin; TM, transmembrane; Trop-2, trophoblast cell surface antigen 2.

Parisi C, et al. *Cancer Treat Rev.* 2023;118:102572.

Sacituzumab Govitecan Is a First-in-Class Trop-2–Directed Antibody-Drug Conjugate

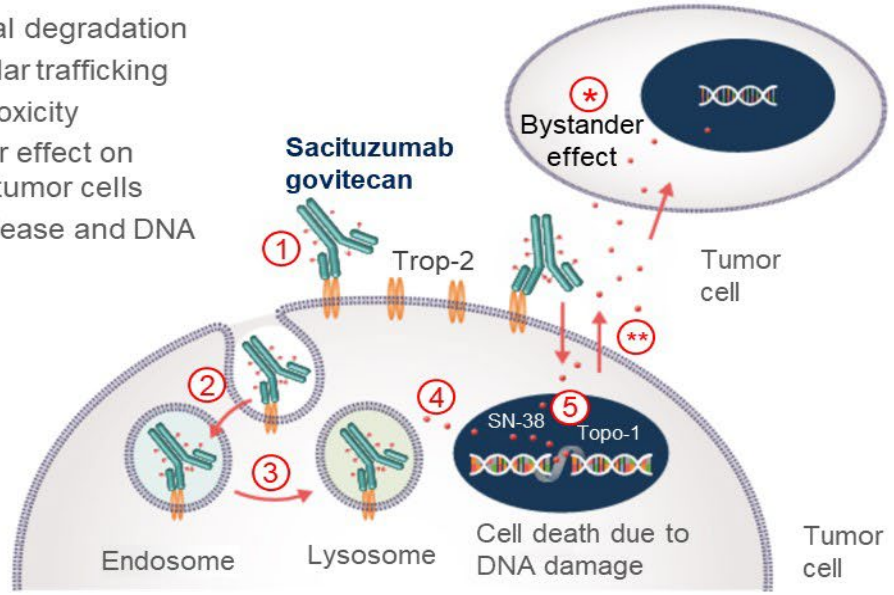
SN-38 payload
- SN-38 is more potent than the parent compound, irinotecan (Topo-1 inhibitor)
- SN-38 is rapidly internalized and efficiently released to the tumor with minimized effect on healthy tissues



Linker for SN-38
- pH-sensitive, hydrolyzable linker for SN-38 release in targeted tumor cells and tumor microenvironment, allowing bystander effect
- High drug-to-antibody ratio (7.6:1)[1]

Humanized anti–Trop-2 antibody
- Binds with high (K_D = 0.3 nM) affinity to Trop-2, an epithelial antigen expressed on many solid tumors[2]

① Binding
② Internalization
③ Lysosomal degradation
④ Intracellular trafficking
⑤ Cell cytotoxicity
* Bystander effect on adjacent tumor cells
** SN-38 release and DNA damage



- Trop-2 is a transmembrane calcium signal transducer expressed on many solid tumors[3,4]
- SG is a first-in-class Trop-2–directed ADC that selectively delivers SN-38, an active metabolite of irinotecan[1]

ADC, antibody-drug conjugate; SG, sacituzumab govitecan; Topo-1, topoisomerase-1; Trop-2, trophoblast cell surface antigen 2. 1. Goldenberg DM, et al. *Oncotarget*. 2015;6:22496-22512. 2. Agatsuma T, et al. Patent: US 9850312 B2. Daiichi Sankyo. 2017. 3. Ambrogi F, et al. *PLoS One*. 2014;9:e96993. 4. Trerotola M, et al. *Oncogene*. 2013;32(2):222-233.

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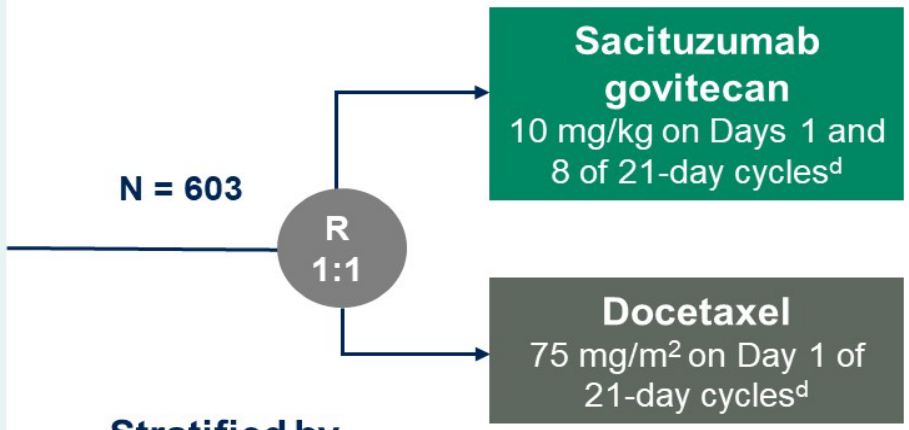
EVOKE-01: Global, Randomized, Open-Label, Phase 3 Study

Key eligibility criteria

- Measurable stage IV NSCLC
- ECOG PS 0–1
- Radiographic progression after platinum-based and anti-PD-(L)1–containing regimen[a]
- In addition, patients with known AGAs must have received ≥ 1 approved TKI[b]
  - *EGFR/ALK* test required. Testing of other AGAs recommended[c]
- Previously treated stable brain metastases were included
- No prior treatment with Topo-1 inhibitors, Trop-2–targeted therapies, or docetaxel



End points

Primary

- OS

Secondary

- PFS, ORR, DOR, and DCR by INV per RECIST v1.1
- Safety and tolerability
- QoL using NSCLC-SAQ

Stratified by

- **Histology** (squamous vs nonsquamous)
- **Response to last anti-PD-(L)1–containing regimen** (responsive [best response CR/PR] vs nonresponsive [PD/SD])
- **Received prior targeted therapy for AGA** (yes vs no)

At data cutoff (29 November 2023), the study median follow-up was 12.7 months (range, 6.0–24.0)

[a](Neo)adjuvant therapy counted if progression within 6 months of platinum treatment and while on maintenance with checkpoint inhibitor agent. [b]If local approval exists for targeted therapy to that genomic alteration. [c]Based on local SOC and availability of testing/approved targeted agent. [d]Until PD or unacceptable toxicity. AGA, actionable genomic alteration; CR, complete response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; INV, investigator; NSCLC, non-small cell lung cancer; NSCLC-SAQ, Non-small Cell Lung Cancer Symptom Assessment Questionnaire; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; PFS, progression-free survival; PR, partial response; QoL, quality of life; R, randomization; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; SOC, standard of care; TKI, tyrosine kinase inhibitor; Topo-1, topoisomerase-1; Trop-2, trophoblast cell surface antigen 2.

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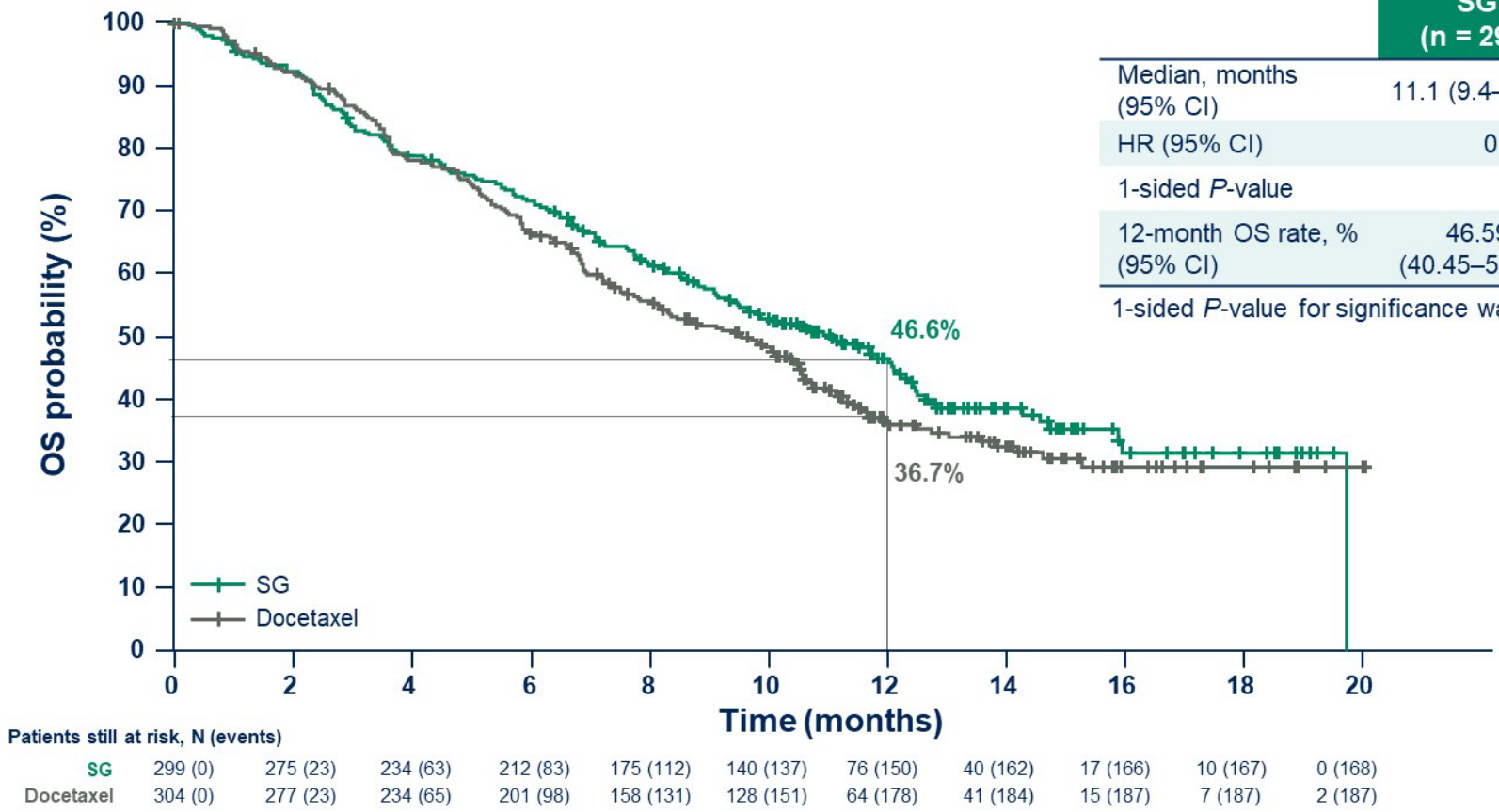
Primary End Point: Overall Survival (ITT)



	SG (n = 299)	Docetaxel (n = 304)
Median, months (95% CI)	11.1 (9.4–12.3)	9.8 (8.1–10.6)
HR (95% CI)	0.84 (0.68–1.04)	
1-sided *P*-value	0.0534	
12-month OS rate, % (95% CI)	46.59 (40.45–52.50)	36.72 (30.88–42.57)

1-sided *P*-value for significance was $P \leq 0.0223$

CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; SG, sacituzumab govitecan.

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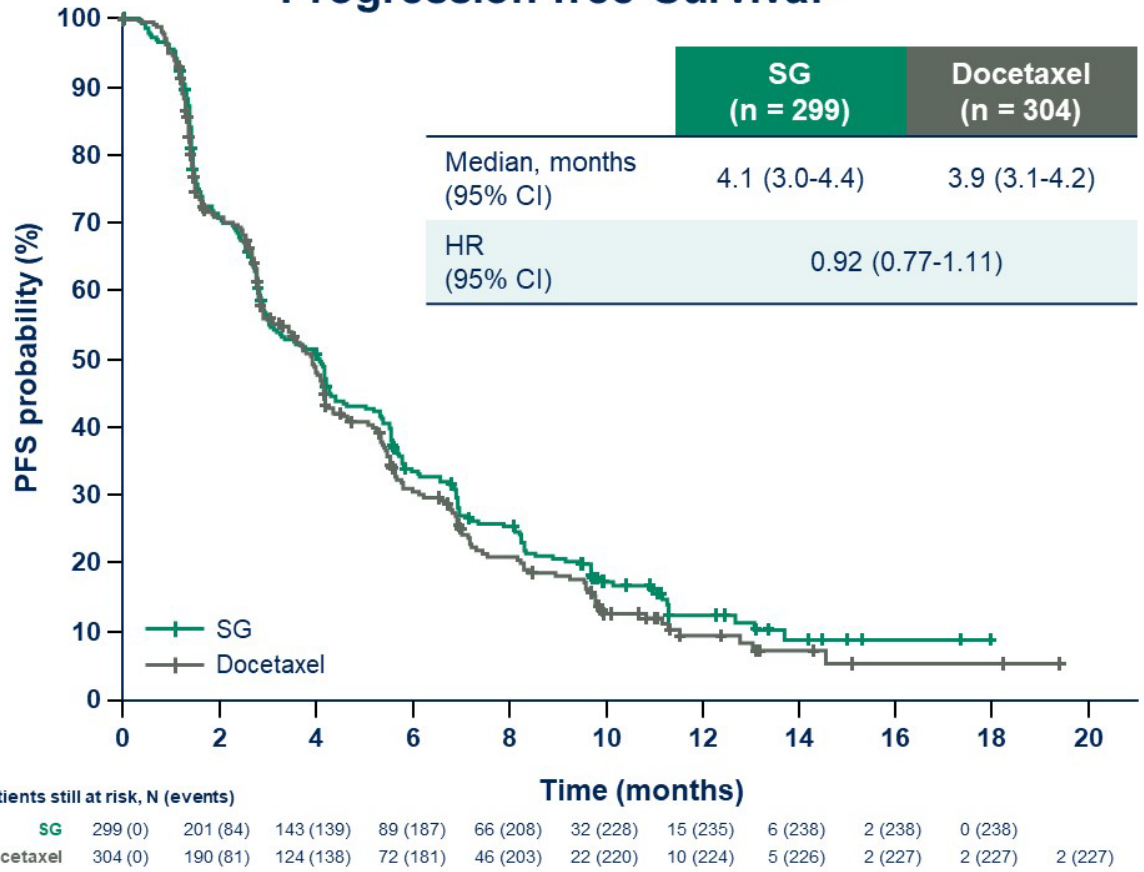
Secondary End Points (ITT)

Progression-free Survival[a]



	SG (n = 299)	Docetaxel (n = 304)
Median, months (95% CI)	4.1 (3.0-4.4)	3.9 (3.1-4.2)
HR (95% CI)	0.92 (0.77-1.11)	

Objective Response Rate[a]

	SG (n = 299)	Docetaxel (n = 304)
ORR, % (95% CI)	13.7 (10.0–18.1)	18.1 (13.9–22.9)
DCR, % (95% CI)	67.6 (61.9–72.8)	67.1 (61.5–72.4)
Median DOR, months (95% CI)	6.7 (4.4–9.8)	5.8 (4.1–8.3)
DOR rate at 6 months, % (95% CI)	52.5 (35.6–66.9)	46.5 (31.9–59.8)

[a]By INV assessment. CI, confidence interval; DCR, disease control rate; DOR, duration of response; HR, hazard ratio; INV, investigator; ITT, intent-to-treat; ORR, objective response rate; PFS, progression-free survival; SG, sacituzumab govitecan.

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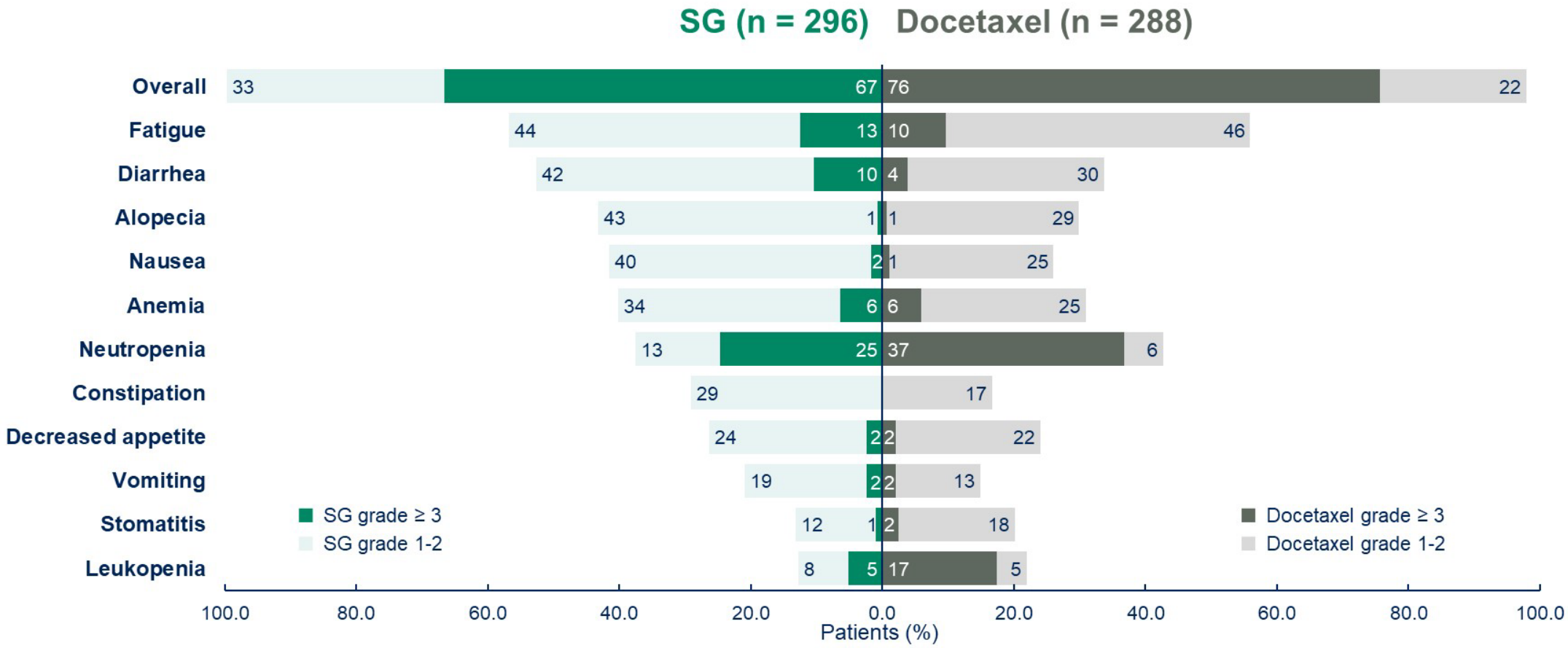
Treatment-Emergent Adverse Events

In ≥ 20% of patients receiving SG or docetaxel



SG, sacituzumab govitecan.

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Conclusions

- EVOKE-01 did not meet the statistical significance for the primary end point of OS in ITT
  - A numerical improvement in OS favoring SG was observed, with a 16% reduction in risk of death (HR [95% CI], 0.84 [0.68–1.04]) and a higher 12-month OS rate (SG, 46.6%; docetaxel, 36.7%)
  - Improvement in OS with SG was seen in both squamous and nonsquamous histologies
- A prespecified subgroup analysis showed meaningful improvement in OS of 3.5 months (HR [95% CI], 0.75 [0.58–0.97]) with SG in mNSCLC that was nonresponsive (SD/PD) to last anti-PD-(L)1–containing regimen
- SG had a favorable safety profile and was better tolerated than docetaxel
  - Grade ≥ 3 AEs and AEs leading to discontinuation were lower among patients receiving SG than docetaxel
- Patients reported improvement in NSCLC-related symptoms, reflective of better tolerability and disease control with SG
- SG is an active and tolerable treatment option for patients with previously treated mNSCLC
  - SG is being evaluated in combination with immunotherapy in the first-line setting (EVOKE-02, NCT05186974; EVOKE-03, NCT05609968)

AE, adverse event; CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat population; mNSCLC, metastatic NSCLC; NSCLC, non-small cell lung cancer; OS, overall survival; PD, progressive disease; PD-(L)1, programmed death (ligand) 1; SD, stable disease; SG, sacituzumab govitecan.

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TROPION-Lung01: Study Design and Efficacy

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel

Without actionable genomic alterations

- 1 or 2 prior lines, including platinum CT and anti-PD-(L)1 mAb therapy

With actionable genomic alterations

- Positive for *EGFR, ALK, NTRK, BRAF, ROS1, MET* exon 14 skipping, or *RET*
- 1 or 2 prior approved targeted therapies + platinum-based CT, and ≤1 anti-PD-(L)1 mAb

R 1:1

- **Dato-DXd 6 mg/kg Q3W (N=299)**
- **Docetaxel 75 mg/m² Q3W (N=305)**

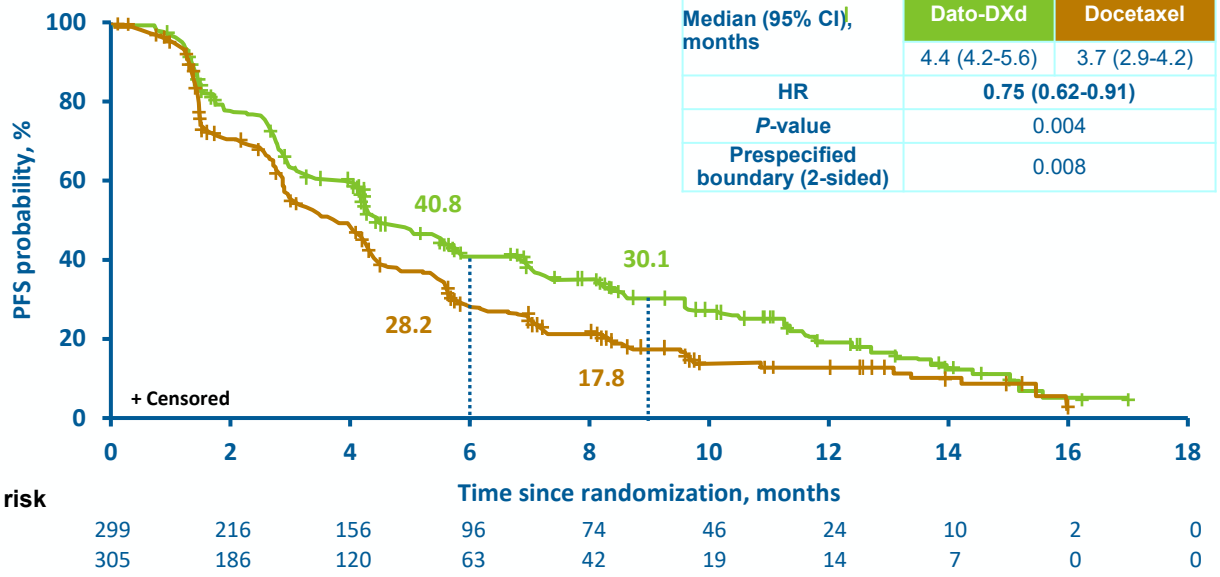
Dual Primary Endpoints

- PFS by BICR
- OS

Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

Progression-Free Survival: ITT



Median (95% CI), months	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	0.75 (0.62-0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

No. at risk										
Dato-DXd	299	216	156	96	74	46	24	10	2	0
Docetaxel	305	186	120	63	42	19	14	7	0	0

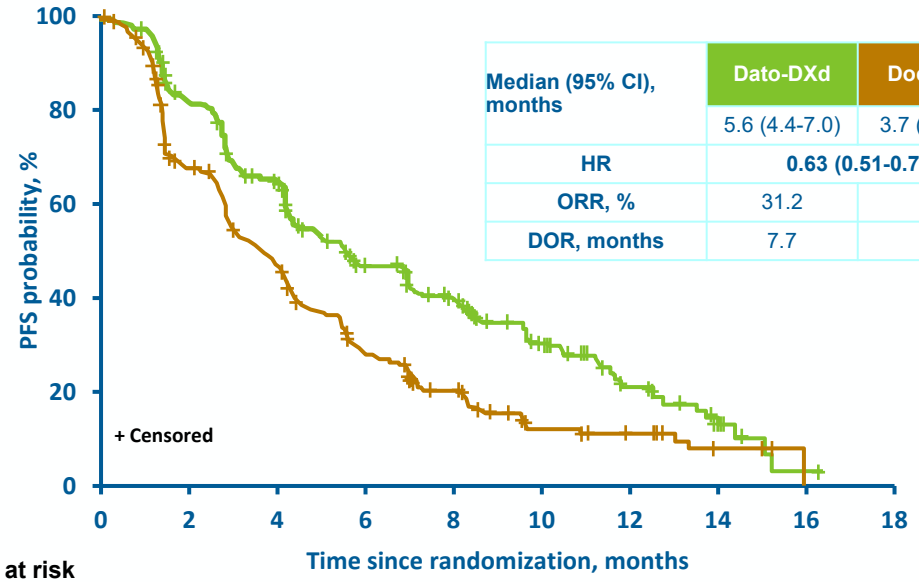
	Dato-DXd	Docetaxel
ORR (95% CI), %	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

BICR, blinded independent central review; CT, chemotherapy; Dato-DXd, datopotamab deruxtecan; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; ITT, intention to treat; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death ligand 1; PFS, progression-free survival.

Ahn MJ, Lisberg A, et al. *Ann Oncol.* 2023;34(S2):S1305-S1306.

TROPION-Lung01: Efficacy of Datopotamab Deruxtecan

Non-squamous
(with and without AGAs)

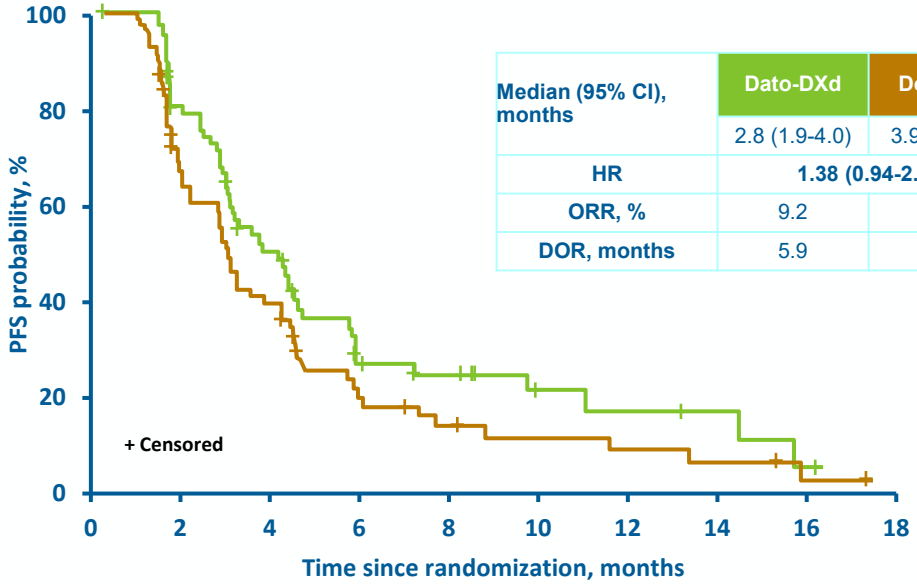


Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	0.63 (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6

No. at risk

Dato-DXd	229	178	134	86	68	41	20	7	1	0
Docetaxel	232	135	90	50	32	14	10	4	0	0

Squamous
(with and without AGAs)



Median (95% CI), months	Dato-DXd	Docetaxel
	2.8 (1.9-4.0)	3.9 (2.8-4.5)
HR	1.38 (0.94-2.02)	
ORR, %	9.2	12.7
DOR, months	5.9	8.1

No. at risk

Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

PFS HR for non-squamous without AGAs: 0.71 (0.56, 0.91)

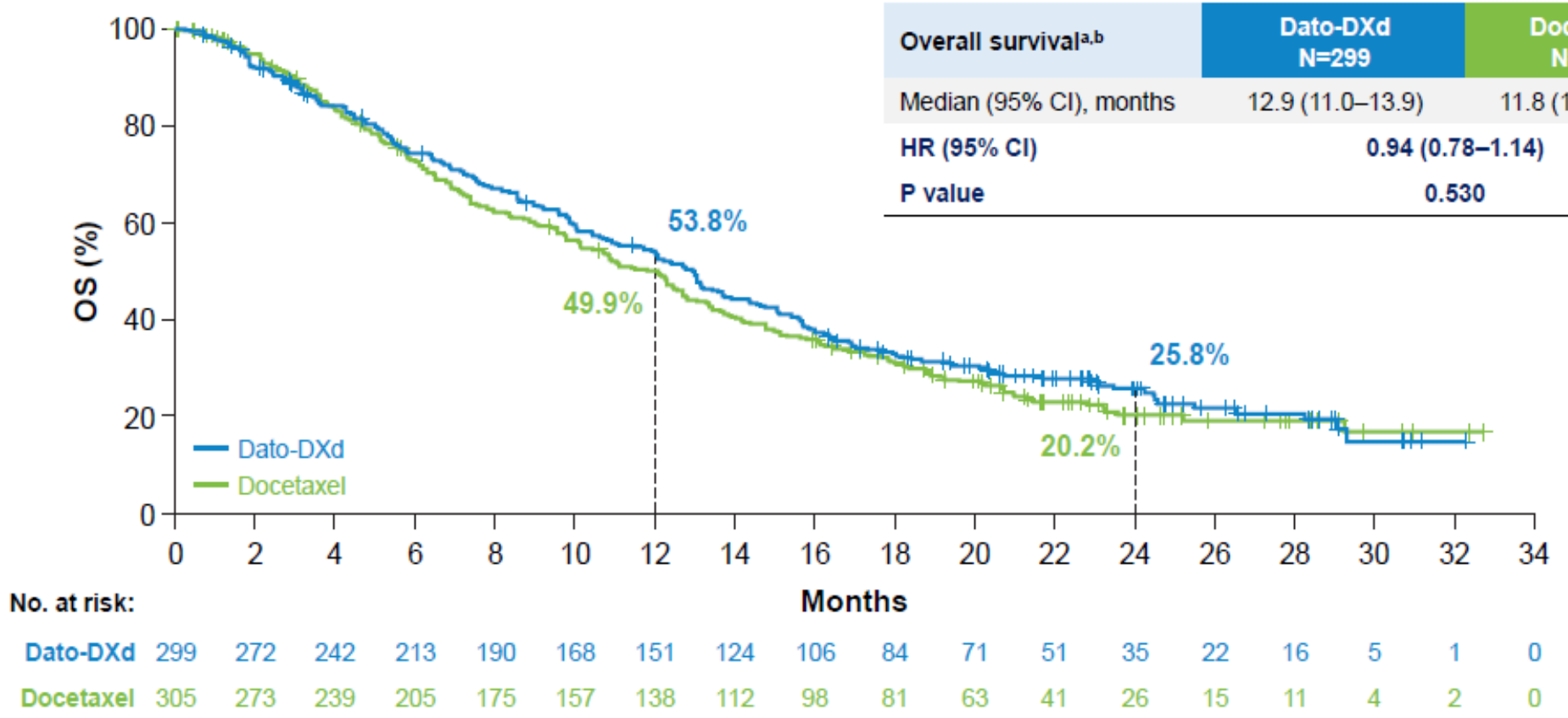
AGAs, actionable genomic alterations; Dato-DXd, datopotamab deruxtecan; DOR, duration of response; HR, hazard ratio; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Ahn MJ, Lisberg A, et al. *Ann Oncol.* 2023;34(S2):S1305-S1306.

Overall Survival: ITT

TROPION-Lung01

Overall survival[a,b]	Dato-DXd N=299	Docetaxel N=305
Median (95% CI), months	12.9 (11.0–13.9)	11.8 (10.0–12.8)
HR (95% CI)	0.94 (0.78–1.14)	
P value	0.530	



[a]Median (95% CI) OS follow-up was 23.1 (22.0, 24.8) months for Dato-DXd and 23.1 (21.7, 24.2) months for docetaxel. [b]At primary OS analysis (data cutoff: March 1, 2024), 433 OS events (IF) were observed.
IF, information fraction.

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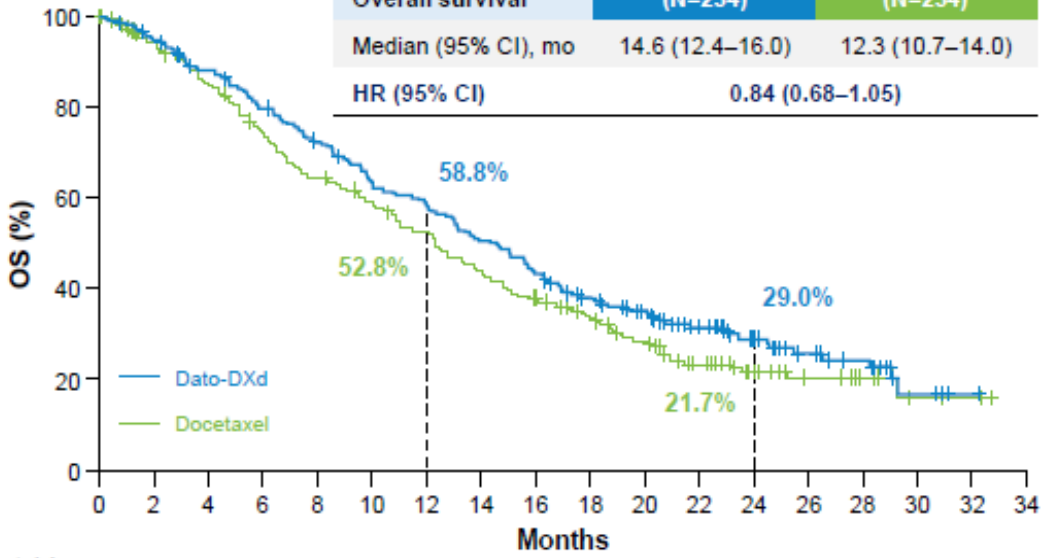
Overall Survival by Histology

TROPION-Lung01

Nonsquamous

Overall survival	Dato-DXd (N=234)	Docetaxel (N=234)
Median (95% CI), mo	14.6 (12.4–16.0)	12.3 (10.7–14.0)
HR (95% CI)	0.84 (0.68–1.05)	

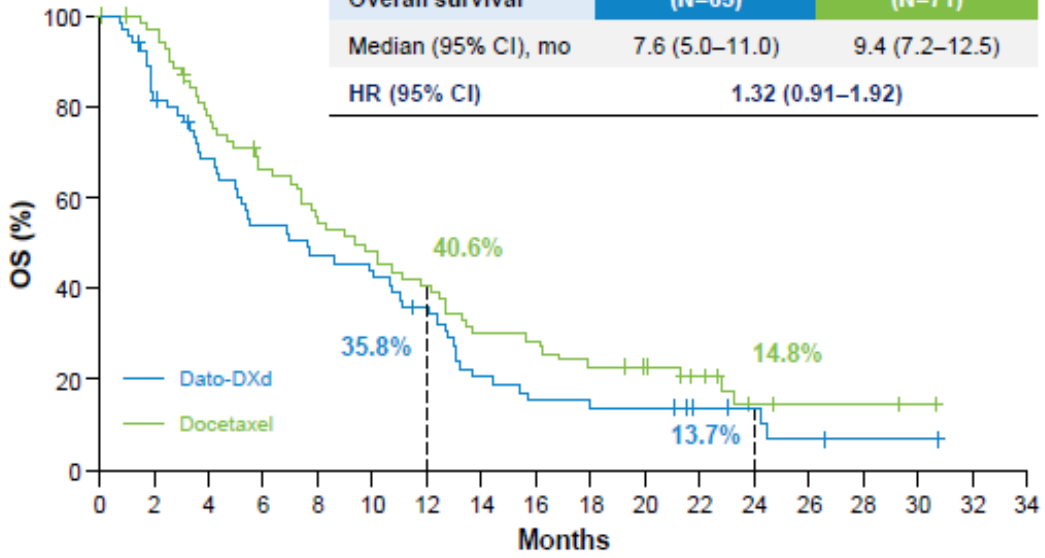


No. at risk:

Dato-DXd	234	220	200	180	161	141	130	112	97	76	63	46	31	20	15	4	1	0
Docetaxel	234	206	186	161	139	125	111	92	79	66	50	32	22	12	8	3	2	0

Squamous

Overall survival	Dato-DXd (N=65)	Docetaxel (N=71)
Median (95% CI), mo	7.6 (5.0–11.0)	9.4 (7.2–12.5)
HR (95% CI)	1.32 (0.91–1.92)	



	65	52	42	33	29	27	21	12	9	8	8	5	4	2	1	1	0	0
	71	67	53	44	36	32	27	20	19	15	13	9	4	3	3	1	0	0

- In patients with NSQ histology, 16% risk reduction for death and 2.3-month improvement in median OS with Dato-DXd
- OS improvements in the NSQ subset were seen regardless of actionable genomic alteration status[a]:
  - **Present**: 15.6 vs 9.8 months (HR [95% CI], 0.65 [0.40–1.08]); **Absent:** 13.6 vs 12.3 months (HR [95% CI], 0.89 [0.70–1.13])

Data cutoff: March 1, 2024.
[a]Based on the number of patients in the respective actionable genomic alteration subsets. Values were calculated based on patient data in the electronic case report forms.

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TRAEs ≥15% and Adjudicated Drug-Related ILD

TROPION-Lung01

TRAEs,[a] n (%)	Dato-DXd (N=297)		Docetaxel (N=290)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Stomatitis	141 (47)[b]	20 (7)	45 (16)	3 (1)
Nausea	101 (34)	7 (2)	48 (17)	3 (1)
Alopecia	95 (32)	0	101 (35)	1 (<1)[c]
Decreased appetite	68 (23)	1 (<1)	46 (16)	1 (<1)
Asthenia	56 (19)	8 (3)	56 (19)	5 (2)
Anemia[d]	44 (15)	12 (4)	60 (21)	12 (4)
Diarrhea	30 (10)	1 (<1)	55 (19)	4 (1)
Neutropenia[e]	14 (5)	2 (1)	76 (26)	68 (23)
Leukopenia[f]	9 (3)	0	45 (16)	38 (13)
Adjudicated drug-related ILD or pneumonitis	26 (9)[g]	11 (4)	12 (4)	4 (1)

- Stomatitis events, the most common TRAE with Dato-DXd, were primarily grade 1 (23%) or grade 2 (18%)
- Hematologic toxicities, including neutropenia and febrile neutropenia[h], were more common with docetaxel
- No new adjudicated drug-related ILD events or deaths occurred since the PFS database lock
- Similar safety profiles were seen for the full safety analysis set and the NSQ subgroup

Data cutoff: March 1, 2024.
[a]Occurring in ≥15% of patients in either treatment group, plus all events of adjudicated drug-related ILD or pneumonitis. [b]Due to rounding, summed rates may not reflect total percentage of TRAEs. [c]Includes an event incorrectly reported as grade 3. [d]Grouped preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased. [e]Grouped preferred terms of neutropenia and neutrophil count decreased. [f]Grouped preferred terms of leukopenia and white blood cell count decreased. [g]Includes one patient in the Dato-DXd group who experienced a grade 2 event that was adjudicated to be drug-related ILD by the adjudication committee. The investigator attributed the event to disease progression and removed the patient from the clinical database. [h]0.3% vs 6.9% for Dato-DXd and docetaxel, respectively.

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Conclusions

TROPION-Lung01

- TROPION-Lung01 **met its dual primary endpoint of PFS** with a statistically significant improvement for Dato-DXd over docetaxel in the overall population
- The dual primary endpoint of **OS showed a numerical improvement** but **was not statistically significant**
- Consistent benefit seen with Dato-DXd across all efficacy endpoints in patients with **NSQ histology**
- The tolerability profile remains manageable and **no new safety signals** were identified
- TROP2 normalized membrane ratio as measured by quantitative continuous scoring has been shown to predict clinical response to Dato-DXd in an exploratory TROPION-Lung01 analysis[1]

The results of TROPION-Lung01 support the use of Dato-DXd as a potential new therapeutic option for patients with previously treated NSQ NSCLC eligible for subsequent therapy

1. Garassino M, et al. Presented at WCLC 2024, San Diego, CA, USA, September 7–10, 2024 (Abstract PL02.11).

AdventHealth

ADCs - Small Cell Lung Cancer

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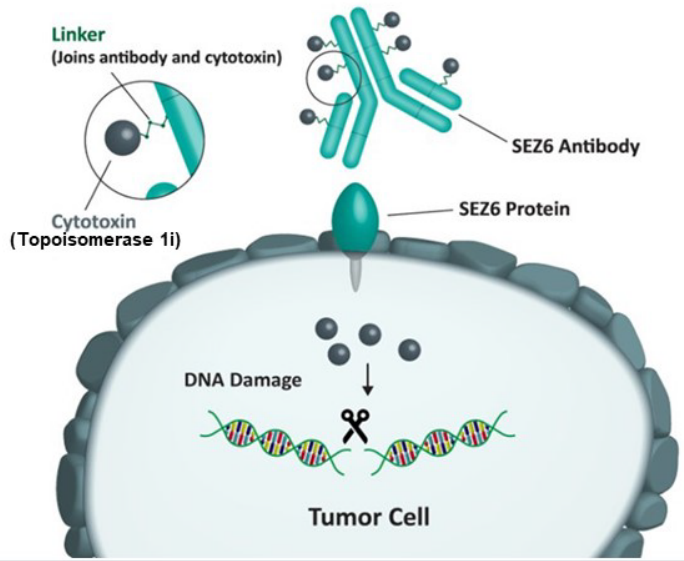
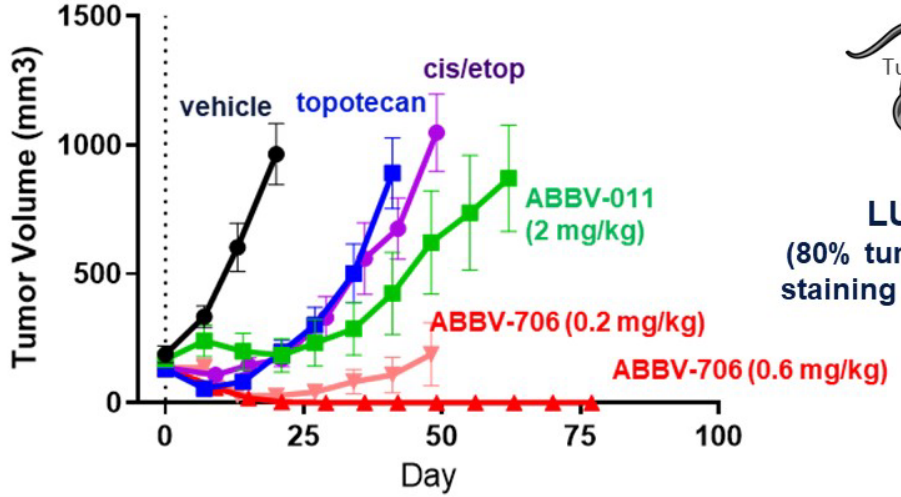
ABBV-706: SEZ6-targeting ADC

- SEZ6-targeting antibody, conjugated to a topoisomerase 1 inhibitor (Top1i) payload with sub-nM cytotoxic activity
- Drug-to-antibody ratio of 6 with stable attachment via a valine-alanine cathepsin cleavable linker
- Tumor-targeted delivery of Top1i[1] with potential for bystander killing of neighboring cancer cells
- Superior antitumor activity vs chemotherapy and ABBV-011, in a SEZ6-expressing SCLC murine model

ABBV-706 Mechanism of Action



ABBV-706 Preclinical Activity – SCLC (SEZ6+) PDX



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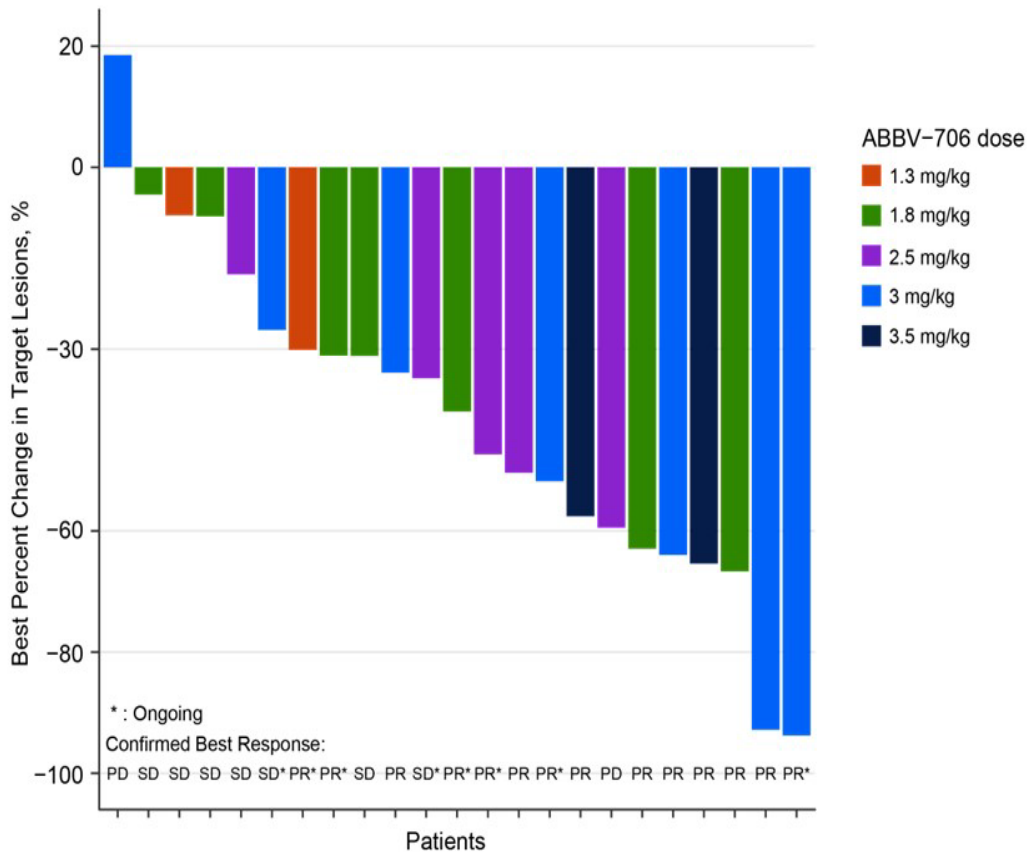
ABBV-706 is highly efficacious across doses in R/R SCLC (N=23)

Change in Target Lesion Size by Dose



Ongoing	3.0 mg/kg	2.5 mg/kg	1.8 mg/kg	1.3 mg/kg
n=8	3	2	2	1

Outcome	SCLC (N=23)
ORR,[a] n (%) [90% exact CI]	**14 (60.9)** [41.7, 77.8]
Best response,[b] n (%)	
CR	0
PR	14 (60.9)
SD	7 (30.4)
PD	2 (8.7)
CBR,[c] n (%) [90% exact CI]	21 (91.3) [75.1, 98.4]

- 21/23 patients with SCLC were 3L+ at study enrollment
- 11/18 patients with available 1L CTFI data were platinum resistant

Chandana S, et al. ASCO 2024. Abstract 3001

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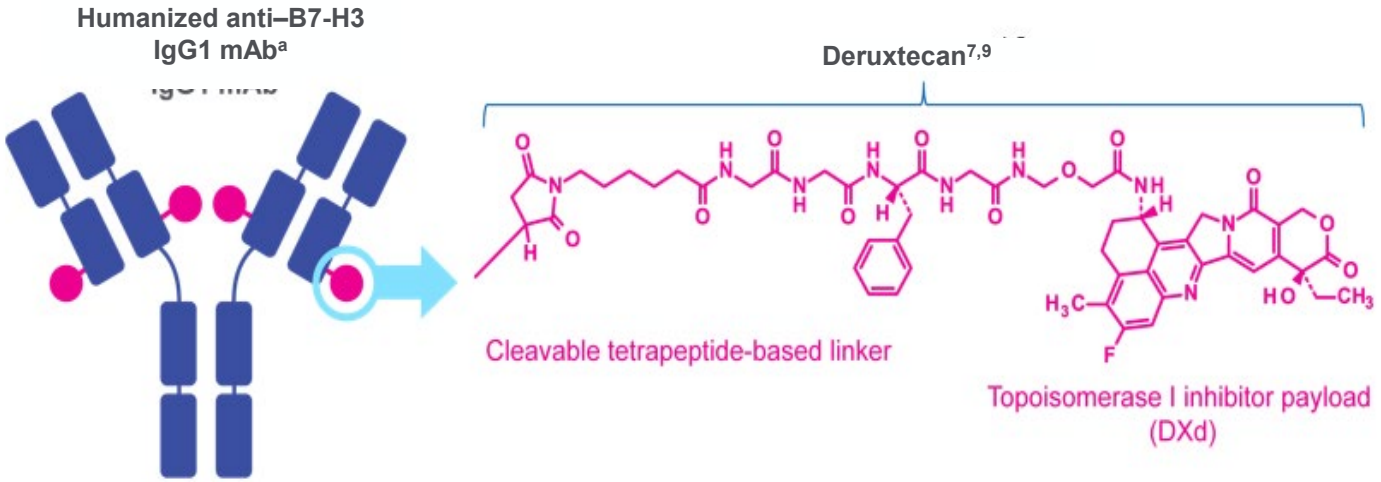
Ifinatamab Deruxtecan (I-DXd; DS-7300) Was Designed With 7 Key Attributes

- B7-H3 is overexpressed in a wide range of cancer types and is associated with disease progression and lower survival[1–5]
- I-DXd is a B7-H3 (CD276)-directed ADC composed of 3 parts:[6–9,11]
  - -A humanized anti–B7-H3 IgG1 monoclonal antibody[9,11]
  - -A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - -A tetrapeptide-based cleavable linker that covalently bonds the other 2 components



Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[9,11,b]
Optimized drug-to-antibody ratio ≈ 4[6–8,10,b]
Payload with short systemic half-life[9,11,b,c]
Stable linker-payload[9,11,b]
Tumor-selective cleavable linker[9,11,b]
Bystander antitumor effect[7,10,11,b]

[a]Image is for illustrative purposes only; actual drug positions may vary. [b]The clinical relevance of these features is under investigation. [c]Based on animal data.
ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; CD276, cluster of differentiation 276; DXd, deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
1. Yamato M, et al. AACR-NCI-EORTC 2020. Abstract 28. 2. Dong P, et al. *Front Oncol*. 2018;8:264. 3. Picarda E, et al. *Clin Cancer Res*. 2016;22(14):3425–3431. 4. Bendell JC, et al. *J Clin Oncol*. 2020;39(15 suppl 1). Abstract TPS3646.
5. Kontos F, et al. *Clin Cancer Res*. 2021;27(5):1227–1235. 6. Okajima D, et al. *Mol Cancer Ther*. 2021;20(12):2329–2340. 7. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173–185. 8. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097–5108.
9. Yamato M, et al. *Mol Cancer Ther*. 2022;21(4):635–646.10. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039–1046. 11. Daiichi Sankyo. Data on file.

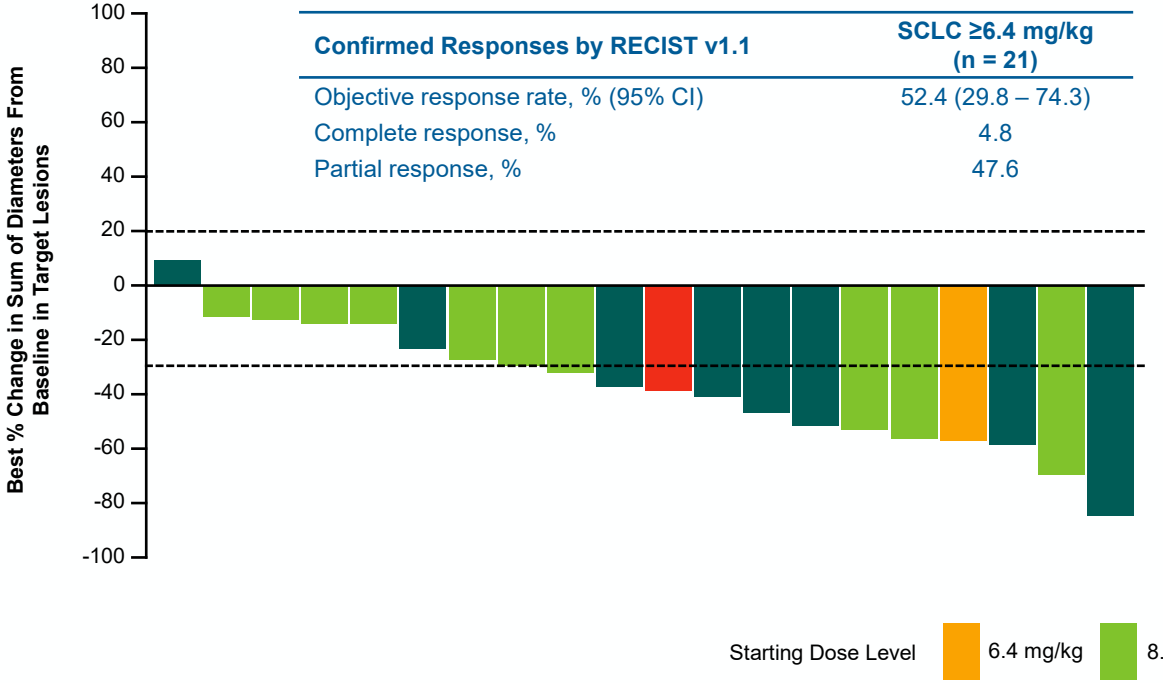
AdventHealth

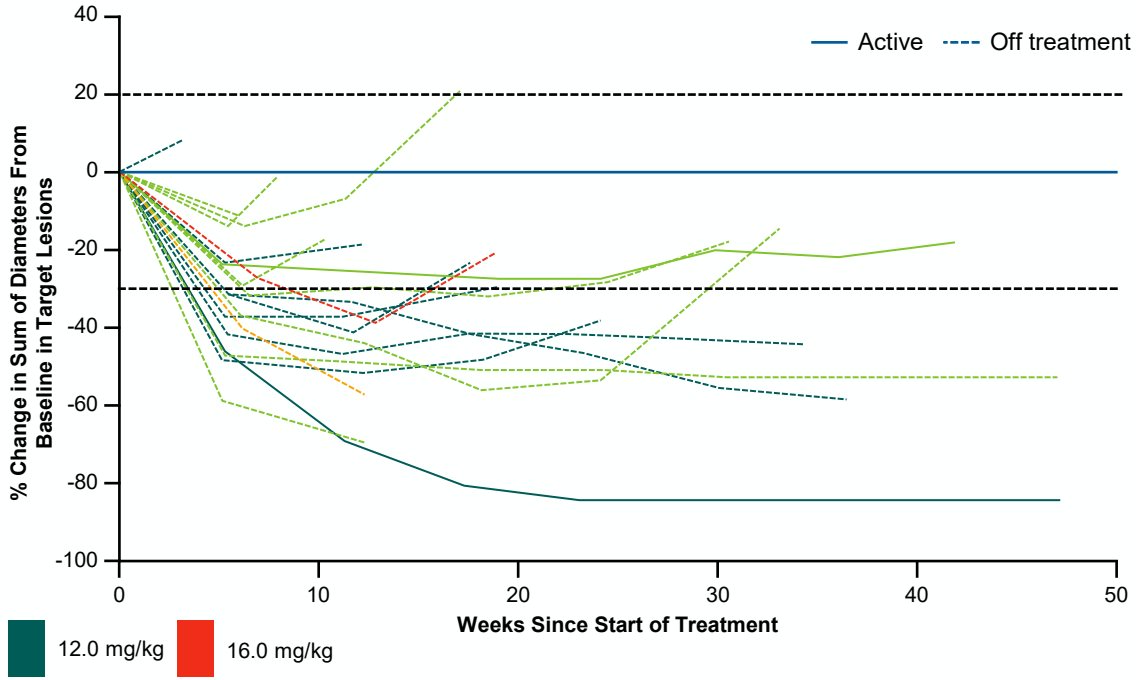
DS7300-A-J101 Study Design (NCT04145622)

- I-DXd is generally well tolerated with early signs of antitumor activity[1,2]
- **Subgroup analysis of patients with SCLC (N = 22[a]) from part 1 treated with I-DXd at all doses studied**

Antitumor Activity[a]

Confirmed Responses by RECIST v1.1	SCLC ≥6.4 mg/kg (n = 21)
Objective response rate, % (95% CI)	52.4 (29.8 – 74.3)
Complete response, %	4.8
Partial response, %	47.6





- Nearly all patients with post-baseline scans had a reduction in target lesions
- Median time to response was 1.2 months (95% CI, 1.2 – 1.4)
- Median duration of response was 5.9 months (95% CI, 2.8 – 7.5); two patients remain on treatment
- Median follow-up was 11.7 months (95% CI, 4.63 – 12.88)

Data cutoff: January 31, 2023.
[a]Patients with SCLC from dose-escalation with measurable disease at baseline and ≥2 post-baseline tumor scans and/or discontinued the treatment at data cutoff are included in best overall response calculations.
1 patient did not have post-baseline tumor scans and is not included in the waterfall or spider plots.
CI, confidence interval; RECIST, Response Evaluation Criteria in Solid Tumors; SCLC, small cell lung cancer.

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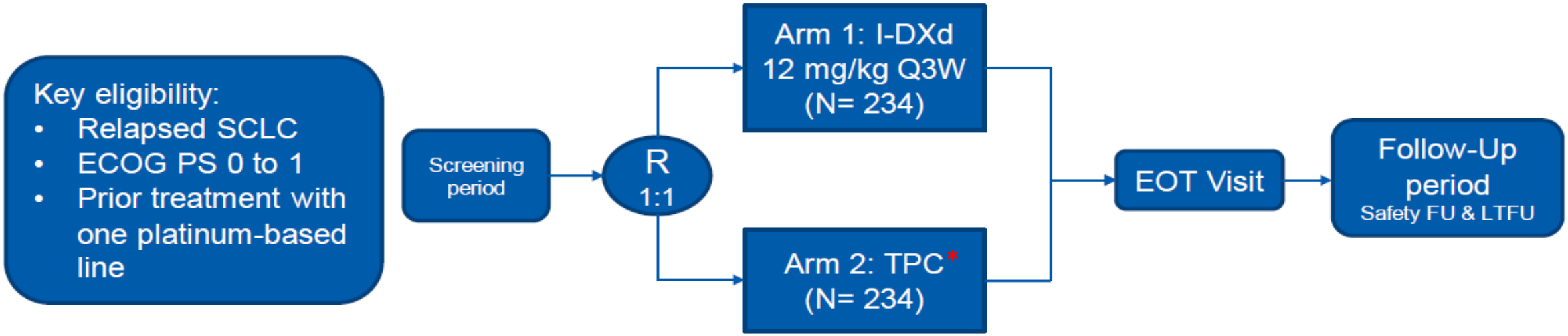
DS7300-188 IDeate-Lung02 Study (CSP v2.0)

A Phase 3, Multicenter, Randomized, Open-label Study of Ifinatamab Deruxtecan (I-DXd), a B7-H3 Antibody Drug Conjugate (ADC), versus Treatment of Physician's Choice (TPC), in Subjects with Relapsed Small Cell Lung Cancer (SCLC)



Stratification Factors:
- Prior treatment with PD-(L)1 (yes vs no)
- Chemotherapy Free Interval (CTFI) following 1L therapy (< 90 vs ≥ 90 days)
- Presence or history of asymptomatic brain metastases, regardless of treatment status (yes versus no)
- Treatment of Physician's Choice (amrubicin vs lurbinectedin vs topotecan)

Capping: < 25% of subjects without prior PD-(L)1

***Treatment of Physician's Choice:**
- Amrubicin
- Lurbinectedin
- Topotecan (≥ 50%)

Dual Primary Endpoints:
OS / ORR by BICR

Secondary Endpoints:
- ORR by investigator
- PFS by BICR and investigator
- DoR by BICR and investigator
- DCR by BICR and investigator
- TTR by BICR and investigator
- Safety
- Pharmacokinetics
- Immunogenicity
- QoL
- B7-H3 expression

Screening Period: The maximum screening period is 28 days
Treatment Period: 21-day cycles
Safety Follow-up (FU) Period: Safety FU Visit will occur 40 (+7) days post last dose
Long-Term Follow-up (LTFU) Period: LTFU visits will occur to assess survival, tumor progression until progressive disease for subjects who discontinued treatment for reason other than disease progression, and to collect information on further anticancer treatments, Q3M (90 ± 14 days) from study drug discontinuation until death, withdrawal of consent, or a study termination criterion is met

ECOG PS, Eastern Cooperative Oncology Group Performance Status; EOT, end of treatment; FU, follow-Up; ICF, informed consent form; IV, intravenous; LTFU, long-term follow-up; PD: Progressive Disease; Q3W, every three weeks; R, randomization; SCLC, small cell lung cancer. Daiichi Sankyo Inc. Data on file (IDeate-Lung02 protocol, version 2.0; February 13, 2024).

Small Cell Lung Cancer

AdventHealth

ADRIATIC study design

Phase 3, randomized, double-blind, placebo-controlled, multicenter, international study (NCT03703297)

- Stage I–III LS-SCLC (stage I/II inoperable)
- WHO PS 0 or 1
- Had not progressed following cCRT*
- PCI* permitted before randomization

N=730

R‡

Durvalumab
1500 mg Q4W
N=264

Placebo
Q4W
N=266

Durvalumab + tremelimumab
D 1500 mg Q4W + T 75 mg Q4W for 4 doses, followed by D 1500 mg Q4W
N=200

Stratified by:
Disease stage (I/II vs III)
PCI (yes vs no)

Treatment until investigator-determined progression or intolerable toxicity, or for a **maximum of 24 months**

cCRT components
- Four cycles of platinum and etoposide (three permitted†)
- RT: 60–66 Gy QD over 6 weeks or 45 Gy BID over 3 weeks
- RT must commence no later than end of cycle 2 of CT

Dual primary endpoints:
- Durvalumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Key secondary endpoints:
- Durvalumab + tremelimumab vs placebo
  - OS
  - PFS (by BICR, per RECIST v1.1)

Other secondary endpoints:
- OS/PFS landmarks
- Safety

*cCRT and PCI treatment, if received per local standard of care, must have been completed within 1–42 days prior to randomization.
†If disease control was achieved and no additional benefit was expected with an additional cycle of chemotherapy, in the opinion of the investigator.
‡The first 600 patients were randomized in a 1:1:1 ratio to the 3 treatment arms; subsequent patients were randomized 1:1 to either durvalumab or placebo.

BICR, blinded independent central review; BID, twice daily; CT, chemotherapy; D, durvalumab; PCI, prophylactic cranial irradiation; PS, performance status; Q4W, every 4 weeks; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; T, tremelimumab; WHO, World Health Organization.

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Baseline characteristics

		Durvalumab (n=264)	Placebo (n=266)
Age, years	Median (range)	62.0 (28–84)	62.0 (28–79)
Sex, %	Male / Female	67.4 / 32.6	70.7 / 29.3
Race, %	White / Asian / Other	49.2 / 49.6 / 1.1	51.5 / 45.5 / 3.0
WHO performance status, %	0 / 1	50.0 / 50.0	47.4 / 52.6
Smoking status, %	Current / Former / Never	23.9 / 67.4 / 8.7	20.7 / 69.5 / 9.8
AJCC disease stage at diagnosis, %	I / II / III	3.0 / 9.5 / 87.5	4.1 / 8.6 / 87.2
Prior chemotherapy regimen, %*	Cisplatin-etoposide / Carboplatin-etoposide	65.5 / 34.5	66.9 / 33.1
Prior radiation schedule, %	Once daily / Twice daily	73.9 / 26.1	70.3 / 29.7
Best response to prior cCRT, %	CR / PR / SD	11.7 / 72.3 / 15.9	12.8 / 75.2 / 12.0
Prior PCI, %	Yes / No	53.8 / 46.2	53.8 / 46.2

*Based on the first cycle of chemotherapy.

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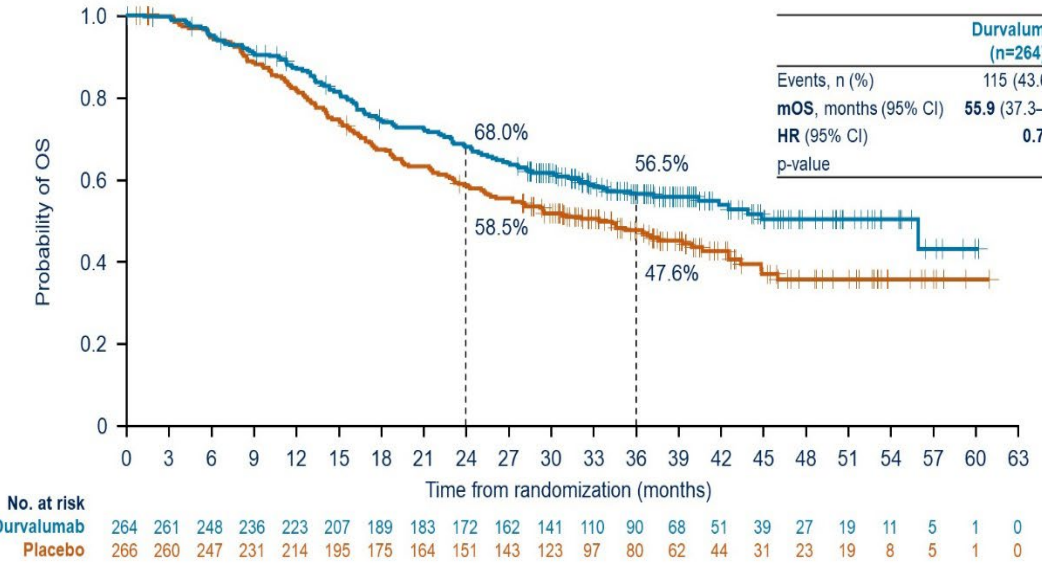
AJCC, American Joint Committee on Cancer; CR, complete response; PR, partial response; SD, stable disease.

ADRIATIC

Overall survival (dual primary endpoint)

- Median duration of follow up in censored patients: 37.2 months (range 0.1–60.9)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	115 (43.6)	146 (54.9)
mOS, months (95% CI)	**55.9** (37.3–NE)	**33.4** (25.5–39.9)
HR (95% CI)	**0.73** (0.57–0.93)	
p-value	0.0104	

No. at risk																						
Durvalumab	264	261	248	236	223	207	189	183	172	162	141	110	90	68	51	39	27	19	11	5	1	0
Placebo	266	260	247	231	214	195	175	164	151	143	123	97	80	62	44	31	23	19	8	5	1	0

OS was analyzed using a stratified log-rank test adjusted for receipt of PCI (yes vs no). The significance level for testing OS at this interim analysis was 0.01679 (2-sided) at the overall 4.5% level, allowing for strong alpha control across interim and final analysis timepoints.

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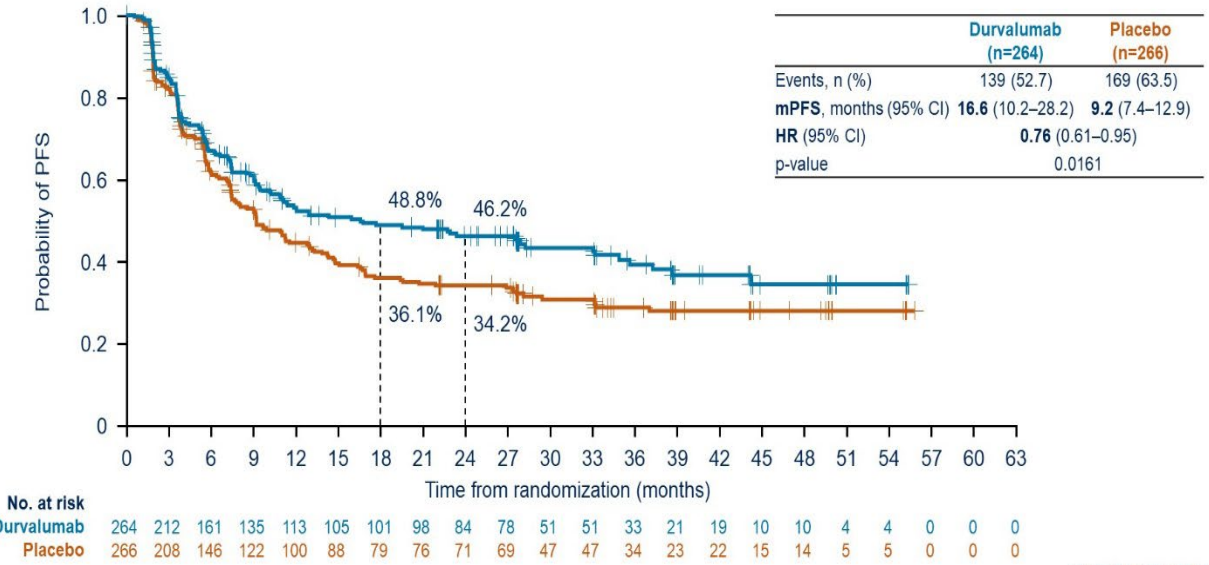
CI, confidence interval; mOS, median OS; NE, not estimable.

Progression-free survival* (dual primary endpoint)

- Median duration of follow up in censored patients: 27.6 months (range 0.0–55.8)



	Durvalumab (n=264)	Placebo (n=266)
Events, n (%)	139 (52.7)	169 (63.5)
mPFS, months (95% CI)	**16.6** (10.2–28.2)	**9.2** (7.4–12.9)
HR (95% CI)	**0.76** (0.61–0.95)	
p-value	0.0161	

No. at risk																						
Durvalumab	264	212	161	135	113	105	101	98	84	78	51	51	33	21	19	10	10	4	4	0	0	0
Placebo	266	208	146	122	100	88	79	76	71	69	47	47	34	23	22	15	14	5	5	0	0	0

*By BICR per RECIST v1.1.

PFS was analyzed using a stratified log-rank test adjusted for disease stage (I/II vs III) and receipt of PCI (yes vs no). The significance level for testing PFS at this interim analysis was 0.00184 (2-sided) at the 0.5% level, and 0.02805 (2-sided) at the overall 5% level. Statistical significance for PFS was achieved through the recycling multiple testing procedure framework and testing at the 5% (2-sided) alpha level (adjusted for an interim and final analysis).

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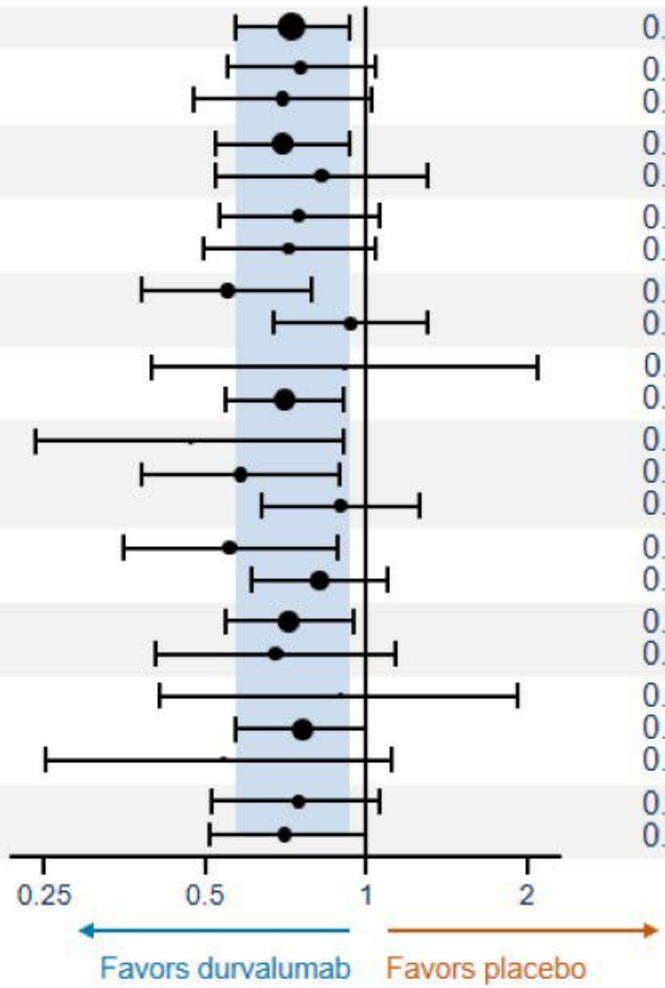
mPFS, median PFS.

OS subgroup analysis

		Events/Patients n/N		HR (95% CI)
		Durvalumab	Placebo	
All patients		115/264	146/266	0.73 (0.57–0.93)
Age	<65 years	69/160	83/162	0.76 (0.55–1.04)
	≥65 years	46/104	63/104	0.70 (0.48–1.02)
Sex	Male	79/178	108/188	0.70 (0.52–0.93)
	Female	36/86	38/78	0.83 (0.52–1.31)
Race	White	60/130	77/137	0.75 (0.53–1.05)
	Asian	53/131	64/121	0.72 (0.50–1.04)
WHO performance status	0	48/133	74/131	0.55 (0.38–0.79)
	1	67/131	72/135	0.94 (0.67–1.31)
AJCC disease stage at diagnosis	I/II	11/33	12/34	0.92 (0.40–2.11)
	III	104/231	134/232	0.71 (0.55–0.91)
Time from end of cCRT* to randomization	<14 days	14/32	24/32	0.47 (0.24–0.91)
	≥14 days to <28 days	37/79	51/80	0.59 (0.38–0.90)
	≥28 days	64/153	71/154	0.90 (0.64–1.27)
Prior chemotherapy regimen	Carboplatin-etoposide	31/ 91	46/88	0.56 (0.35–0.89)
	Cisplatin-etoposide	84/173	100/178	0.82 (0.61–1.10)
Prior radiation schedule	Once daily	92/195	107/187	0.72 (0.55–0.95)
	Twice daily	23/69	39/79	0.68 (0.40–1.14)
Best response to prior cCRT	Complete response	12/31	15/34	0.90 (0.41–1.92)
	Partial response	88/191	116/200	0.76 (0.57–1.00)
	Stable disease	15/42	15/32	0.54 (0.25–1.13)
Prior PCI	Yes	53/142	67/143	0.75 (0.52–1.07)
	No	62/122	79/123	0.71 (0.51–0.99)



*End of chemotherapy or radiotherapy, whichever was latest.
Intention-to-treat analysis stratified, subgroup analyses unstratified. Not all prespecified subgroups are included in the plot.
Size of circle is proportional to number of events across both arms.

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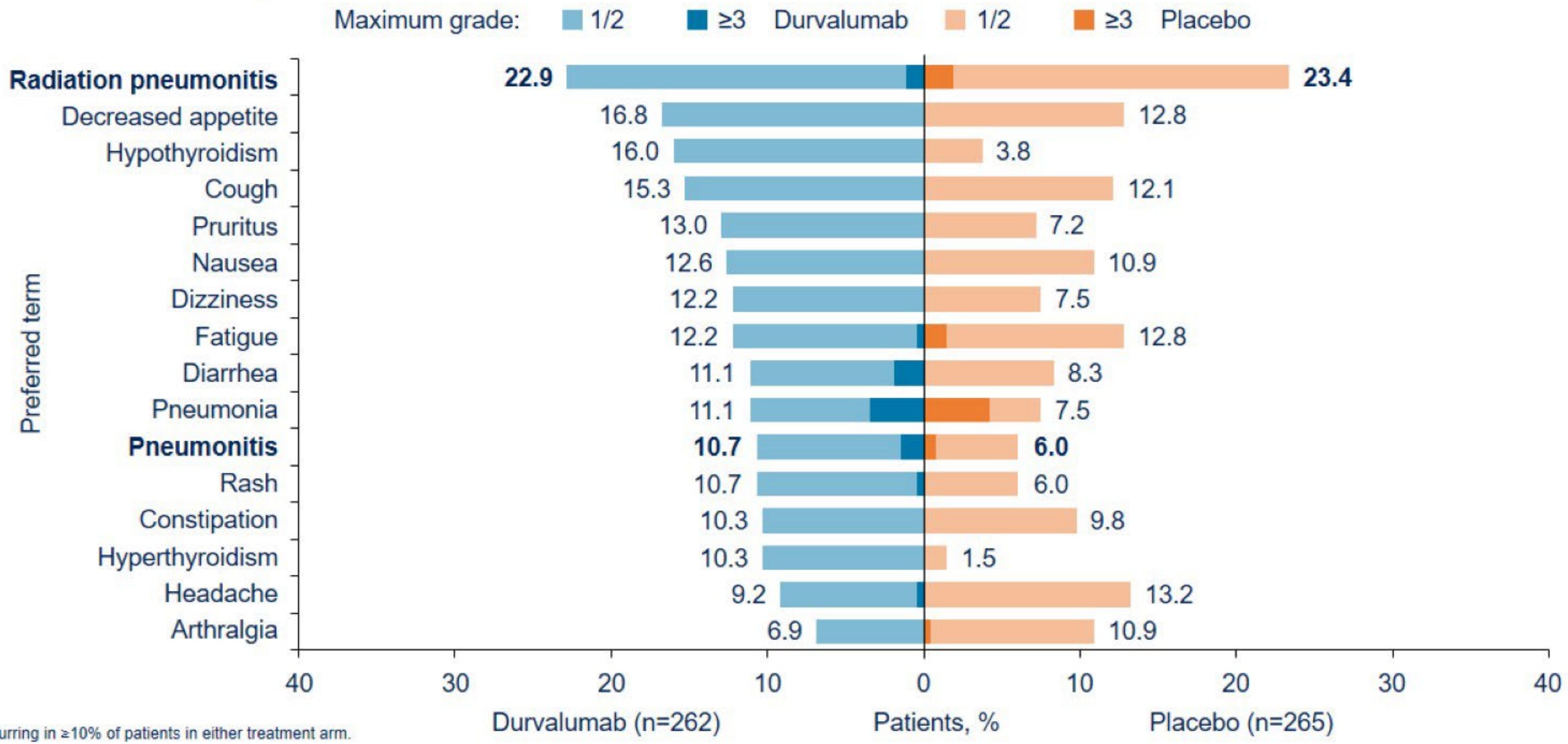
KNOWLEDGE CONQUERS CANCER

Most frequent AEs*



*Occurring in ≥10% of patients in either treatment arm.

PRESENTED BY: Dr David R. Spigel

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Pneumonitis/radiation pneumonitis

Pneumonitis or radiation pneumonitis (grouped terms*), n (%)	Durvalumab (n=262)	Placebo (n=265)
Any grade	100 (38.2)	80 (30.2)
Maximum grade 3/4	8 (3.1)	7 (2.6)
Leading to death	1 (0.4)	0
Leading to treatment discontinuation	23 (8.8)	8 (3.0)

*Includes the preferred terms of immune-mediated lung disease, interstitial lung disease, pneumonitis, radiation fibrosis – lung, and radiation pneumonitis. Events are included irrespective of etiology and AE management.

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Conclusions

- **Durvalumab as consolidation treatment after cCRT demonstrated statistically significant and clinically meaningful improvement in OS and PFS compared with placebo in patients with LS-SCLC**
  - **OS HR 0.73** (95% CI 0.57–0.93), p=0.0104; mOS 55.9 (95% CI 37.3–NE) vs 33.4 (95% CI 25.5–39.9) months
  - **PFS HR 0.76** (95% CI 0.61–0.95), p=0.0161; mPFS 16.6 (95% CI 10.2–28.2) vs 9.2 (95% CI 7.4–12.9) months
  - Treatment benefit was generally consistent across predefined patient subgroups for both OS and PFS
- **Durvalumab consolidation treatment for up to 2 years was well tolerated, and safety findings were consistent with the known safety profile of durvalumab monotherapy in the post-cCRT setting**

Consolidation durvalumab will become the new standard of care for patients with LS-SCLC who have not progressed after cCRT

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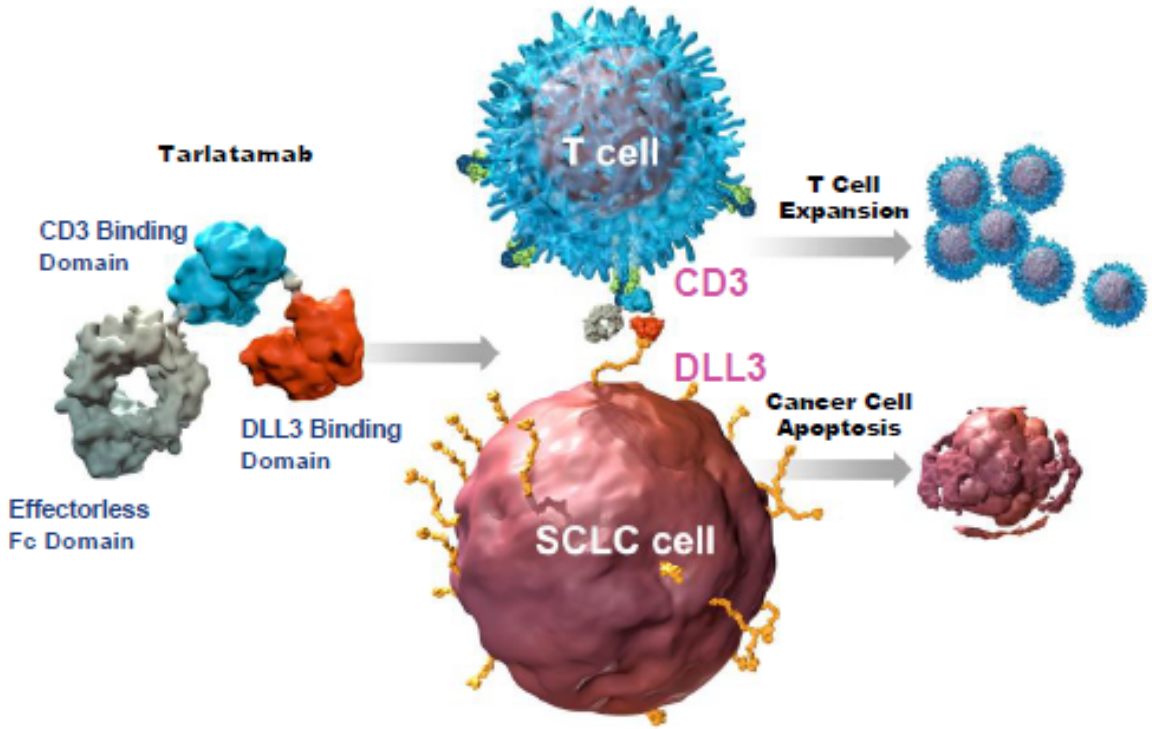
Small Cell Lung Cancer - BiTES

AdventHealth

Background

- Small cell lung cancer (SCLC) is an aggressive disease with poor survival outcomes and no approved therapies in the third-line and beyond[1–3]
- Tarlatamab is a BiTE® (bispecific T-cell engager) immunotherapy that binds to both delta-like ligand 3 (DLL3) on SCLC cells and CD3 on T cells, leading to T cell-mediated cancer cell lysis[4]
- Tarlatamab showed manageable safety and promising antitumor activity in a phase 1 study in previously treated SCLC[5]



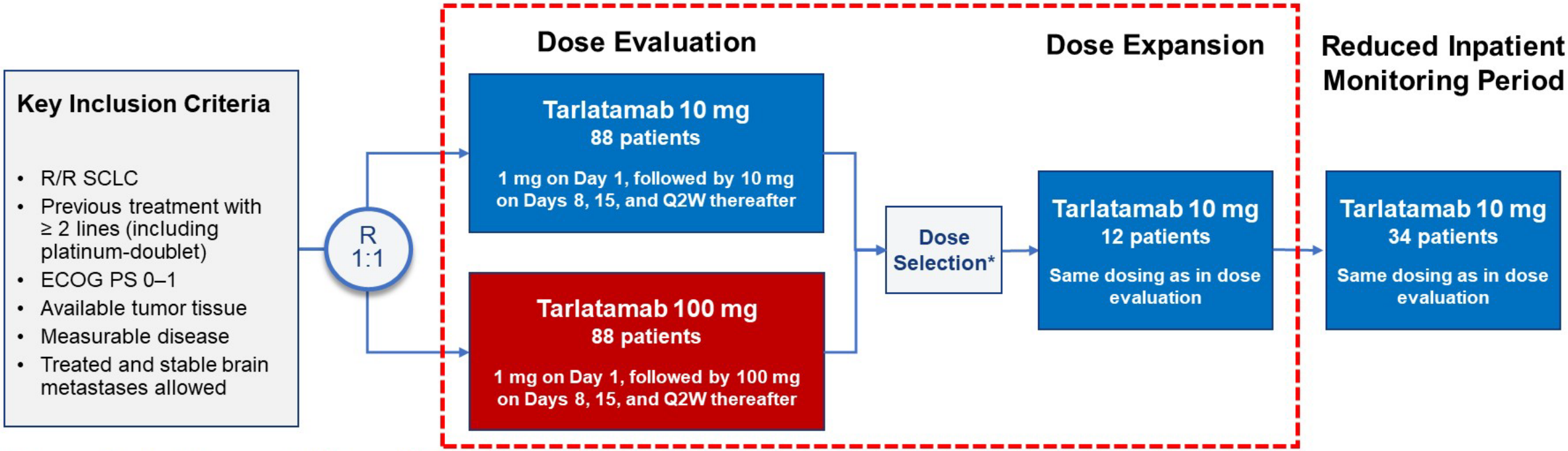
Tarlatamab activates T cells without relying on MHC-I

Here, we present the phase 2 DeLLphi-301 study of tarlatamab in patients with advanced SCLC previously treated with 2 or more lines of therapy

MADRID 2023 ESMO congress

CD3, cluster of differentiation 3; Fc, fragment crystallizable; MHC-I, major histocompatibility complex-I.

Phase 2 DeLLphi-301 Study Design



Primary Endpoint: ORR per RECIST v1.1 by BICR, TEAEs, tarlatamab serum concentrations
Secondary Endpoints: DOR, DCR, PFS per RECIST v1.1 by BICR, OS

Subgroup Analysis: Efficacy by BICR and safety, by presence or absence of baseline brain metastases
Post-hoc Analysis: Intracranial activity

NCT05060016. Post-enrollment, brain imaging was performed if clinically indicated. *Once 30 patients per dose level had the opportunity to confirm an objective response after the first post-treatment scan or up to 13 weeks of follow-up, whichever occurred first. **BICR**, blinded independent central review; **DCR**, disease control rate; **DOR**, duration of response; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **R**, randomization; **RECIST**, Response Evaluation Criteria in Solid Tumors; **R/R SCLC**, relapsed/refractory small cell lung cancer; **TEAE**, treatment-emergent adverse event.
Ahn MJ, et al. *N Engl J Med*. 2023;389:2063-2075.

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Baseline Characteristics

	Part 1 + 2 Tarlatamab 10 mg (n = 100)	Part 1 Tarlatamab 100 mg (n = 88)	Part 3 Tarlatamab 10 mg (n = 34)
Median age, years (range)	64 (35–82)	62 (34–80)	66 (49–80)
Male, %	72	70	71
Asian / Black or African American / White,* %	41 / 0 / 58	41 / 0 / 58	6 / 3 / 91
Ever smoker / non-smoker, %	92 / 8	94 / 6	97 / 3
ECOG performance status: 0 / 1, %	26 / 74	27 / 73	29 / 71
Prior lines of therapy, median (range)	2 (1–6)	2 (1–8)	2 (2–6)
2 prior lines of therapy, %	65	55	65
≥ 3 prior lines of therapy, %	33	43	35
Prior anti-PD-(L)1 treatment, %	73	70	82
< 90 days to progression after first-line platinum therapy,† %	28	20	21
Brain / liver metastases, %	23 / 39	36 / 34	12 / 35
DLL3 expression (> 0%), n/N evaluable (%)	80/83 (96)	71/74 (96)	N/A‡

Data cutoff, June 27, 2023. Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg.
*No patients of American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander race were enrolled.
†Platinum sensitivity was calculated as end of first-line platinum therapy to date of first progression.
‡DLL3 sample analysis from Part 3 in progress.
DLL3, delta-like ligand 3; **ECOG**, Eastern Cooperative Oncology Group; **N/A**, not available; **PD-(L)1**, programmed death 1 / ligand 1.

Tarlatamab Anti-Tumor Activity

Outcome	Tarlatamab 10 mg (n = 100)	Tarlatamab 100 mg (n = 88)
Objective response rate, n (%) (97.5% CI)	40 (40) (29, 52)	28 (32) (21, 44)
Complete response	1 (1)	7 (8)
Partial response	39 (39)	21 (24)
Stable disease	30 (30)	27 (31)
Progressive disease	20 (20)	13 (15)
Not evaluable / no post-baseline scan*	10 (10)	20 (23)
Observed duration of response ≥ 6 months, n/N (%)	23/40 (58)	17/28 (61)
Disease control rate, n (%) (95% CI)	70 (70) (60, 79)	55 (63) (52, 73)

Tarlatamab 10 mg demonstrated anti-tumor activity in heavily pre-treated SCLC with an objective response rate of 40%

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Data cutoff, June 27, 2023. Median follow-up was 10.6 months for tarlatamab 10 mg and 10.3 months for tarlatamab 100 mg. The efficacy analysis set consists of patients in Parts 1 and 2 (N = 188). Part 3 did not have adequate follow-up for response analysis.

*Not evaluable and no post-baseline scan were considered non-responders for response analysis. **SCLC**, small cell lung cancer.

Efficacy Summary

Baseline brain metastases:	Tarlatamab 10 mg Q2W* (n = 100)†	
	Yes (n = 23)	No (n = 77)
ORR, % (95% CI)	52 (31–73)	38 (27–49)
Median DOR, months (range)	NE (3–12+)	NE (2–12+)
DOR probability at 12 months, KM estimate, % (95% CI)	55 (22–78)	50 (29–68)
Median PFS, months (95% CI)	6.7 (3–NE)	4.0 (3–6)
Median OS‡, months (95% CI)	14.3 (14–NE)	NE (9–NE)

Tarlatamab demonstrated durable response with promising survival regardless of the presence of treated, stable brain metastases at baseline

Data cutoff, June 27, 2023. Median follow-up: 10.6 months. *Given as 1 mg on Day 1, followed by 10 mg on Days 8, 15, and Q2W thereafter. For 100 mg data, scan QR code or see https://meetings.asco.org/abstracts-presentations/232383. †The intention-to-treat analysis set consists of all patients who were randomized and enrolled according to assigned treatment dose levels. ‡OS data yet to mature. **CI,** confidence interval; **DOR**, duration of response; **KM**, Kaplan-Meier; **NE**, not estimable; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q2W**, every 2 weeks.

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Summary of Adverse Events*

TEAEs, n (%)	Part 1 + 2 Tarlatamab 10 mg (n = 99)	Part 1 Tarlatamab 100 mg (n = 87)	Part 3 Tarlatamab 10 mg (n = 34)
Any grade	96 (97)	87 (100)	34 (100)
≥ Grade 3	57 (58)	56 (64)	22 (65)
Related to tarlatamab, any grade	89 (90)	81 (93)	29 (85)
≥ Grade 3	29 (29)	29 (33)	5 (15)
Fatal	0	0	1 (3)†
Leading to dose interruption/reduction	14 (14)	25 (29)	3 (9)
Leading to discontinuation	4 (4)	3 (3)	0

Most Common TEAEs in ≥ 20% of Patients, n (%)	Part 1 + 2 Tarlatamab 10 mg (n = 99)	Part 1 Tarlatamab 100 mg (n = 87)	Part 3 Tarlatamab 10 mg (n = 34)
CRS	49 (49)	53 (61)	19 (56)
Grade 1–2	49 (49)	48 (55)	18 (53)
≥ Grade 3	0	5 (6)	1 (3)
Decreased appetite	25 (25)	38 (44)	13 (38)
Pyrexia	38 (38)	29 (33)	8 (24)
Constipation	28 (28)	22 (25)	8 (24)
Anemia	26 (26)	22 (25)	9 (26)
Asthenia	20 (20)	21 (24)	10 (29)
Dysgeusia	24 (24)	12 (14)	14 (41)
Fatigue	21 (21)	17 (20)	9 (26)

- **Tarlatamab demonstrated a favorable safety profile, with a low rate of discontinuations due to treatment-related adverse events (TRAEs)**
- **Shorter inpatient monitoring (Part 3) did not alter the safety profile**

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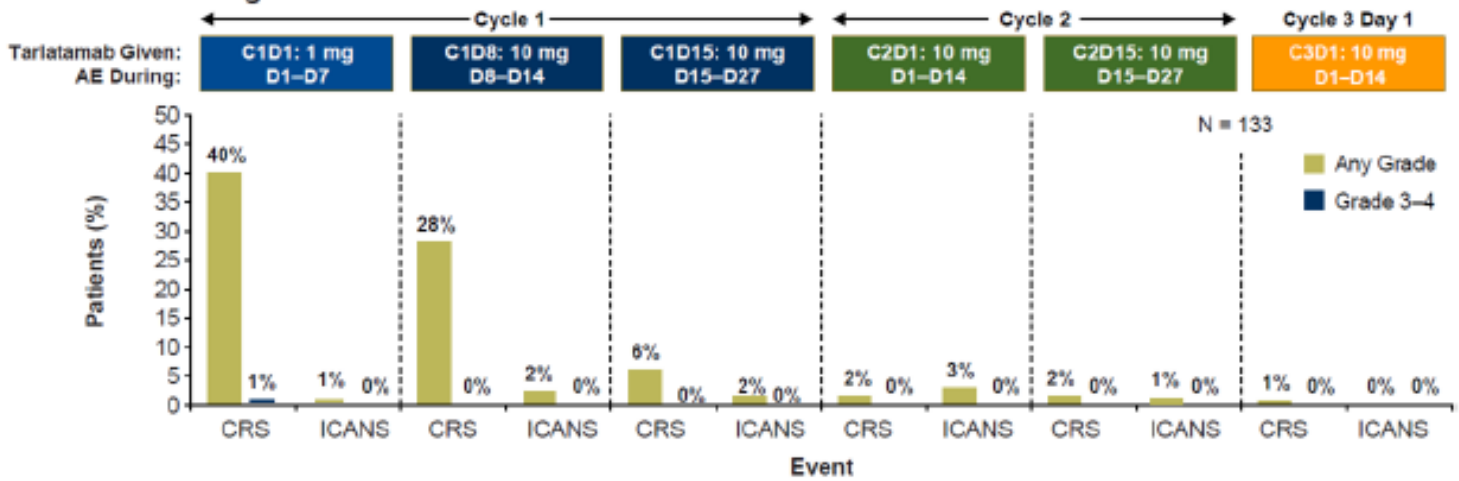
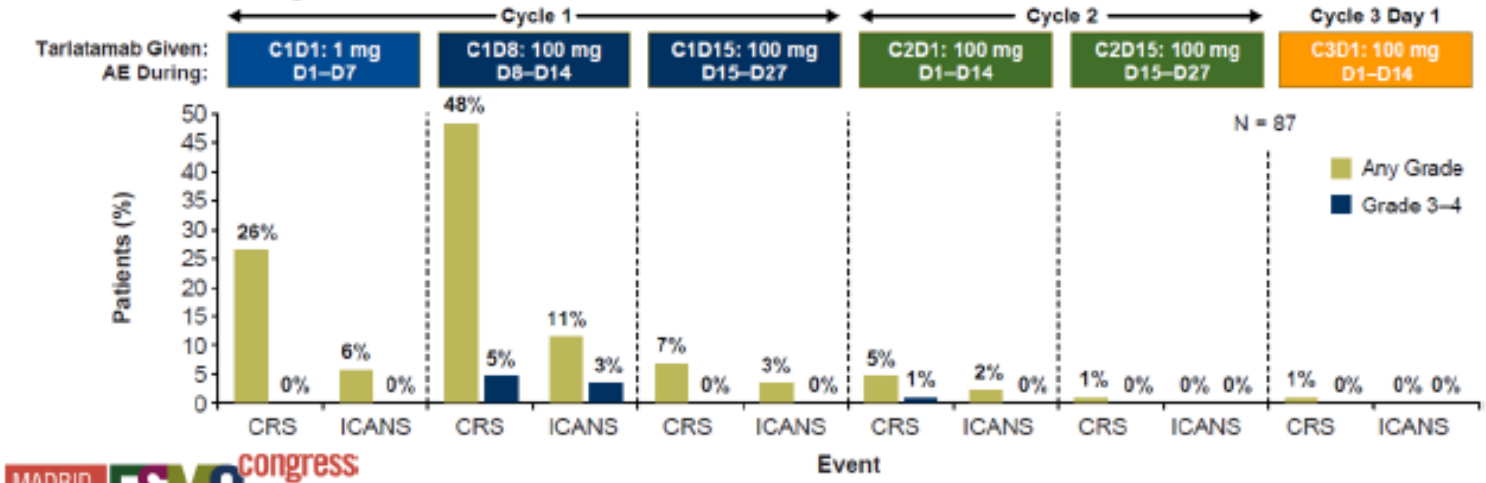
*The safety analysis set includes all patients in Part 1, Part 2, and Part 3 who received at least one dose of tarlatamab (N = 220). †Fatal TRAE was respiratory failure.
CRS, cytokine release syndrome; **TEAE**, treatment-emergent adverse event.

CRS and Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)*

Tarlatamab 10 mg



Tarlatamab 100 mg



- CRS was largely confined to the first or second dose, primarily grade 1–2
- ICANS* occurred infrequently overall and was predominantly observed with tarlatamab 100 mg

Additional Interventions for CRS:

Patients receiving tarlatamab, n (%)	10 mg (n = 133)	100 mg (n = 87)
Tocilizumab	7 (5)	9 (10)
Supplemental oxygen	11 (8)	8 (9)
Vasopressor support	1 (1)	1 (1)

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*ICANS includes associated neurologic events based on a broad search using 61 selected preferred terms from MedDRA version 26.0.
AE, adverse event; C, cycle; CRS, cytokine release syndrome; D, day; ICANS, immune effector cell-associated neurotoxicity syndrome.

TABLE II. ASTCT grading scale for CRS

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
With				
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
And/or				
Hypoxia	None	Requiring low-flow nasal cannula or blow-by	Requiring high-flow cannula, face mask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation, and mechanical ventilation)

TABLE IV. ASTCT ICANS consensus grading for adults

Neurotoxicity domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (unable to perform)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Unarousable, requires vigorous or repetitive tactile stimuli to arouse. Stupor or coma
Seizure	N/A	N/A	Any clinical seizure that resolves rapidly or nonconvulsive seizures on EEG that resolve without intervention	Life-threatening prolonged seizure (>5 min) or repetitive clinical or electric seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated intracranial pressure/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

From Lee et al.[43]

CTCAE, Common Terminology Criteria for Adverse Events; *EEG*, electroencephalogram; *ICE*, immune effector cell–associated encephalopathy; *N/A*, not applicable.

ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, raised intracranial pressure/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is classified as having grade 3 ICANS.

*A patient with an ICE score of 0 may be classified as having grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as having grade 4 ICANS if unarousable.

†Depressed level of consciousness should be attributable to no other cause (eg, no sedating medication).

Conclusions

- Tarlatamab 10 mg Q2W demonstrated a favorable benefit-risk profile in patients with previously treated SCLC irrespective of the presence of treated and stable brain metastases (BM) at baseline
  - ORR was 52% in patients with BM (n = 23) and 38% in patients without BM (n = 77)
  - In patients with BM, median PFS was 6.7 months and median OS was 14.3 months
  - The safety profile of tarlatamab in patients with BM was manageable and consistent with the overall safety profile from the tarlatamab program
- CNS tumor shrinkage was observed after radiotherapy in some patients treated with tarlatamab

Results support further study of tarlatamab in patients with previously treated SCLC irrespective of the presence of brain metastases at baseline

CNS, central nervous system; **ORR**, objective response rate; **OS**, overall survival; **PFS**, progression-free survival; **Q2W**, every 2 weeks; **SCLC**, small-cell lung cancer.

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Tarlatamab - Ongoing Trials

Setting	Trial	NCT	Phase	Question
LS-SCLC	DeLLphi-306	06117774	III	Vs Placebo following CRT
ES-SCLC	DeLLphi-305	06211036	III	Durva ± Tarlatamab maintenance
ES-SCLC (2nd L)	DeLLphi-304	05740566	III	Tarlatamab Vs SOC 2nd Line
ES-SCLC (1st L)	DeLLphi-303	05361395	Ib	CbEtopAtezo + Tarlatamab

Jazz Pharmaceuticals Announces Statistically Significant Overall Survival and Progression-Free Survival Results for Zepzelca® (lurbinectedin) and Atezolizumab Combination in First-Line Maintenance Therapy for Extensive-Stage Small Cell Lung Cancer

- DUBLIN, Oct. 15, 2024 /PRNewswire/ -- Jazz Pharmaceuticals plc (Nasdaq: JAZZ) today announced positive top-line results from the Phase 3 clinical trial evaluating Zepzelca® (lurbinectedin) in combination with the PD-L1 inhibitor atezolizumab (Tecentriq®) compared to atezolizumab alone when administered as a maintenance treatment for adults with extensive-stage small cell lung cancer (ES-SCLC) following induction therapy with carboplatin, etoposide and atezolizumab. The combination of *Zepzelca* and atezolizumab demonstrated a statistically significant improvement in the primary endpoints of overall survival (OS) and progression-free survival (PFS), as assessed by an independent review facility (IRF), compared to treatment with atezolizumab alone.

Thank You

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Q&A

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Clinical Session

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Lunch

Enjoy your lunch and
please return at 1:00pm

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