CARCINOMA DEL POLMONE: QUALI NOVITÀ NEL 2024? V Edizione

Sessione V - La ricerca clinica e traslazionale nel carcinoma polmonare

I Risultati della Ricerca: lo Sviluppo di ADC nel Carcinoma Polmonare

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Disclosures

- Advisory Boards / Speakers' fee:
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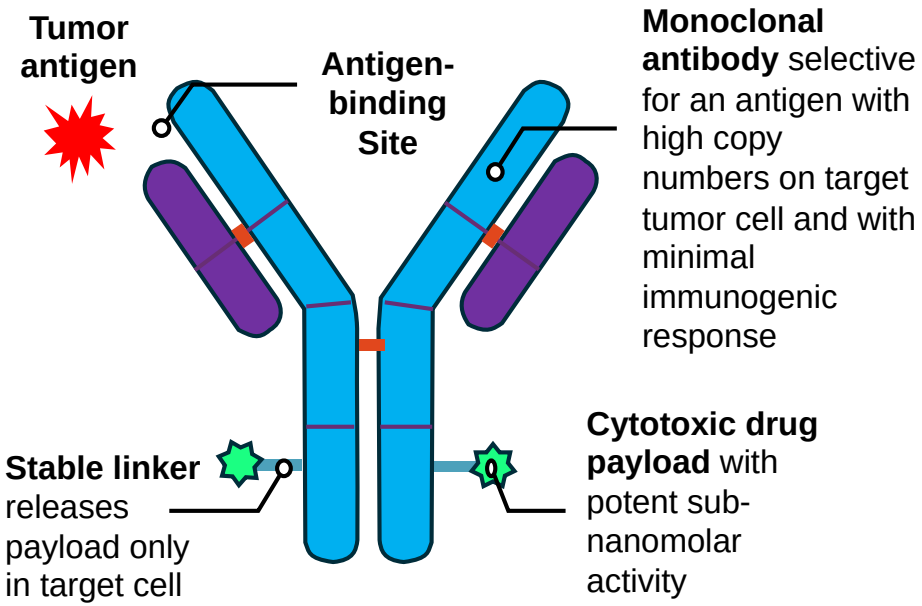
Targets of Antibody Drug Conjugates (ADC)

- **Molecularly <u>UNSELECTED</u> pts' NSCLC/SCLC populations:**
  - **TROP2, Nectin4, ROR1, AXL, Tissue Factor, B7H4, B7H3, Integrin-Beta6**

- **Molecularly '<u>ENRICHED</u>' pts' NSCLC populations:**
  - **EGFR, ALK, HER2, HER3, CEACAM, MET**



Drago JZ, Nat Rev Clin Oncol 2021

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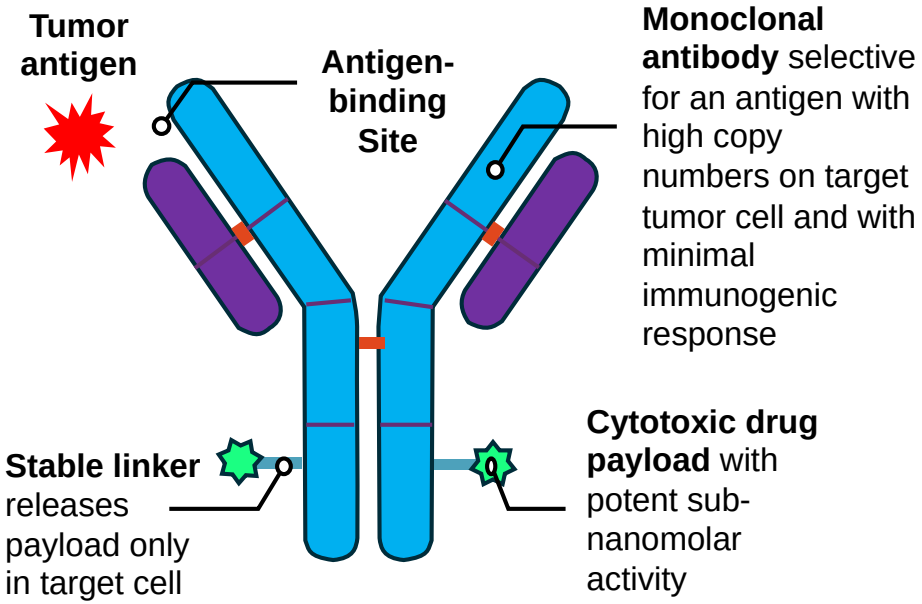
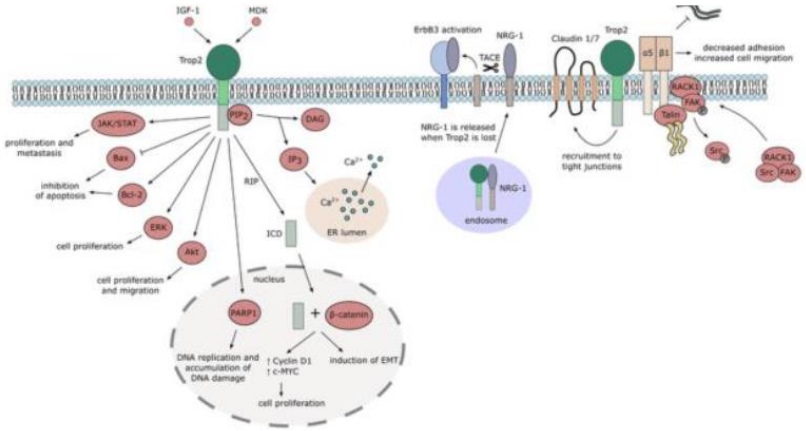
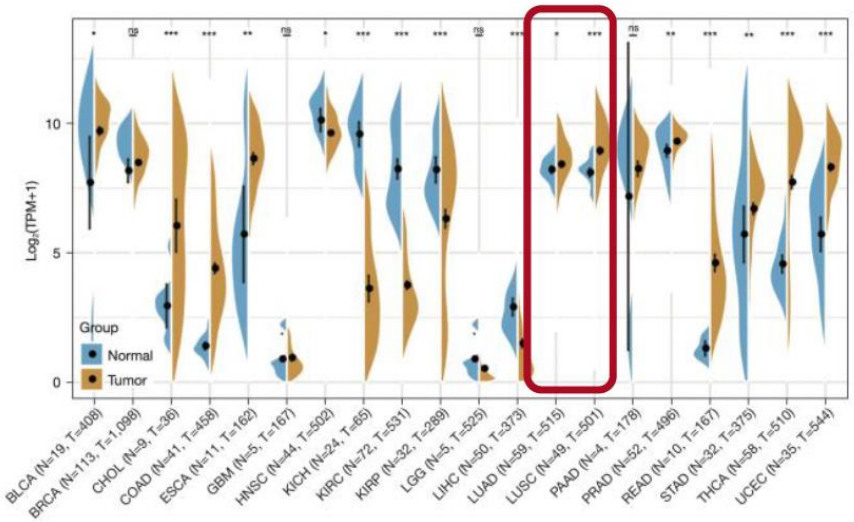
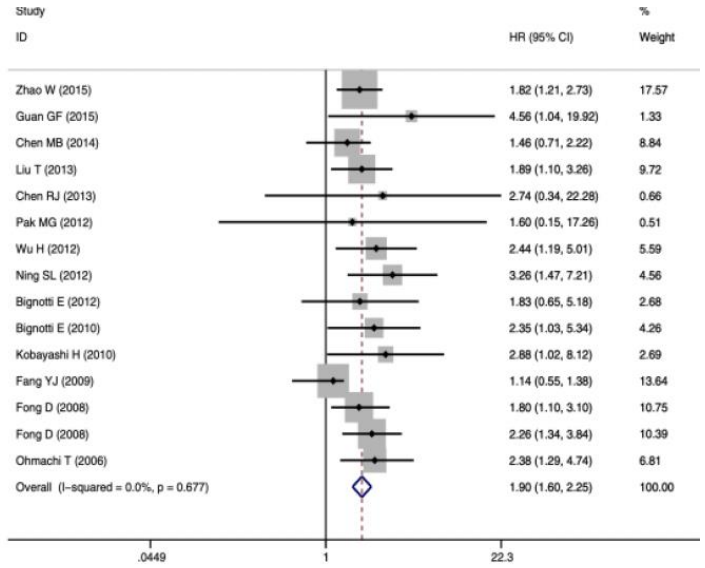


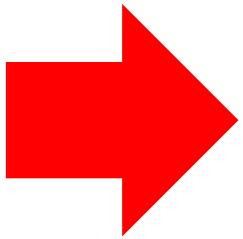
Drago JZ, Nat Rev Clin Oncol 2021

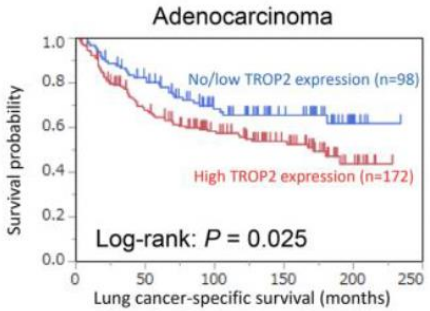
Why TROP2?



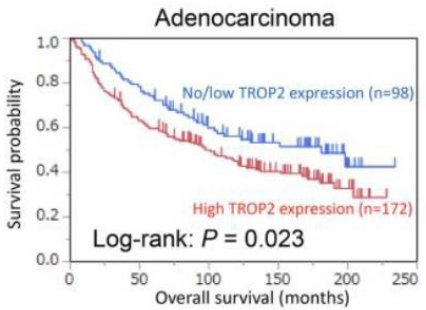




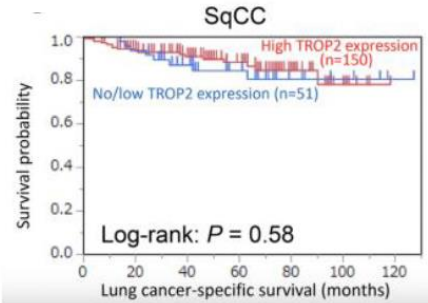




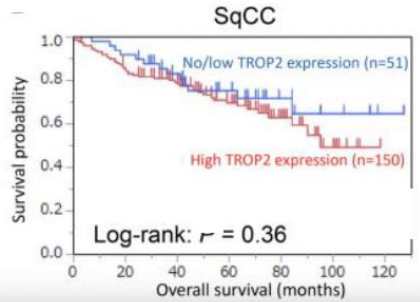
Lung cancer-specific survival



Overall survival



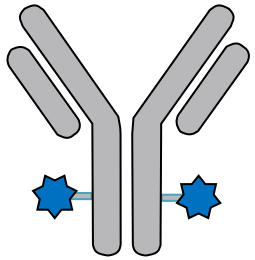
Lung cancer-specific survival



Overall survival

Lénart S, Cancers 2020; Liu X, Pharmacol Thera 2022; Zeng P, Sci Rep 2016; Inamura K, Oncotarget 2017

Antibody–Drug Conjugates (ADC): Components

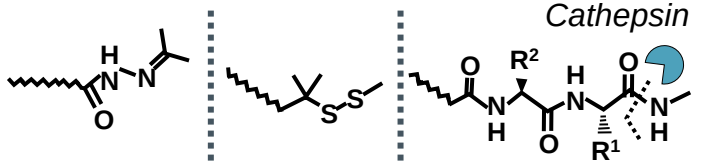


Antibodies

	IgG1	IgG2	IgG3	IgG4
Serum half-life	21 days	21 days	7-21 days	21 days
C1q binding	Yes	Yes	Yes	No
Fcγ avidity	High	Low	High	Moderate

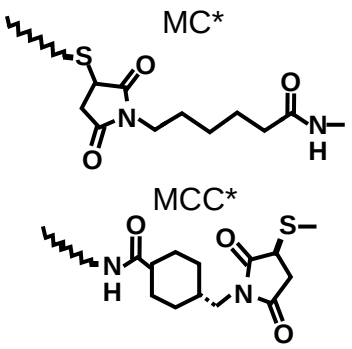
Linkers

Cleavable



Hydrazone (acid cleavable) | Disulfide (reducible) | Dipeptide (protease cleavable)

Noncleavable



Payloads

Auristatins	**Maytansinoids**	**Calicheamicins**	**Camptothecins**
(MoA: antimicrotubule)	(MoA: antimicrotubule)	(MoA: DNA cleavage)	(MoA: Topoisomerase 1 inhibition)

ANTIBODY: Chimeric/humanized monoclonal IgG antibody targeting a protein preferentially expressed on the tumor cell surface

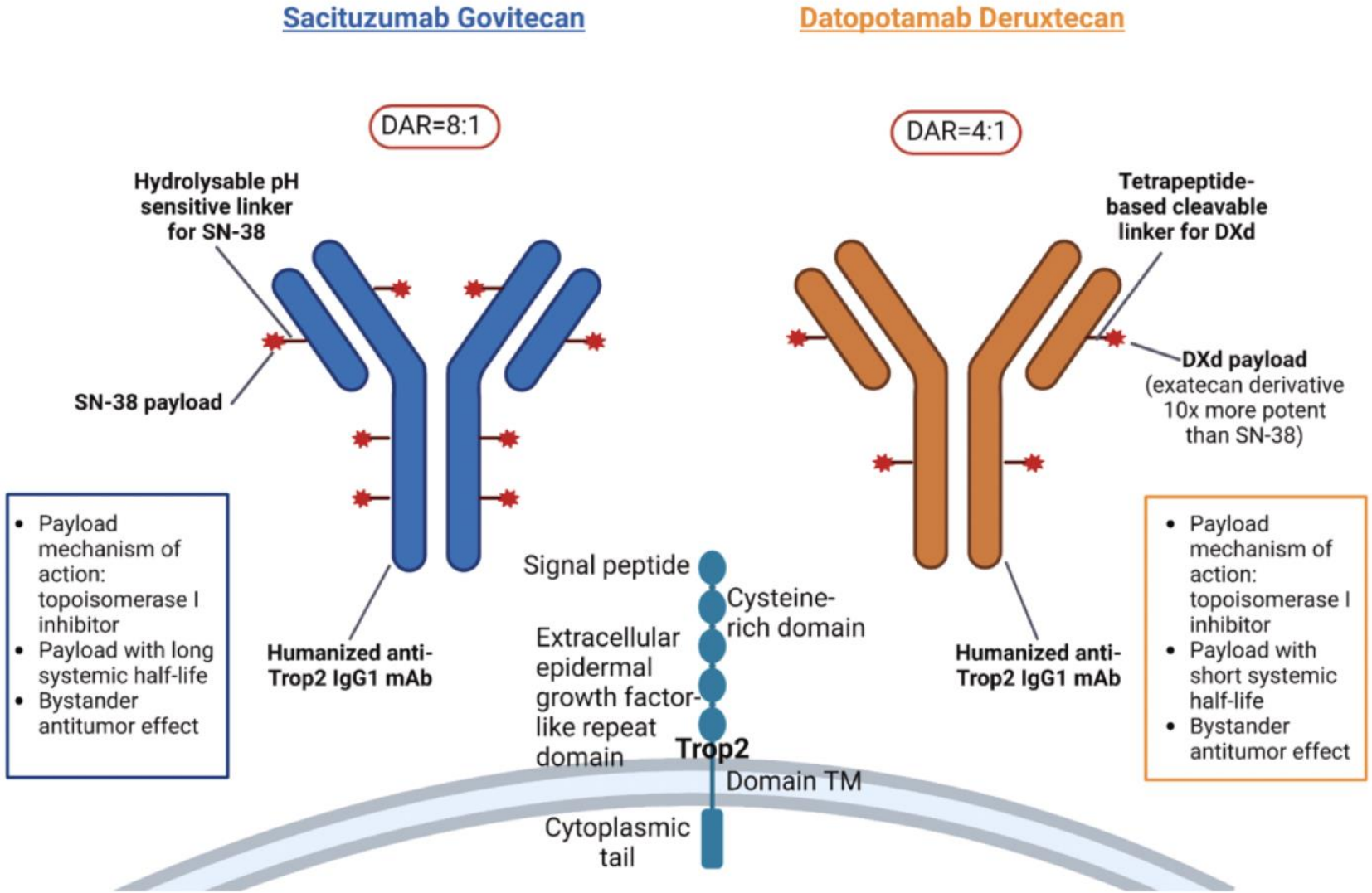
LINKER: Ensures payload is attached to antibody in plasma but is efficiently released in tumor cells. Linkers can be cleavable (via tumor-associated factors) or noncleavable (lysosomal degradation)

PAYLOAD: Enhances cytotoxicity, although variable drug:antibody ratio affects efficacy and clearance

Noncleavable MC and MCC linkers typically used with monomethyl auristatin F and emtansine payloads, respectively; can be cleavable when conjugated with some other payloads.

Drago JZ, Nat Rev Clin Oncol 2021

Why TROP2?



Parisi C et al, Cancer Treat Rev 2023

TROPION-Lung01, Phase 3, Open-Label, (NCT04656652)

Key Eligibility Criteria

- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0 or 1
- No prior docetaxel
  - **Without actionable genomic alterations[a]**
    - 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

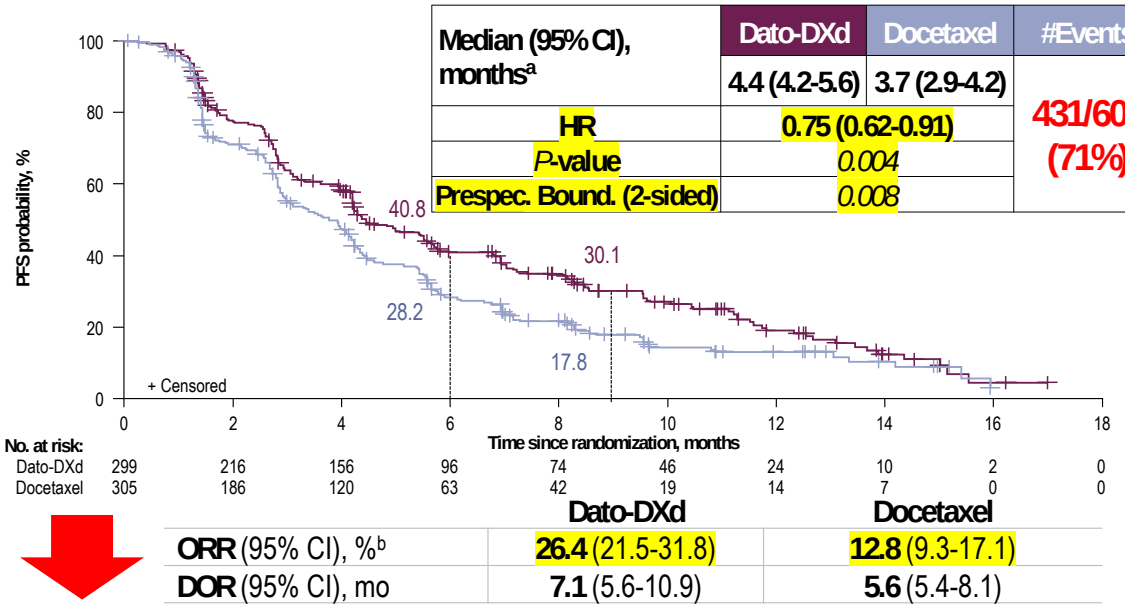
- **Dato-DXd** 6 mg/kg Q3W (N=299)
- **Docetaxel** 75 mg/m² Q3W (N=305)

Dual Primary Endpoints
- PFS by BICR
- OS

Secondary Endpoints
- ORR by BICR
- DOR by BICR
- Safety

Stratified by:
1) histology (SQ vs. NonSQ),
2) [b] actionable genomic alteration (yes vs no);
3) [c] anti–PD-(L)1 mAb included in most recent prior therapy (Presence vs. Absence);
4) geography[d]

- [a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations.



Median (95% CI), months[a]	Dato-DXd	Docetaxel	#Events
	4.4 (4.2-5.6)	3.7 (2.9-4.2)	431/604 (71%)
HR	0.75 (0.62-0.91)		
P-value	*0.004*		
Prespec. Bound. (2-sided)	*0.008*		

	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**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)

Median PFS f.u was 10.9 (95% CI, 9.8-12.5) and 9.6 (95% CI, 8.2-11.9) months for Dato-DXd and D

Characteristic		Dato-DXd N=299	Docetaxel N=305
Current or former smoker, n (%)		238 (80)	251 (82)
Actionable genomic alterations, n (%)	Present	50 (17)	51 (17)
	EGFR mutation	39 (13)	45 (15)
Brain metastasis at baseline, n (%)[b]		50 (17)	47 (15)
Prior lines of therapy, n (%)	1	167 (56)	174 (57)
	2	108 (36)	102 (33)
	≥3	22 (7)	28 (9)
Previous systemic therapy, n (%)[c]	Platinum containing	297 (99)	305 (100)
	Anti–PD-(L)1	263 (88)	268 (88)
	Targeted	46 (15)	50 (16)

TRAEs Occurring in ≥10% of Patients

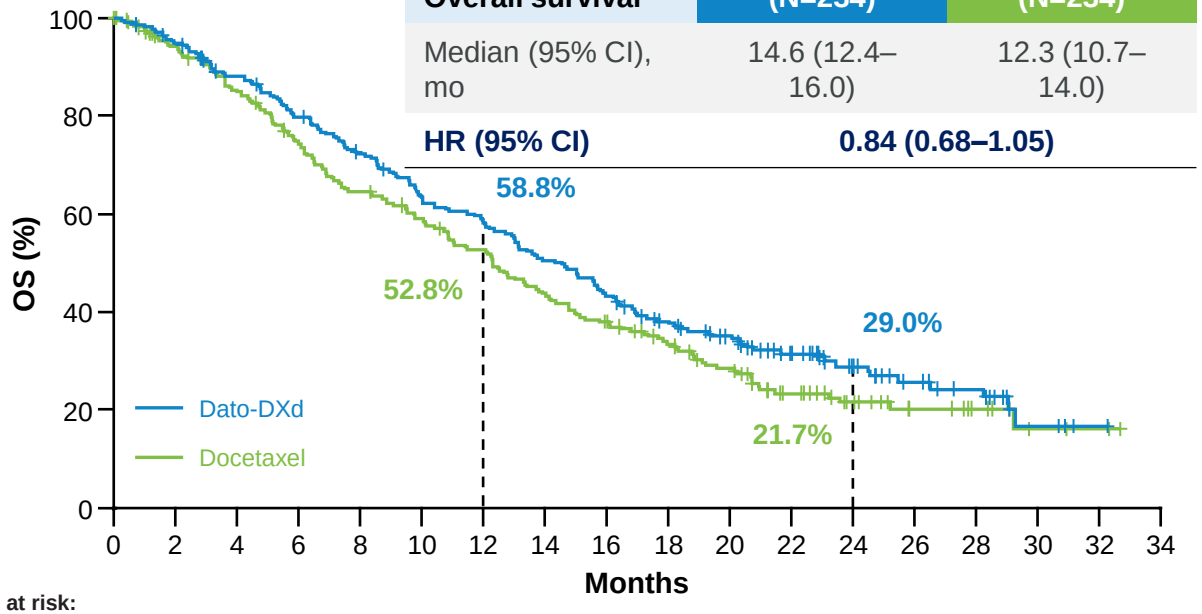
System organ class Preferred term, n (%)	Dato-DXd N=297 Any grade	Dato-DXd N=297 Grade ≥3	Docetaxel N=290 Any grade	Docetaxel N=290 Grade ≥3
Blood and lymphatic system				
Anemia	43 (15)	11 (4)	59 (20)	11 (4)
Neutropenia[a]	12 (4)	2 (1)	76 (26)	68 (23)
Gastrointestinal				
Stomatitis	140 (47)	19 (6)	45 (16)	3 (1)
Nausea	100 (34)	7 (2)	48 (17)	3 (1)
Vomiting	38 (13)	3 (1)	22 (8)	1 (0.3)
Constipation	29 (10)	0	30 (10)	0
Diarrhea	28 (9)	1 (0.3)	55 (19)	4 (1)

Modified from MJ Ahn, A Lisberg et al, ESMO 2023

TROPION-Lung01: OS according to Histology

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)	

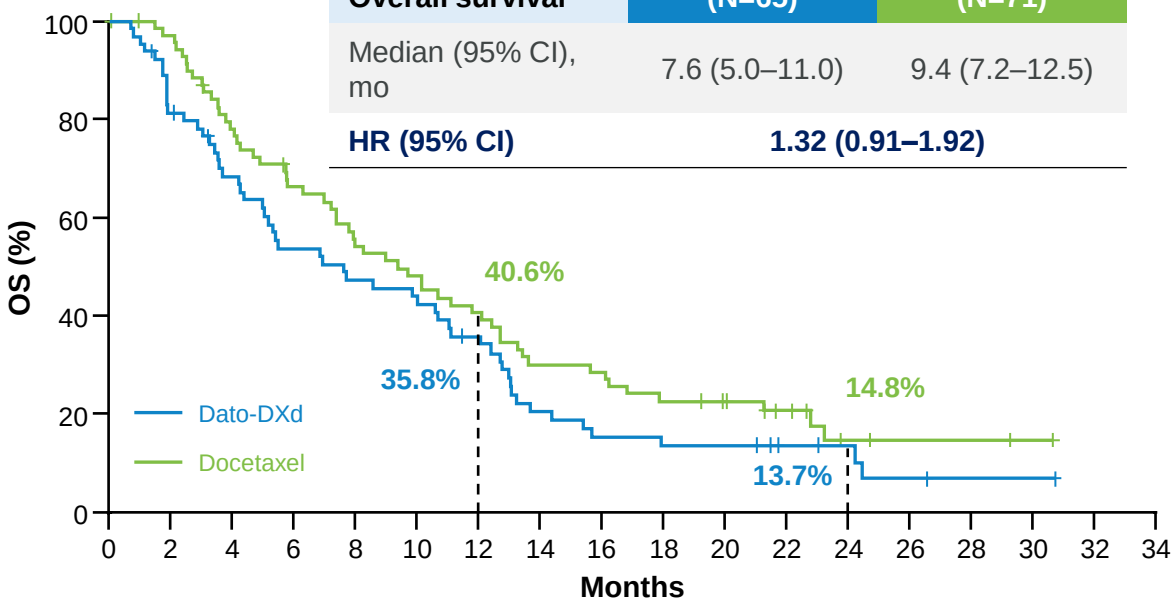


No. at risk:

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

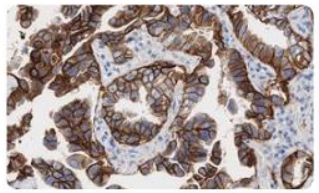
- In patients with NSQ histology, 16% risk reduction for death and 2.3-month improvement in median OS with Dato-DXd
- OS improvements in the NSQ subset were seen regardless of actionable genomic alteration status[a]:
  - **Present:** 15.6 vs 9.8 months (HR [95% CI], 0.65 [0.40–1.08]); **Absent:** 13.6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

Sands J et al, WCLC 2024

TROP2 Normalized Membrane Ratio (NMR) measured by Quantitative Continuous Scoring (QCS)

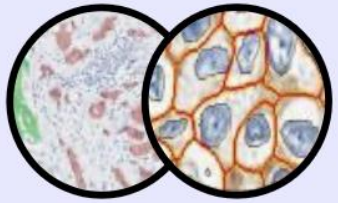
QCS is a novel, fully-supervised computational pathology approach that precisely quantifies and locates targets like TROP2

1 IHC with TROP2 Assay



2 Whole Slide Imaging

3 Automated Image Analysis (QCS)

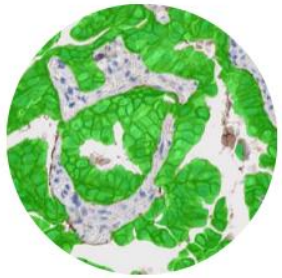


4 Patient Biomarker Status Determination

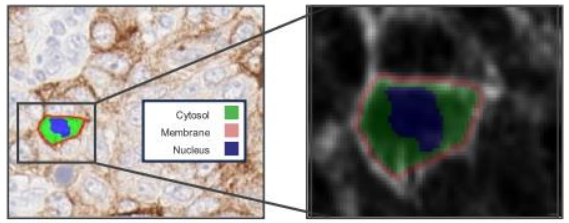
\+ ≥75% of tumor cells with TROP2 NMR ≤0.5585

\- <75% of tumor cells with TROP2 NMR ≤0.5585

Differentiates tumor from non-tumor



Measures OD in each tumor cell



Membrane and cytoplasm optical density (OD)

Calculates TROP2 NMR for every tumor cell

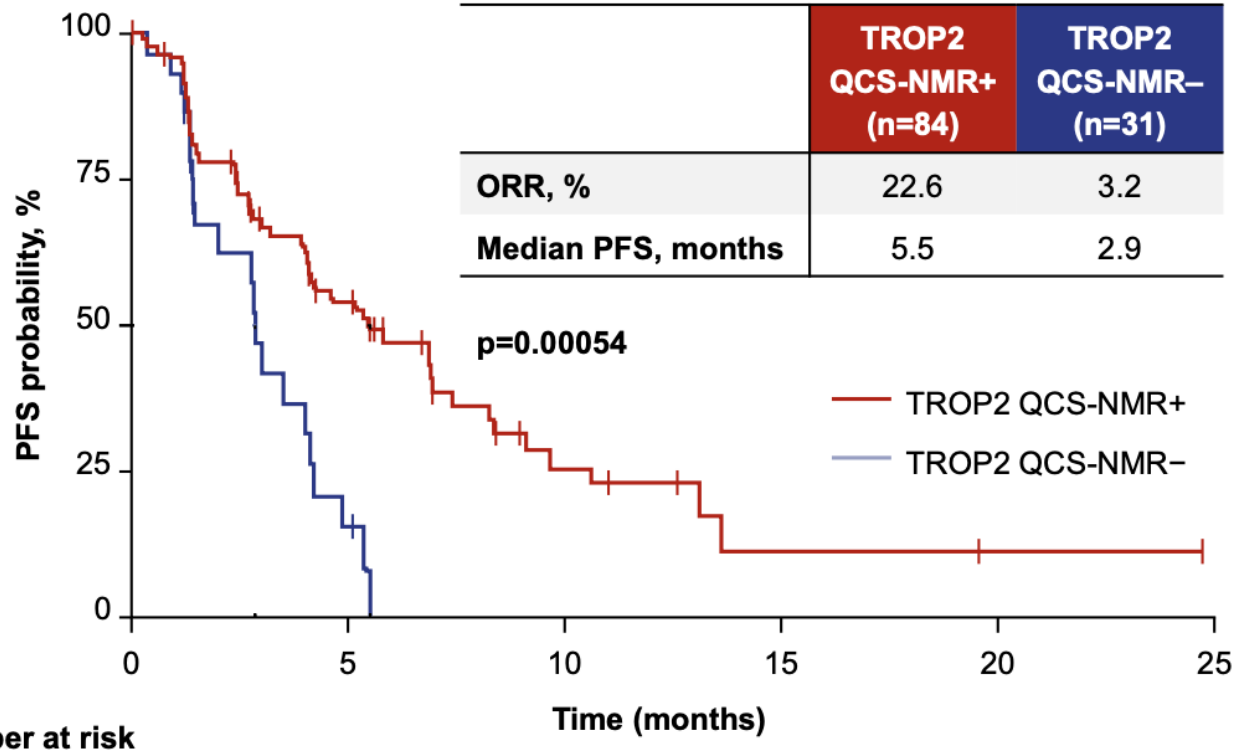
$$\frac{\text{Membrane OD}}{\text{Membrane OD + Cytoplasm OD}}$$

Lower NMR → higher cytoplasm proportion

Garassino M et al, WCLC 2024

Biomarker Discovery: Identification of QCS-NMR

TROPION-PanTumor01 (NCT03401385)*



	TROP2 QCS-NMR+ (n=84)	TROP2 QCS-NMR– (n=31)
ORR, %	22.6	3.2
Median PFS, months	5.5	2.9

p=0.00054

Number at risk

QCS-NMR+	84	33	9	2	1	0
QCS-NMR–	31	3	0	0	0	0

- **Population:** 115 biomarker-evaluable patients out of 180 patients with NSCLC who received Dato-DXd (4, 6, and 8 mg/kg q3w) in dose-expansion cohorts from TROPION-PanTumor01
- **Methods:** A hypothesis-free exploration of multiple QCS features linked with PFS was completed

TROP2 QCS-NMR was identified as the most promising QCS feature based on correlation with PFS

Dr Marina Chiara Garassino | Normalized Membrane Ratio of TROP2 by Quantitative Continuous Scoring is Predictive of Clinical Outcomes in TROPION-Lung01

Spitzmueller A, Schmidt G, Triltsch N & Kapil A, 2023: A scoring method for an anti-TROP2 antibody-drug conjugate therapy. International Patent Application No. PCT/IB2023/052428.

*Analysis based on a Research Use Only IHC assay and early version of the QCS algorithm with alternate cut-points.
NMR, normalized membrane ratio; ORR, objective response rate; q3w, every 3 weeks; QCS, quantitative continuous scoring.

Garassino M et al, WCLC 2024

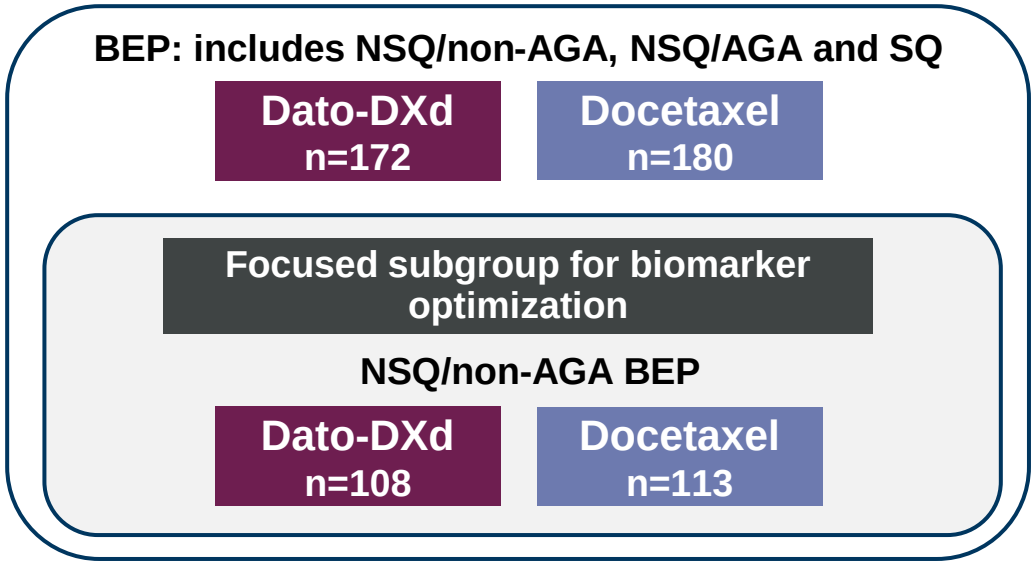
TROP2 QCS-NMR in TROPION-Lung01

352/604 (58.3%)

221/604 (36.5%)

Population and Methods

- Biomarker evaluable population (BEP) are those patients with available tissue samples for QCS determination
- Biomarker cut-points were optimized for PFS in NSQ/non-AGA patients from TROPION-Lung01
- Cut-points were confirmed through a robust statistical analysis plan (including bootstrapping, cross validation, and sensitivity analyses) and replication



Prevalence

Histology subgroup	Prevalence of TROP2 QCS-NMR+, % (n)
Biomarker-evaluable population, n=352	
NSQ	**66%** (179/272)
NSQ/non-AGA	63% (140/221)
NSQ/AGA	**76%** (39/51)
SQ	**44%** (35/80)

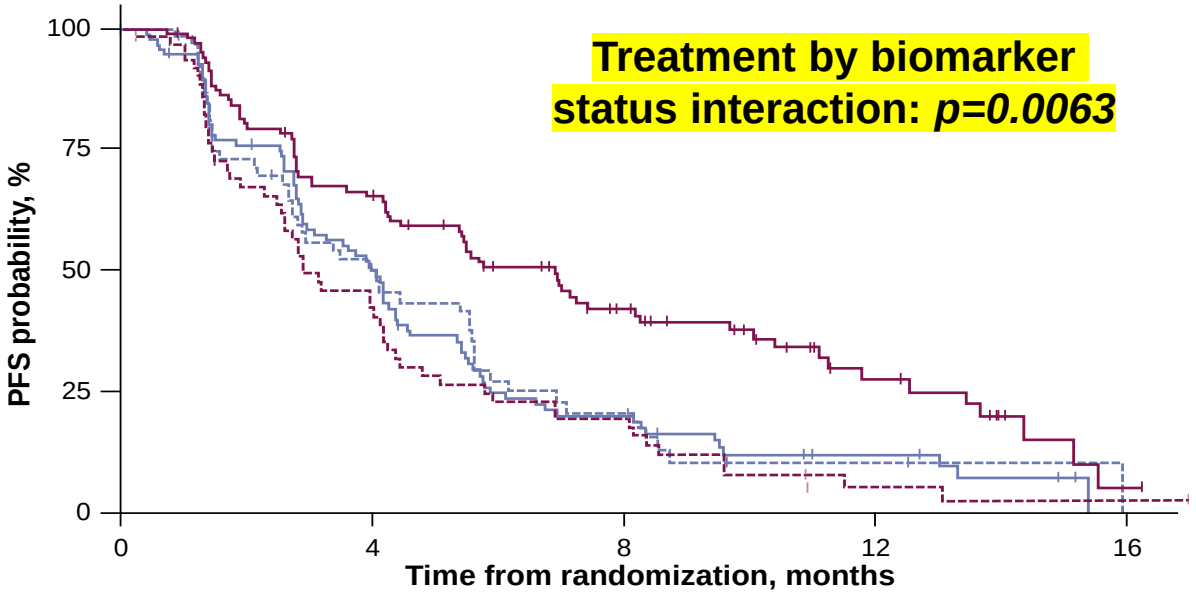
Modified from Garassino M et al, WCLC 2024

Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is PREDICTIVE for longer PFS with Dato-DXd in the biomarker-evaluable population (BEP)

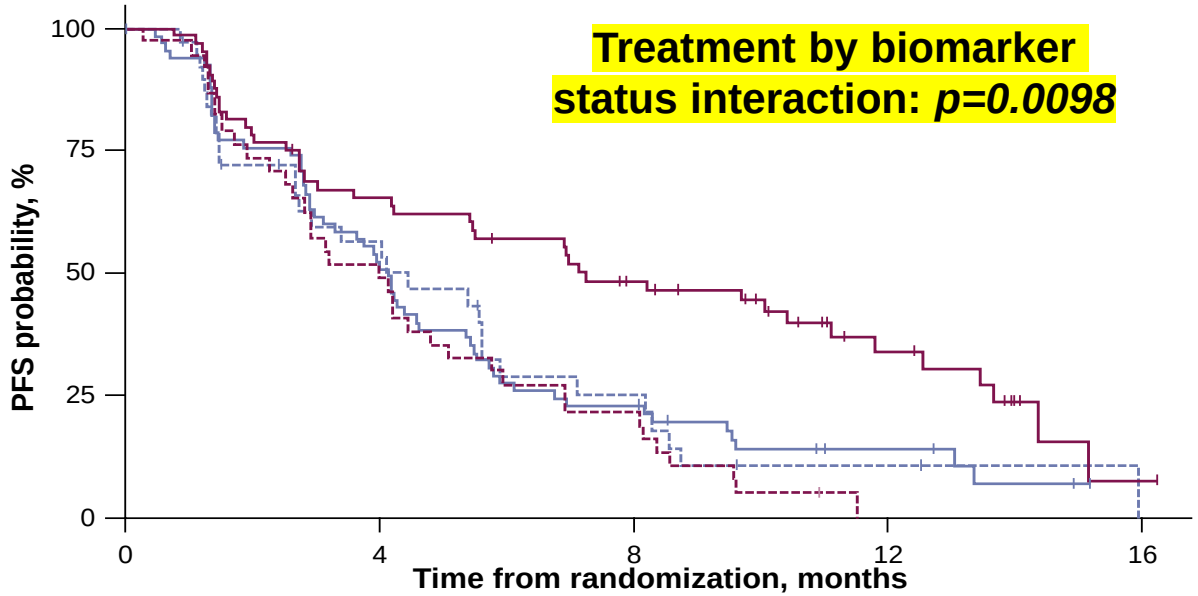
TROP2 QCS-NMR positivity is PREDICTIVE for longer PFS with Dato-DXd in the NSQ/non-AGA biomarker-evaluable population (BEP)

Biomarker-evaluable population, n=352



	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	DOC n=107	Dato-DXd n=65	DOC n=73
ORR, %	32.7	10.3	16.9	15.1
Median PFS, months	6.9	4.1	2.9	4.0
PFS HR (95% CI)	0.57 (0.41–0.79)		1.16 (0.79–1.70)	

NSQ/non-AGA BEP, n=221

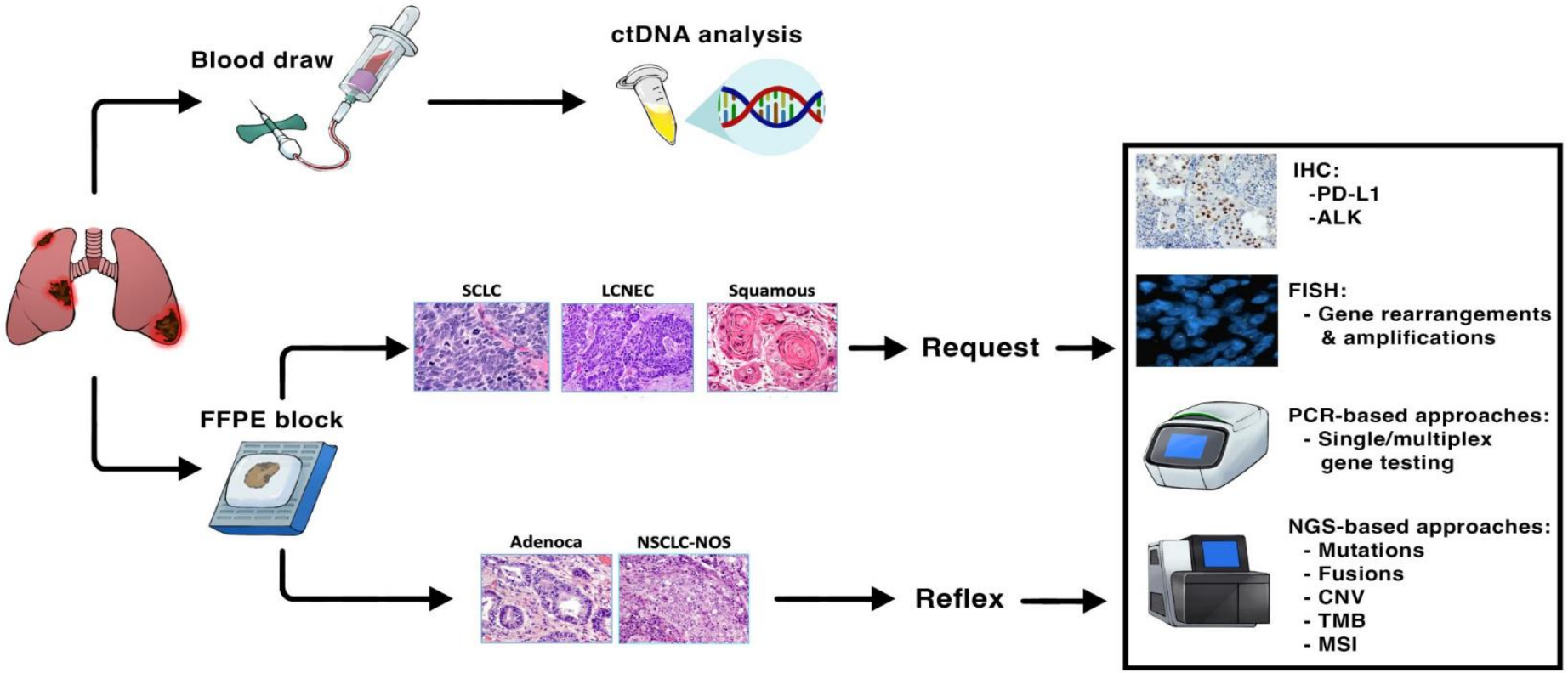


	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=68	DOC n=72	Dato-DXd n=40	ROC n=41
ORR, %	36.8	15.3	22.5	12.2
Median PFS, months	7.2	4.1	4.0	4.4
PFS HR (95% CI)	0.52 (0.35–0.78)		1.22 (0.74–2.00)	

Dato-DXd, QCS-NMR+
Dato-DXd, QCS-NMR–
Docetaxel, QCS-NMR+
Docetaxel, QCS-NMR–

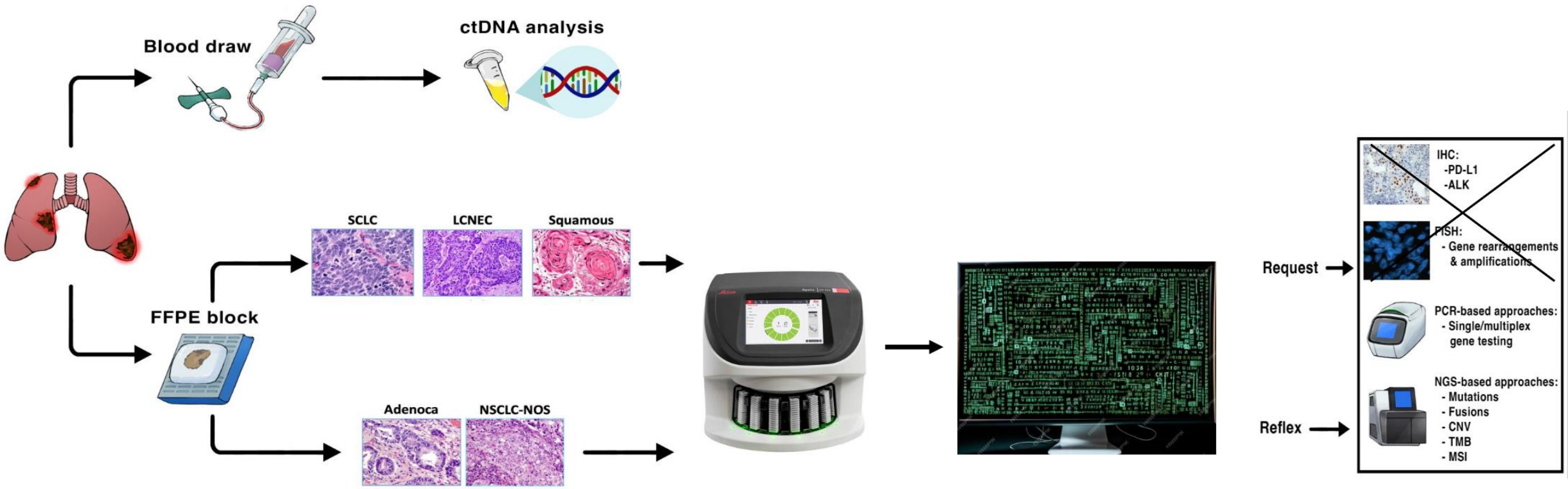
Modified from Garassino M et al, WCLC 2024

Lung cancer and Biomarker Testing



Dacic S, WCLC 2024

Lung cancer and Biomarker Testing



Dacic S, WCLC 2024

Sacituzumab Govitecan: EVOKE01, Unselected, Pretreated NSCLC

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

N = 603

R 1:1

- **Sacituzumab govitecan** 10 mg/kg on Days 1 and 8 of 21-day cycles[d]
- **Docetaxel** 75 mg/m² on Day 1 of 21-day cycles[d]

End points

Primary
- OS

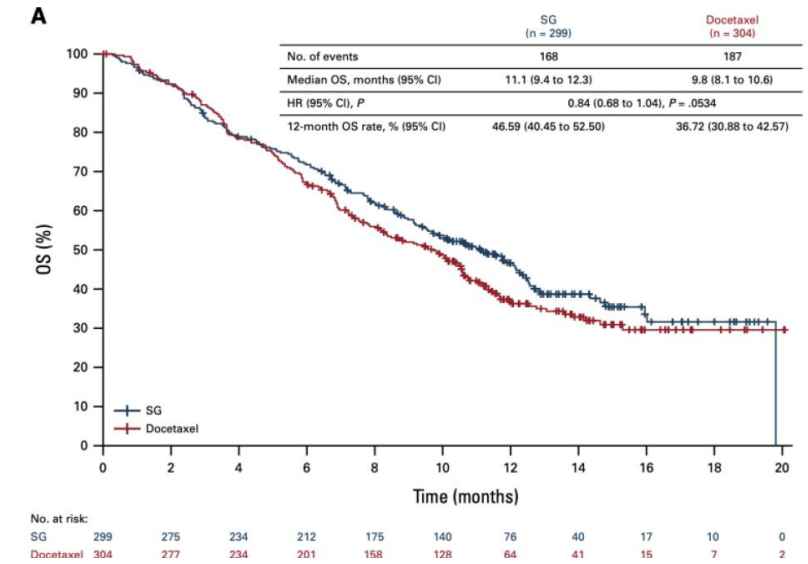
Secondary
- PFS, ORR, DOR, and DCR by INV per RECIST v1.1
- Safety and tolerability
- QoL using NSCLC-SAQ

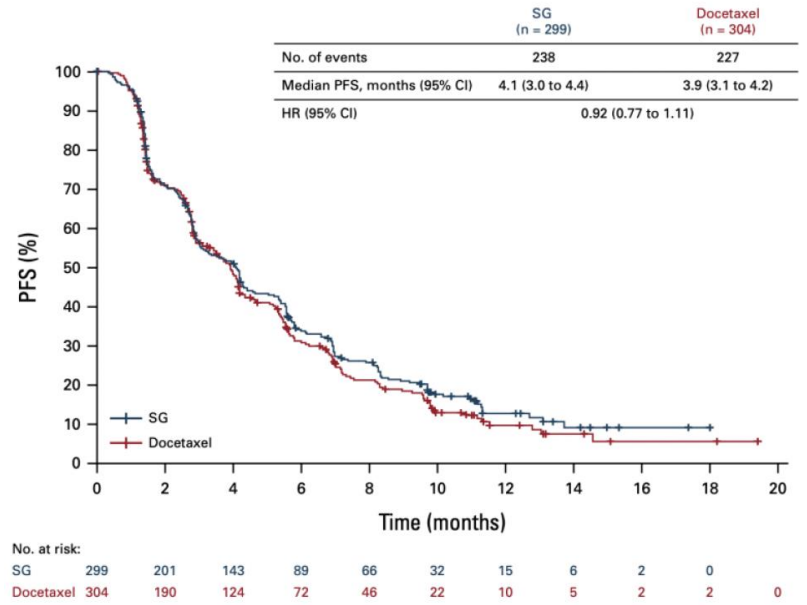
Stratified by
- **Histology** (squamous vs nonsquamous)
- **Response to last anti-PD-(L)1–containing regimen** (responsive [best response CR/PR] vs nonresponsive [PD/SD])
- **Received prior targeted therapy for AGA** (yes vs no)

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

Characteristic	SG (n = 299)	Docetaxel (n = 304)
Median age (range), years	66 (31–84)	64 (32–83)
Male, %	64.9	71.1
Race, %		
Asian	5.7	8.6
Black	2.0	2.3
White	76.6	71.1
Other[a]	15.7	18.1
ECOG PS,[b] %		
0	33.8	29.3
1	66.2	69.7
Disease stage at diagnosis,[c] %		
Stage I-III	25.4	33.6
Stage IV	73.2	66.4
Prior lines of therapy, %		
1	55.9	54.9
2	34.4	33.2
≥ 3	9.7	11.8
History of brain metastasis, %	11.7	12.8

Characteristic	SG (n = 299)	Docetaxel (n = 304)
Histology,[d] %		
Nonsquamous[e]	71.9	73.7
Squamous	28.1	26.3
Best response to last anti-PD-(L)1–containing regimen,[d] %		
Responsive (CR/PR)	35.5	37.2
Nonresponsive (PD/SD)	64.2	62.8
Not available	0.3	0
Prior therapy for AGA,[d] %		
No	93.6	91.8
Yes[f]	6.4	8.2
EGFR	2.0	4.3
ALK	0.3	0.3
Other[g]	5.7	4.9



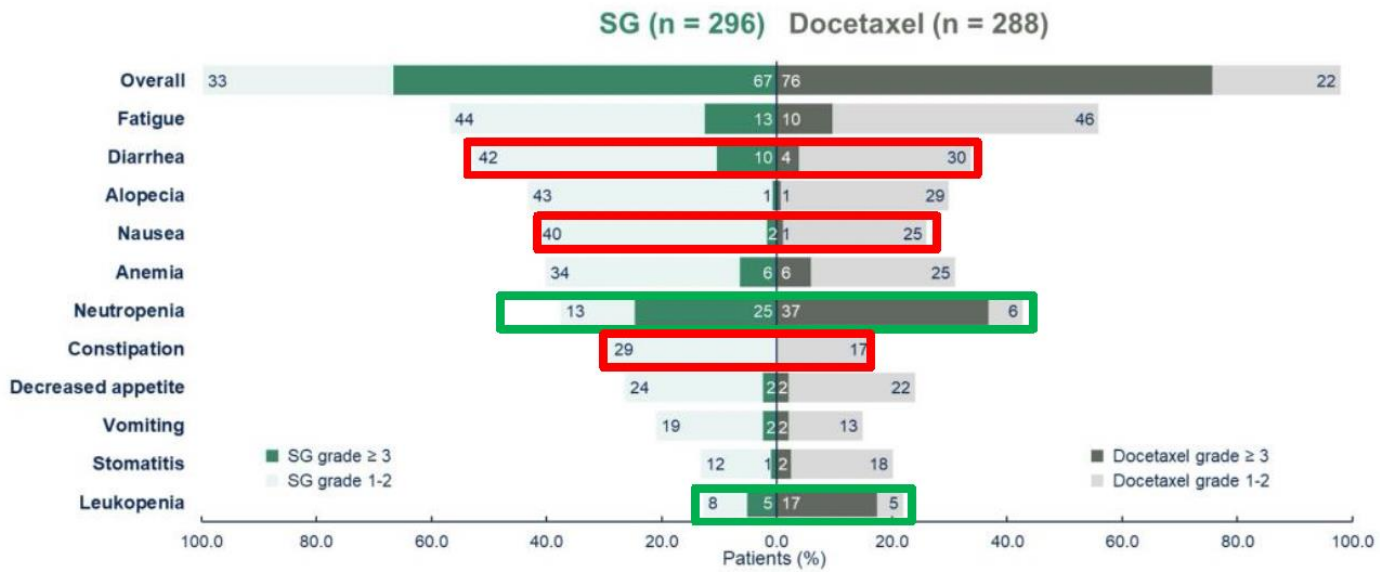


Paz-Ares L et al, ASCO 2024; Paz-Ares L et al JCO 2024

TROP2 ADCs: EVOKE-01, Safety

Safety-evaluable patients, n (%)	SG (n = 296)	Docetaxel (n = 288)
	TEAE	TEAE
Any grade	295 (99.7)	282 (97.9)
Grade ≥ 3	197 (66.6)	218 (75.7)
Serious	137 (46.3)	124 (43.1)
Leading to discontinuation	29 (9.8)	48 (16.7)
Leading to dose reduction	87 (29.4)	112 (38.9)
Leading to death[a]	10 (3.4)	13 (4.5)

In ≥ 20% of patients receiving SG or docetaxel



Favoring SG (Δ ≥10% AEs and/or ≥5% G3 or higher AEs)

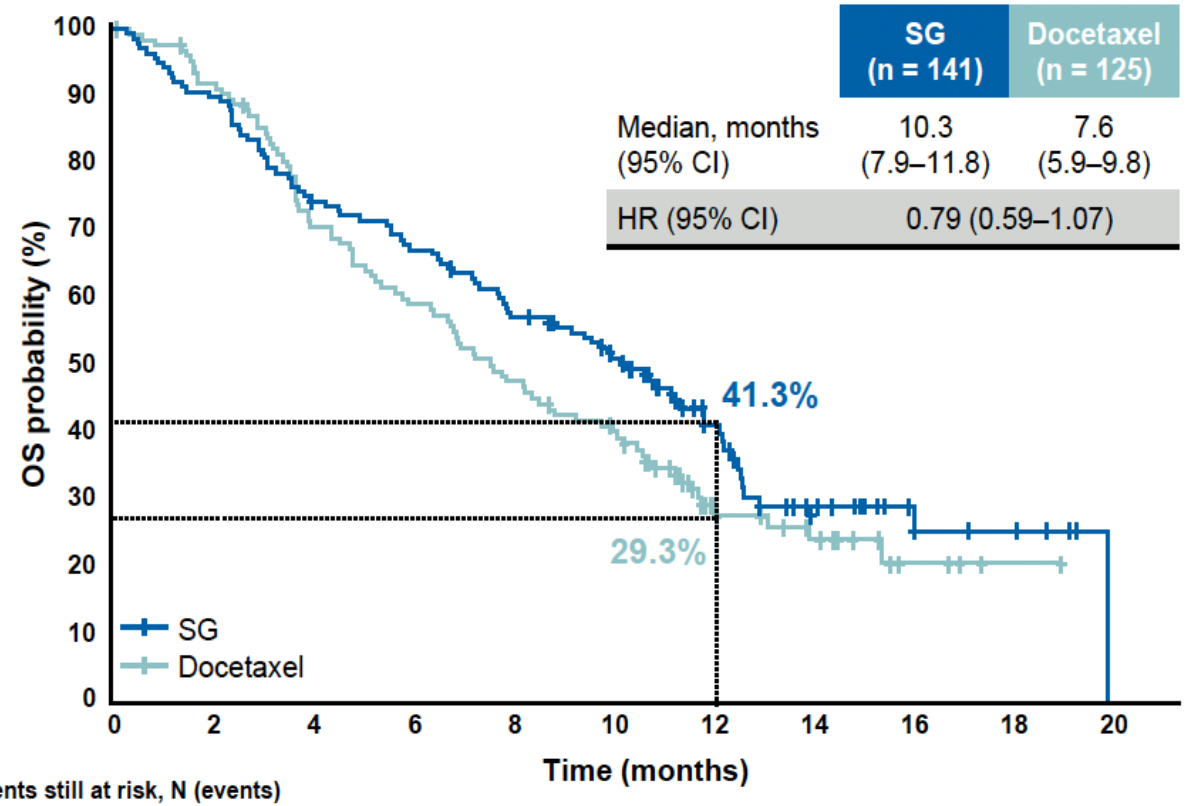
Favoring docetaxel (Δ ≥10% AEs and/or ≥5% G3 or higher AEs)

Modified of Bironzo P, 2024

Paz-Ares L et al, ASCO 2024; Paz-Ares L et al JCO 2024

SG: How to Derive (hopefully Maximize) Treatment Benefit?

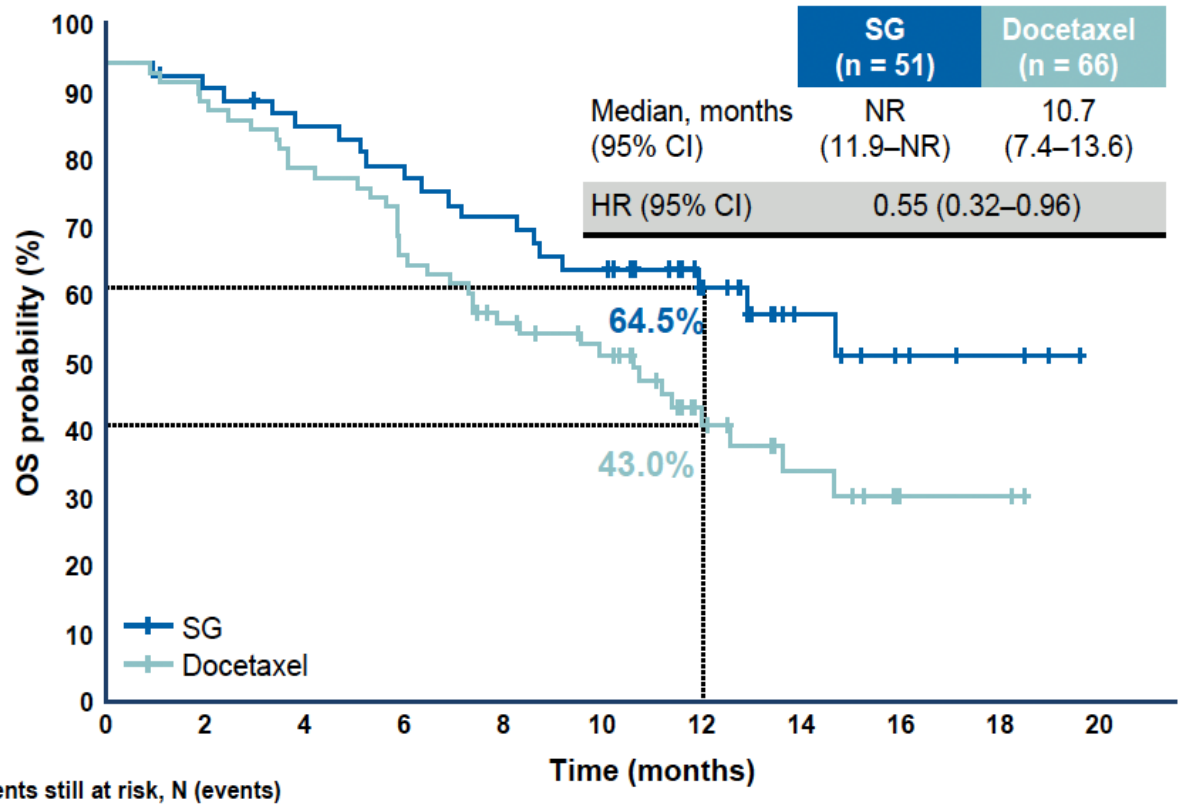
Primary resistance[a] to last anti-PD-(L)1–containing regimen



Patients still at risk, N (events)

SG	141 (0)	127 (14)	105 (36)	94 (46)	79 (60)	65 (68)	32 (78)	17 (87)	6 (88)	5 (88)	0 (89)
Docetaxel	125 (0)	113 (10)	86 (36)	72 (50)	58 (64)	47 (73)	20 (84)	12 (87)	4 (88)	1 (88)	

Secondary resistance[a] to last anti-PD-(L)1–containing regimen



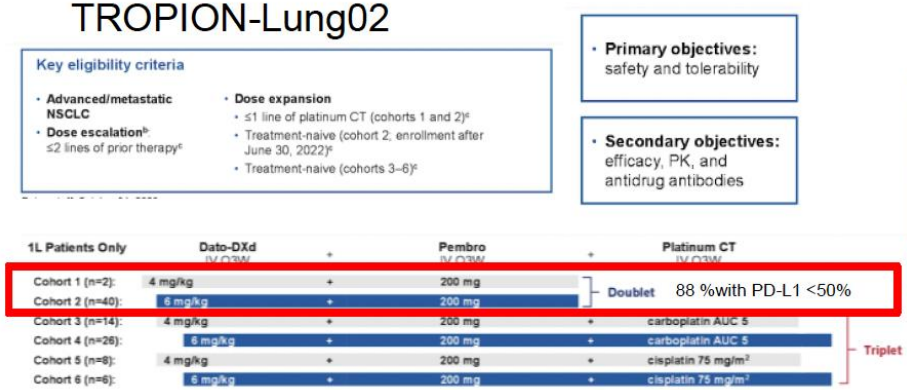
Patients still at risk, N (events)

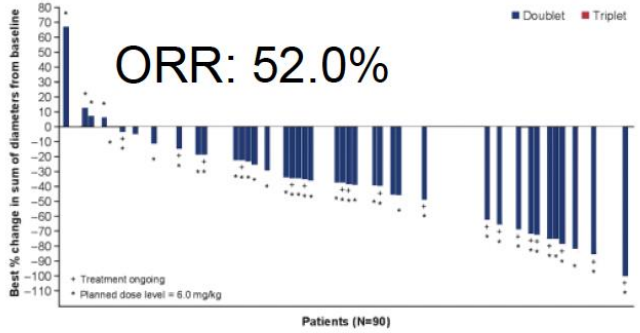
SG	51 (0)	48 (2)	44 (5)	41 (8)	37 (12)	33 (16)	21 (17)	9 (18)	5 (19)	3 (19)	0 (19)
Docetaxel	66 (0)	62 (4)	55 (11)	46 (20)	37 (27)	31 (30)	16 (35)	9 (37)	2 (38)	2 (38)	

Garassino M et al, WCLC 2024

ADC + ICIs in Treatment-naive NSCLC Patients

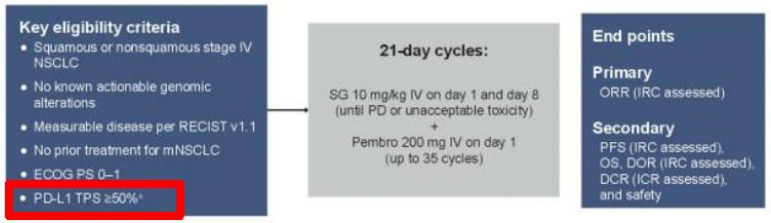
TROPION-Lung02



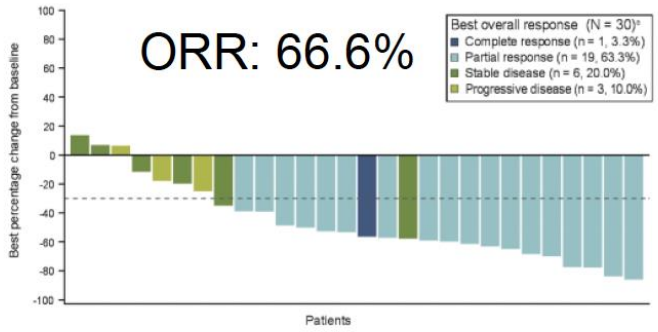


≥3 TRAEs 33%

EVOKE-02

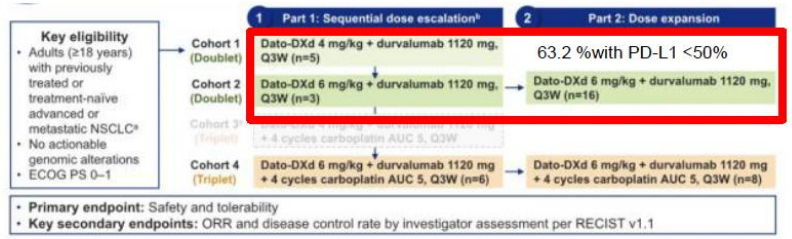


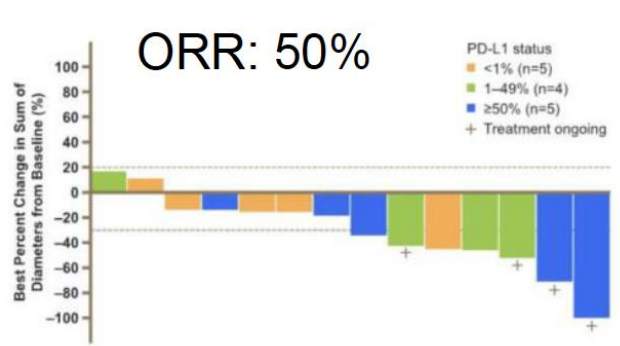
[a]PD-L1 status was determined locally or at the central laboratory by 22C3 assay.
DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; IV, intravenous; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.



≥3 TRAEs 40%

TROPION-Lung04





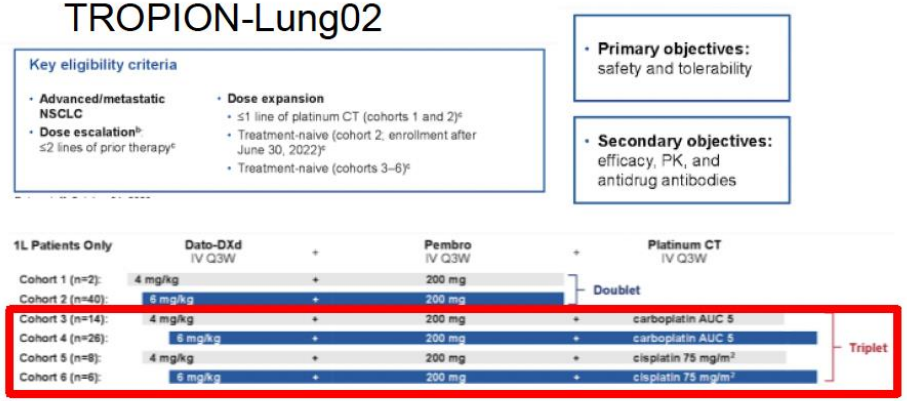
≥3 TRAEs 31.6%

Modified of Bironzo P, 2024

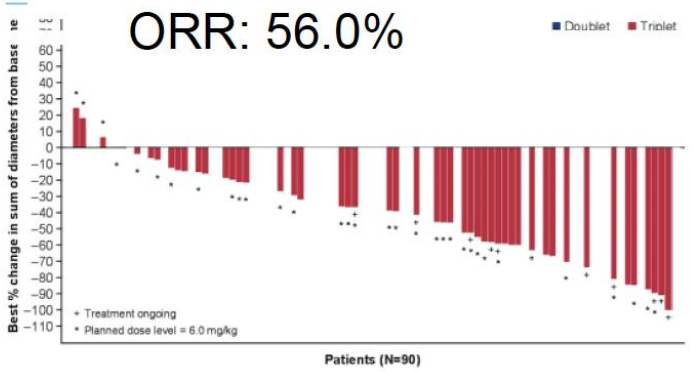
Levy B et al, ASCO 2024; Patel JD et al, ASCO 2024; Papadopoulos KD et al, WCLC 2023

ADC + ICIs + PLATINUM in Treatment-naive NSCLC Patients

TROPION-Lung02

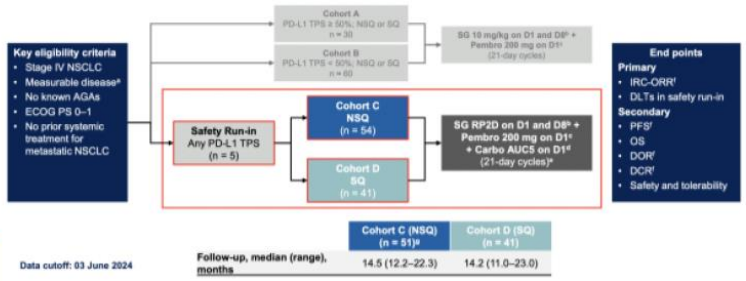


ORR: 56.0%

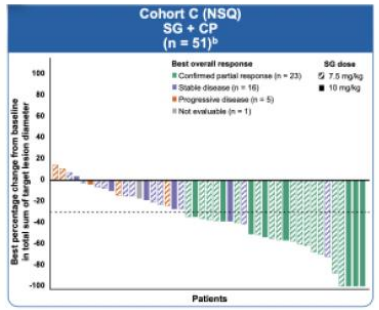


≥3 TRAEs 56%

EVOKE-02

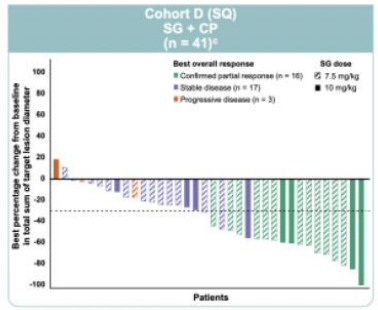


ORR: 45.1%



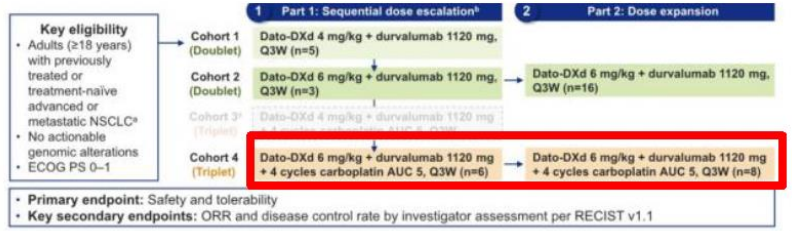
Serious TEAEs 62.1%

ORR: 39.0%

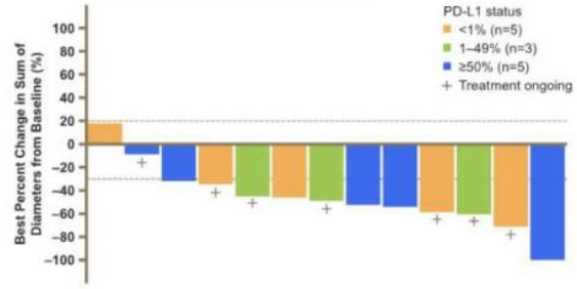


Serious TEAEs 54.5%

TROPION-Lung04



ORR: 76.9%

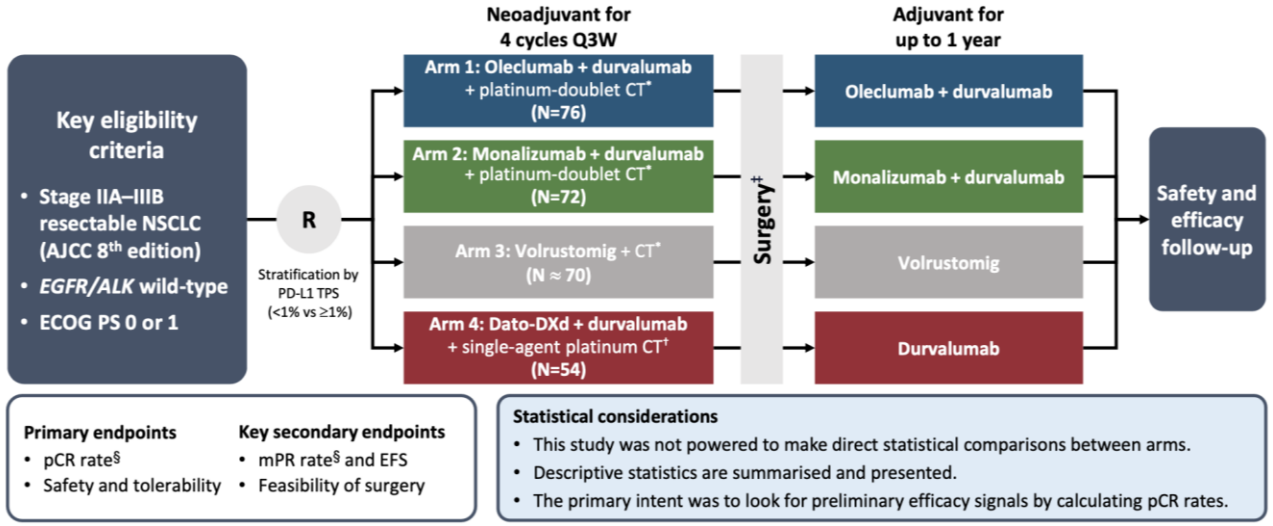


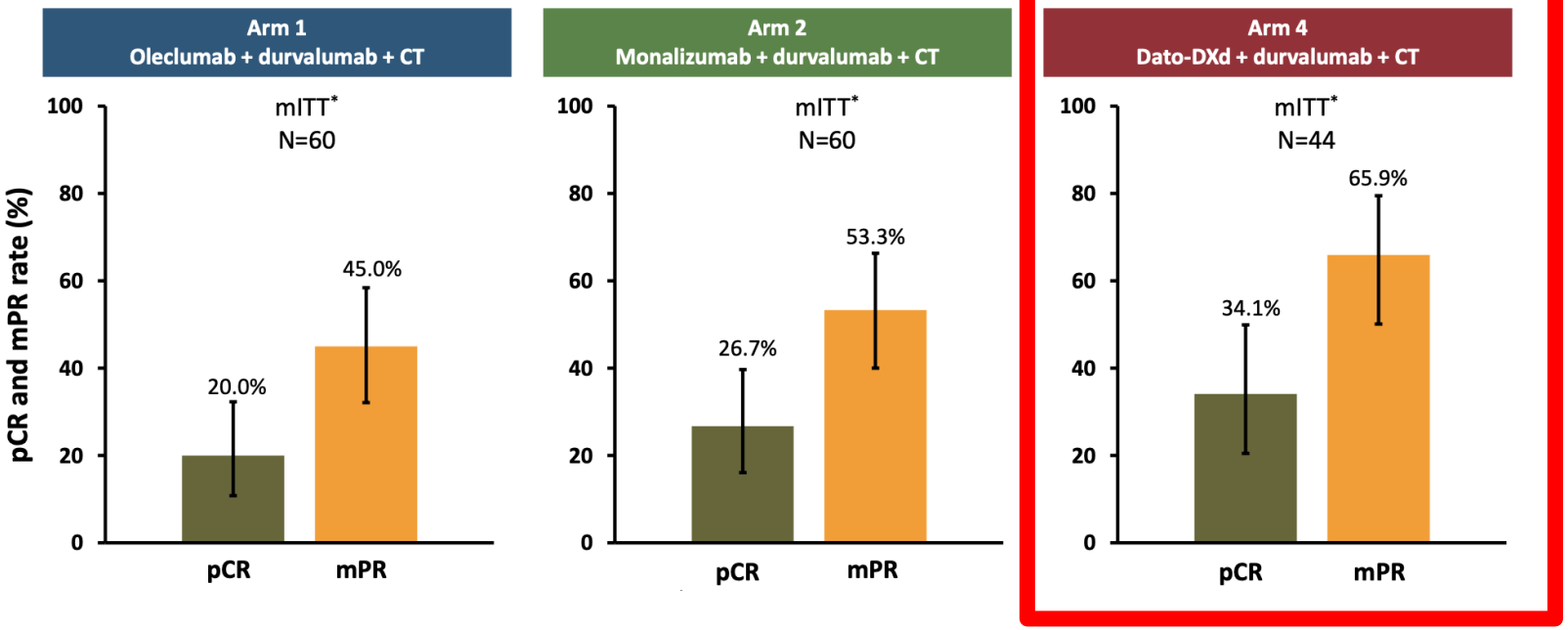
≥3 TRAEs 57.1%

Modified of Bironzo P, 2024

Levy B et al, ASCO 2024; Gray JE et al WCLC 2024

NeoCOAST-2: Open-label, multi-arm platform preoperative study

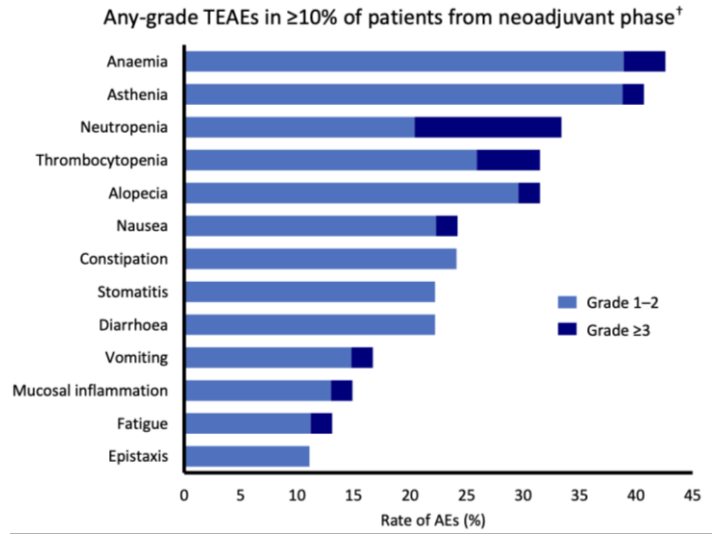




Safety profile of Arm 4: Dato-DXd + durvalumab + CT

n (%)	Neoadjuvant N=54	Post-surgery N=46	Adjuvant N=25
Any TEAE	53 (98.1)	24 (52.2)	11 (44.0)
Any TRAE	52 (96.3)	6 (13.0)	5 (20.0)
Grade ≥3 TEAE	13 (24.1)	4 (8.7)	1 (4.0)
Grade ≥3 TRAE	10 (18.5)	0	0
AE leading to discontinuation	4 (7.4)	0	0
SAE	10 (18.5)	7 (15.2)	1 (4.0)
Any SAE with outcome of death	0	1 (2.2)[a]	0

[a]Due to idiopathic pulmonary fibrosis unrelated to treatment.*

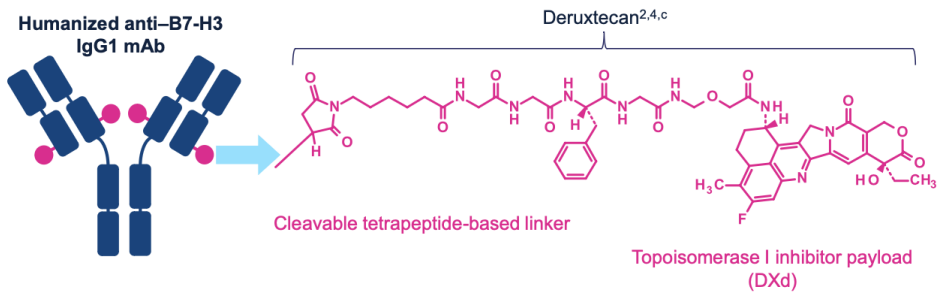


Cascone T et al, WCLC 2024

Ifinatamab Deruxtecan (I-DXd) in ES-SCLC: Interim Analysis (IDeate-Lung01)

I-DXd is a B7-H3 (CD276)–directed ADC with 3 components[1–4]:

- A humanized anti–B7-H3 IgG1 mAb
- A tetrapeptide-based cleavable linker that covalently bonds antibody and payload
- A topoisomerase I inhibitor payload (an exatecan derivative, DXd)



Key patient inclusion criteria

- Extensive-stage SCLC
- ≥1 prior line of platinum-based chemotherapy and ≤3 prior lines of systemic therapy
- Progression on or after most recent systemic therapy
- Asymptomatic brain metastases permitted
- ECOG PS 0–1

(n=88)

R 1:1

- Ifinatamab deruxtecan 8 mg/kg q3w (n=46)
- Ifinatamab deruxtecan 12 mg/kg q3w (n=42)

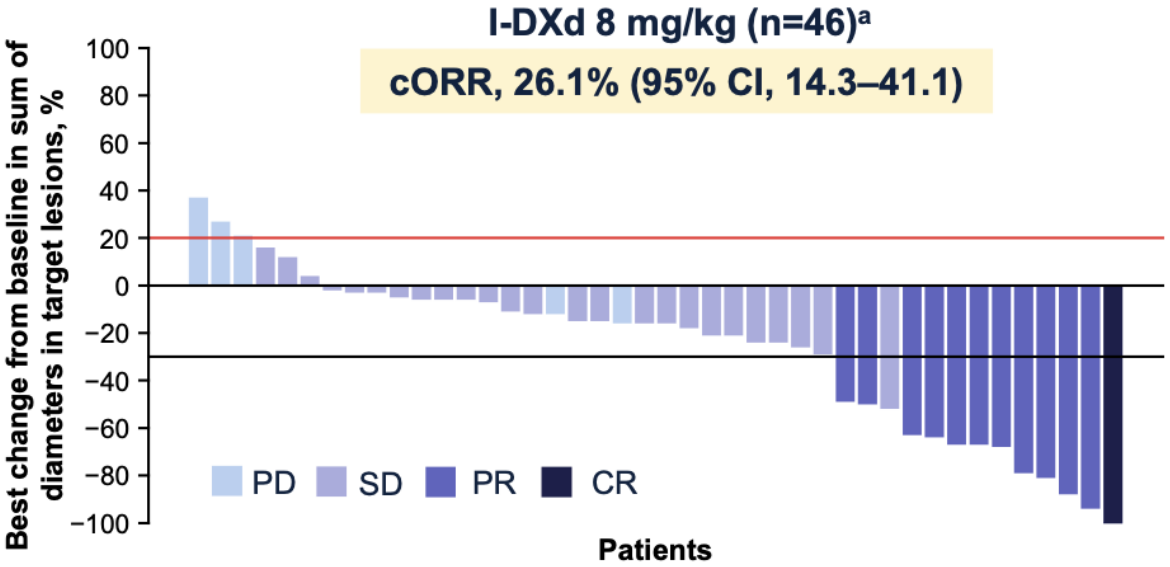
Stratification
- 2L chemotherapy treatment-free interval (<90 vs. ≥90 days), 2L or 3L
- Prior anti-PD-(L)1 (yes vs. no)

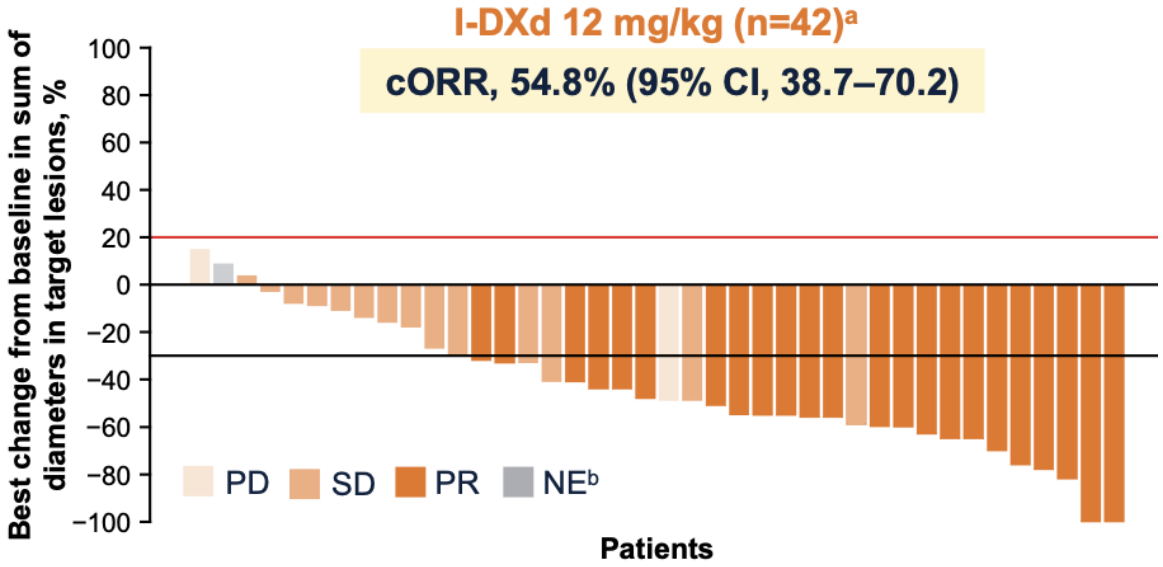
Extended enrollment at RP3D (n≈70 3L+)

Primary endpoint
- ORR (BICR)

Secondary endpoints
- DoR, PFS, OS, DCR, TTR, PK, safety

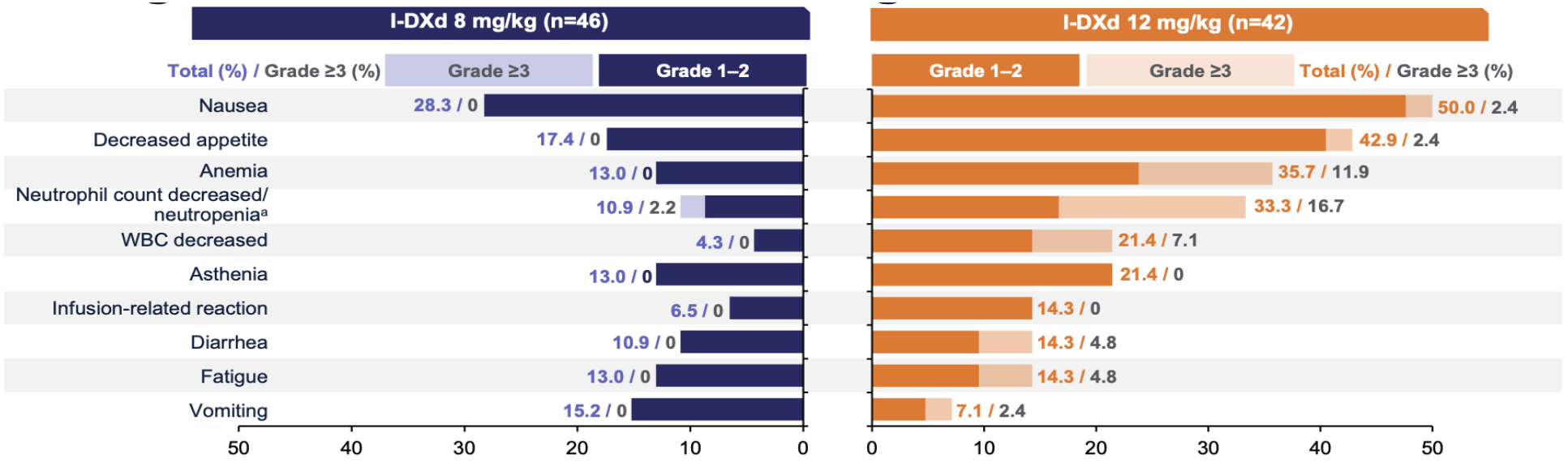
Exploratory endpoint
- Intracranial ORR

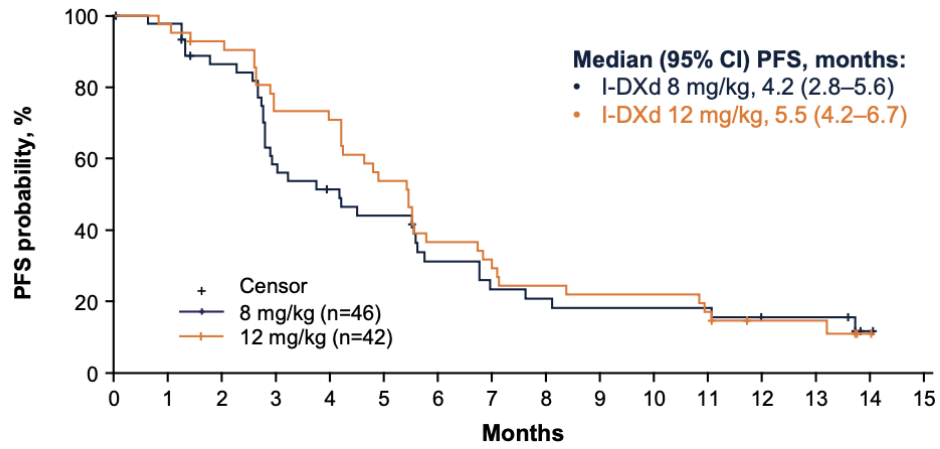




Rudin CM et al, WCLC 2024

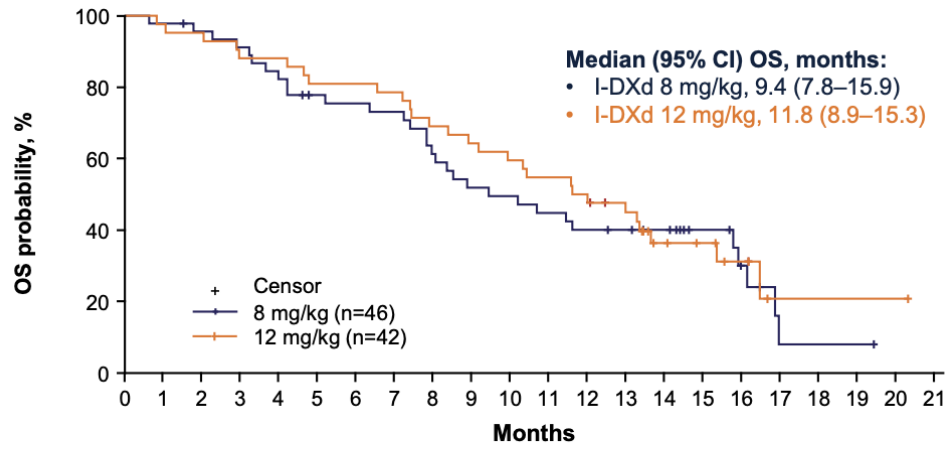
Ifinatamab Deruxtecan (I-DXd) in ES-SCLC: Interim Analysis (IDeate-Lung01)





Number of patients still at risk

8 mg/kg	46	44	37	25	21	18	12	9	8	7	7	7	5	5	1	0
12 mg/kg	42	41	38	30	29	22	15	12	10	9	9	7	4	4	1	0

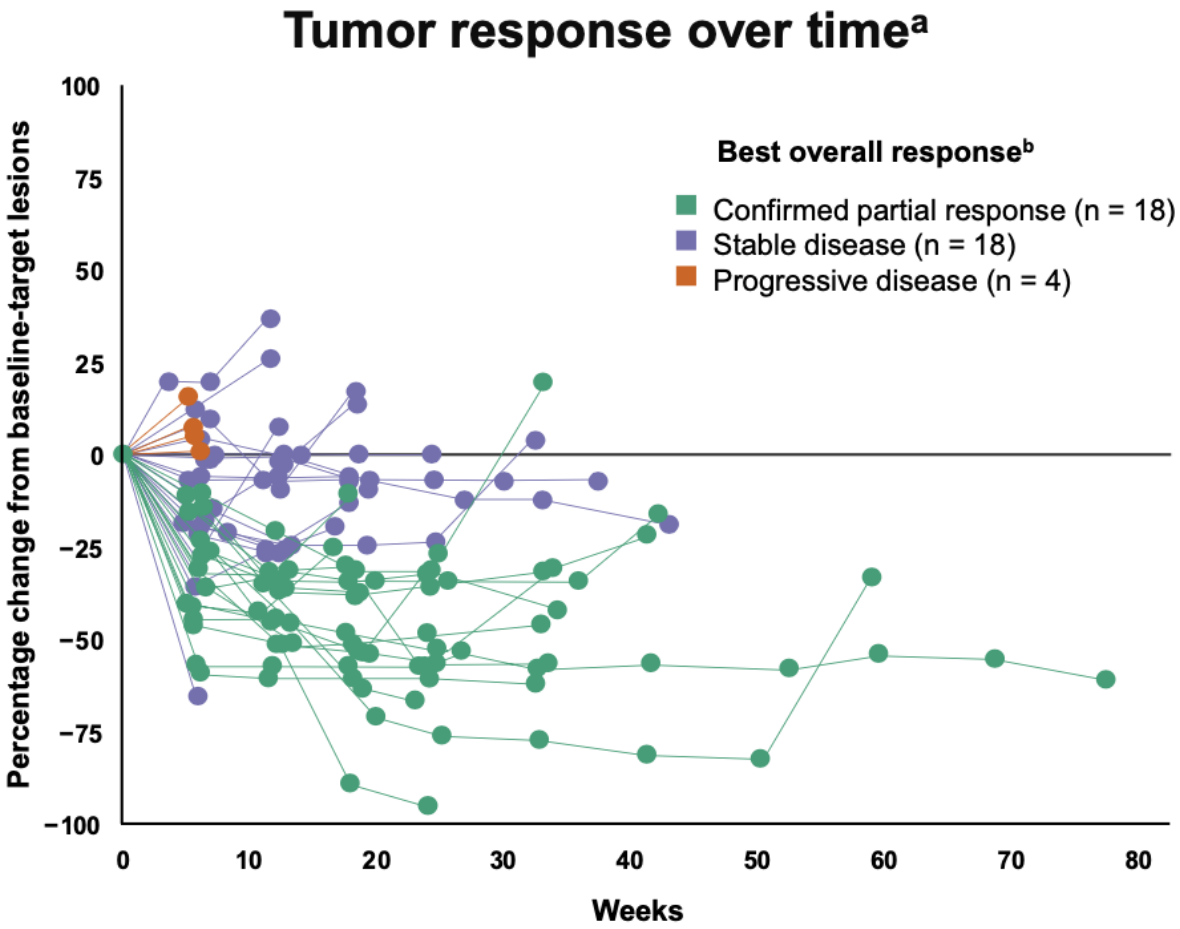


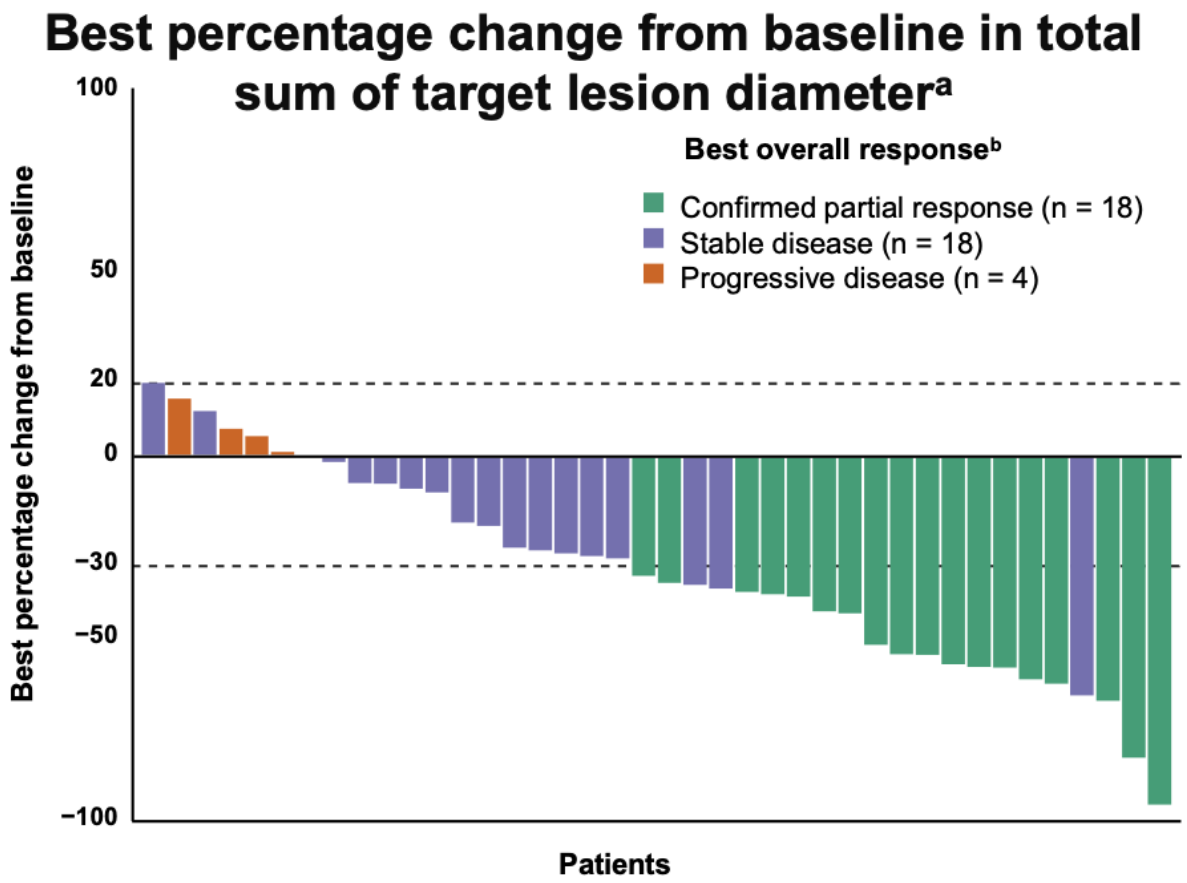
Number of patients still at risk

8 mg/kg	46	45	43	41	37	33	32	31	26	22	21	19	17	16	14	9	5	1	1	1	0	0
12 mg/kg	42	41	40	37	37	34	34	33	29	27	25	23	20	17	10	8	5	1	1	1	1	0

Rudin CM et al, WCLC 2024

Sacituzumab Govitecan as Second-Line Treatment in ES-SCLC

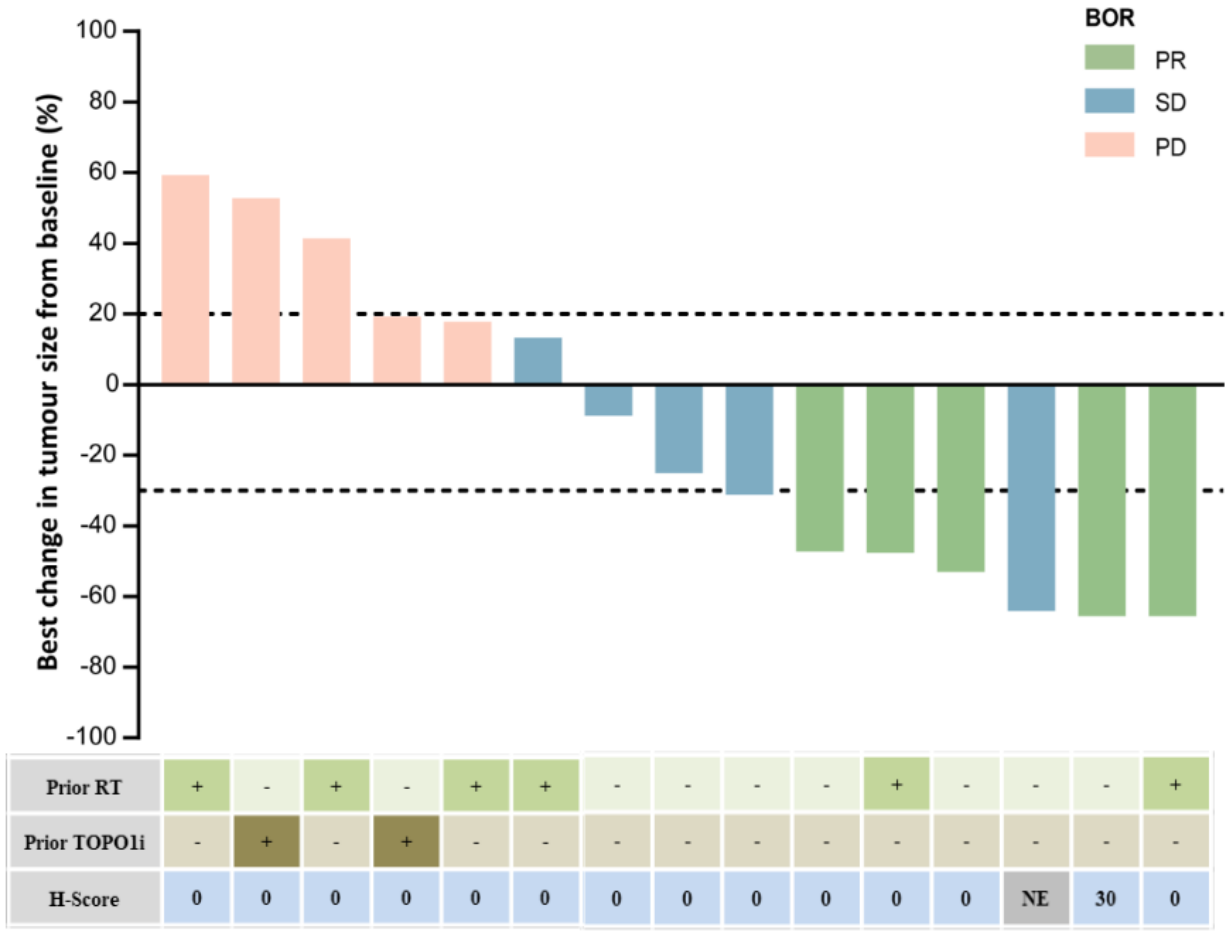


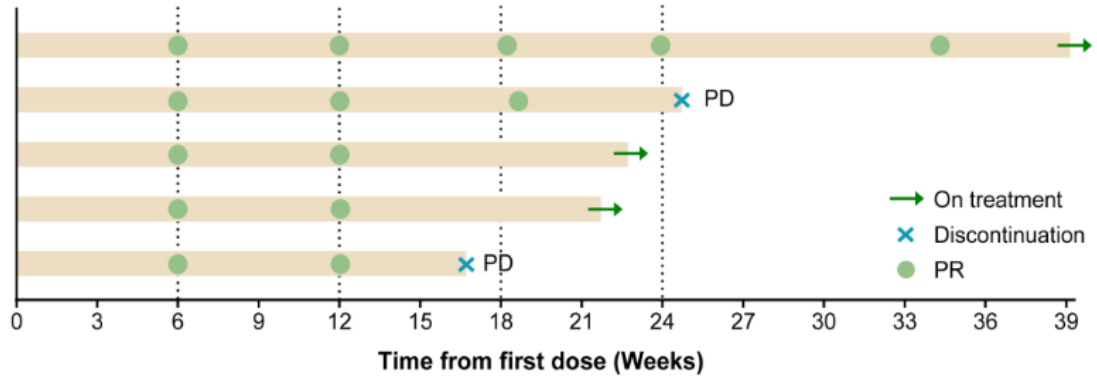


- 76.7% (33/43) of patients had tumor shrinkage
- 48.8% (21/43) of patients had a reduction of >30% in target lesion diameter

Dowlati A et al, WCLC 2024

SHR-A1921 (TROP-2 Targeted ADC) as Second-Line Treatment in ES-SCLC





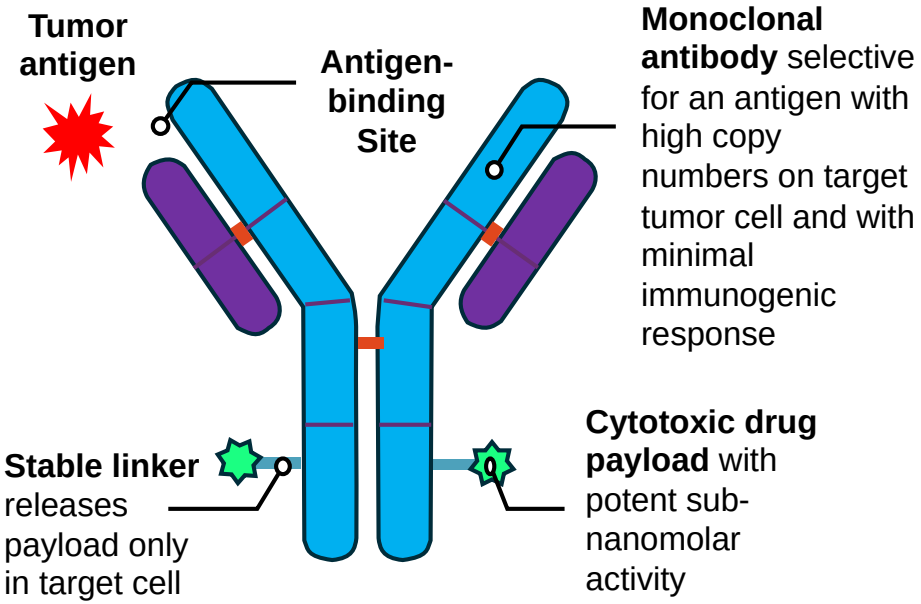
	SCLC cohort (N=17)
Evaluable, N	15
BOR, n (%)	
PR	5 (33.3)
SD	5 (33.3)
PD	5 (33.3)
ORR, % (95% CI)	33.3 (11.8-61.6)
DCR, % (95% CI)	66.7 (38.4-88.2)
DoR, months (95% CI)	4.4 (2.3-NR)

Wang J et al, WCLC 2024

Targets of Antibody Drug Conjugates (ADC)

- Molecularly UNSELECTED pts' NSCLC/SCLC populations:
  - TROP2, Nectin4, ROR1, AXL, Tissue Factor, B7H4, B7H3, Integrin-Beta6

- **Molecularly '<u>ENRICHED</u>' pts' NSCLC populations:**
  - **EGFR, ALK, HER2, HER3, CEACAM, MET**

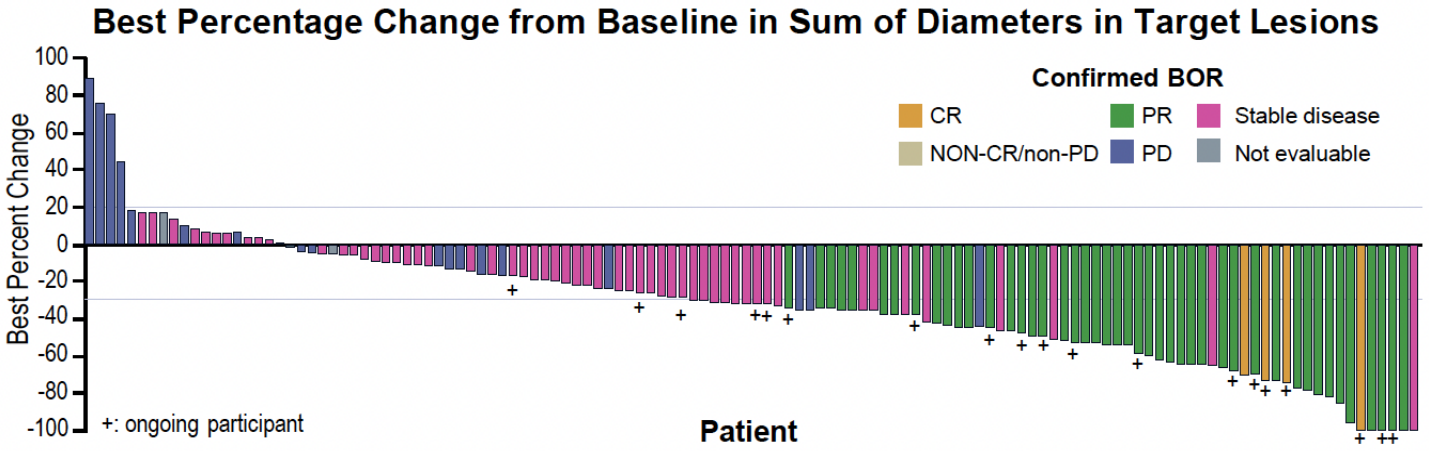


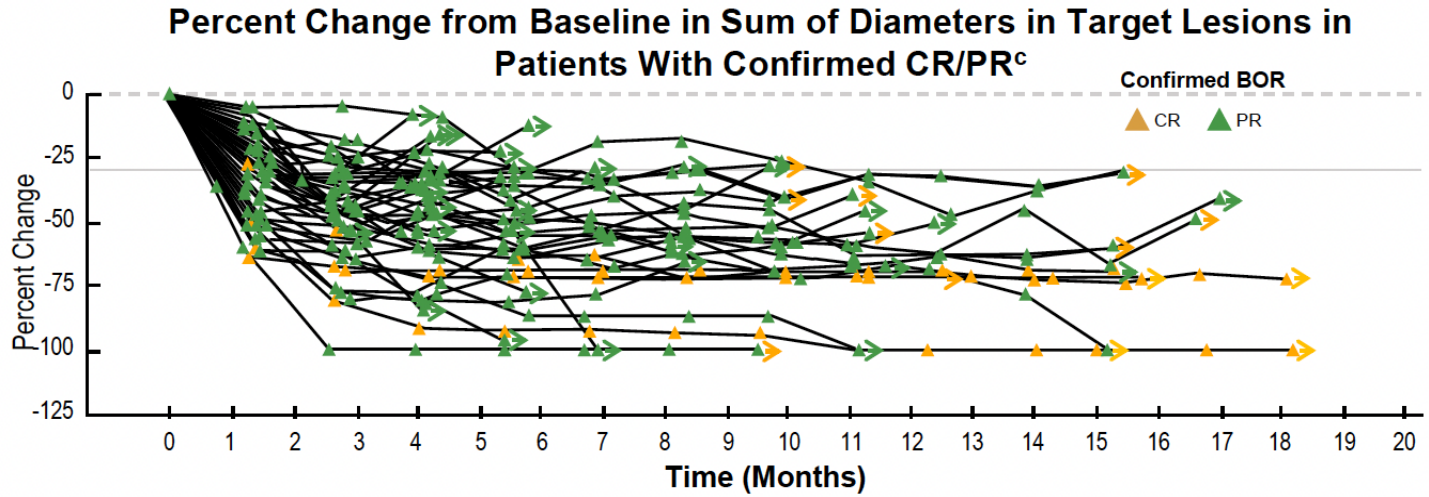
Drago JZ, Nat Rev Clin Oncol 2021

Dato-DXd for AGAs (TROPION-Lung05, Phase 2)

Response per BICR	All treated (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8,44.4]	34 (43.6) [32.4,55.3]	8 (23.5) [10.7,41.2]
Median DOR, months[b] [95% CI]	7.0 [4.2,9.8]	7.0 [4.2,10.2]	7.0 [2.8,8.4]
DCR confirmed, n (%) [95% CI][a]	108 (78.8) [71.0,85.3]	64 (82.1) [71.7,89.8]	25 (73.5) [55.6,87.1]
Median PFS, months[b] [95% CI]	5.4 [4.7,7.0]	5.8 [5.4,8.3]	4.3 [2.6,6.9]

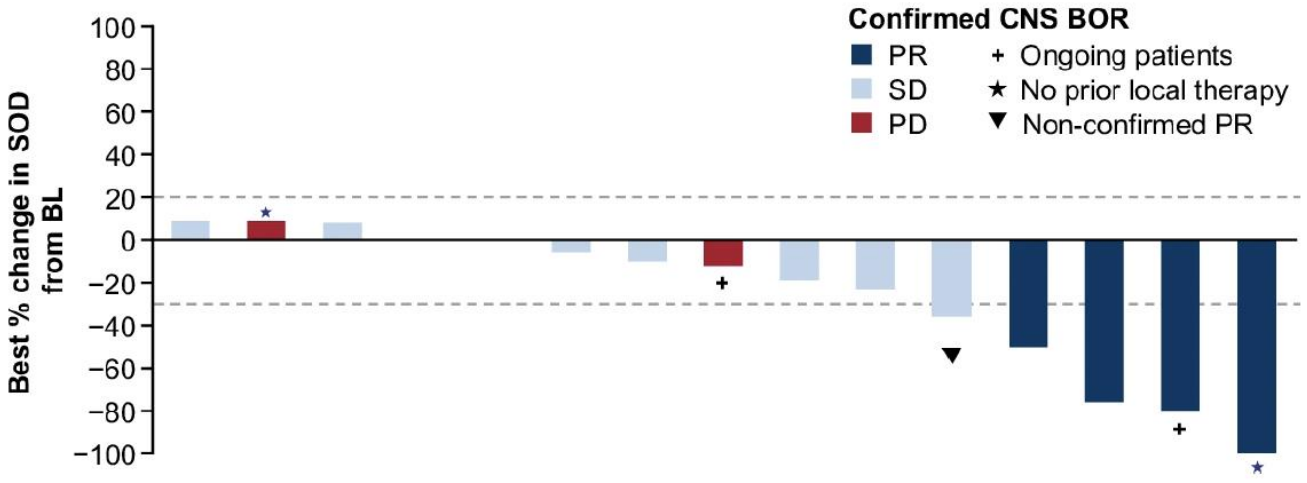
BOR: In the overall population (N=137), 4 (3%) patients achieved a CR and 45 (33%) patients achieved a PR





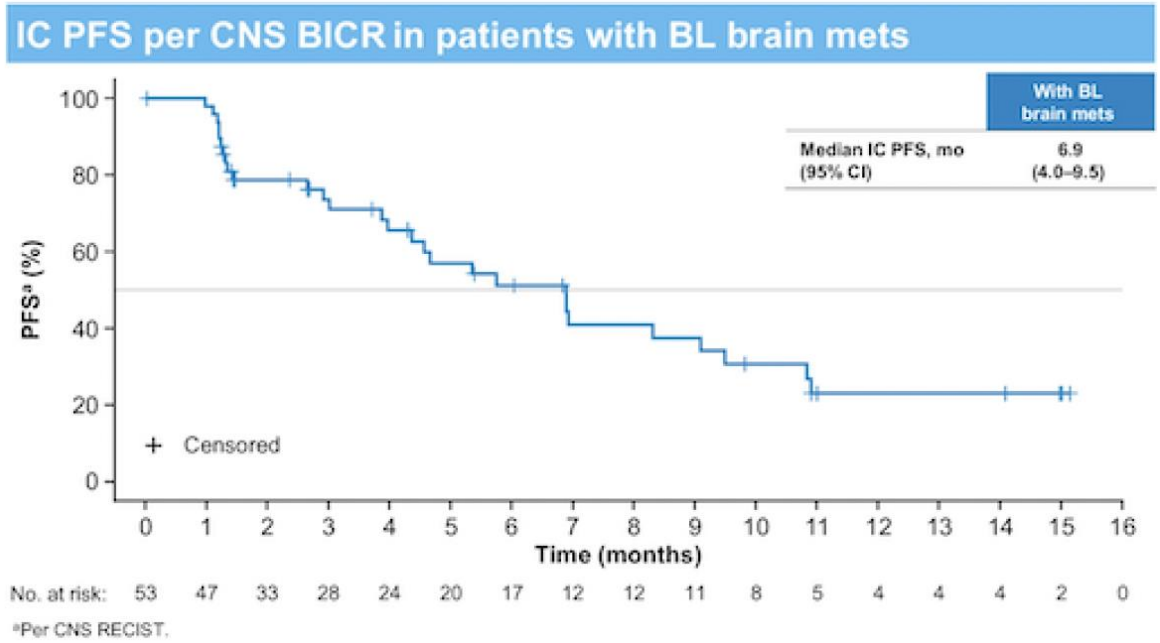
Paz-Ares L et al ESMO 2023

TROPION-Lung05, Phase 2: CNS Activity



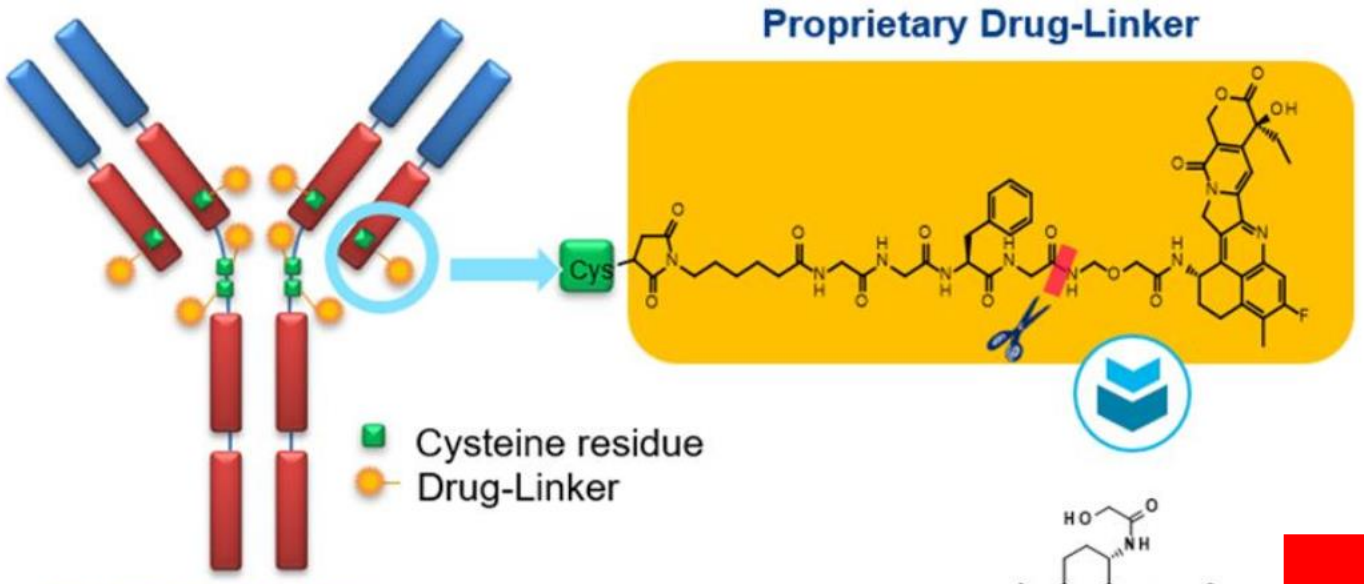
icORR: 22%. icDCR: 72%. icCBR: 44%*

*CR+PR+SD lasting ≥ 6 months



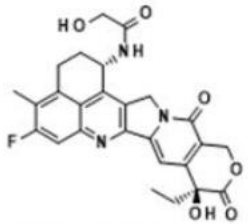
Lisberg A et al, ASCO 2024

Trastuzumab Deruxtecan (T-DXd): A prototype ADC with tumor-agnostic FDA approval



Conjugation chemistry
The tetrapeptide-based cleavable linker is connected to cysteine residues on the humanized anti-HER2 IgG1 monoclonal antibody with the same amino acid sequence as trastuzumab antibody

ADC=antibody-drug conjugate; HER2=human epidermal growth factor receptor 2



Proprietary Payload (DXd)
Exatecan derivative

FDA Accelerated Approval 8/2022*:
- Unresectable/met NSCLC
- Activating HER2 mutation
- Received prior systemic therapy

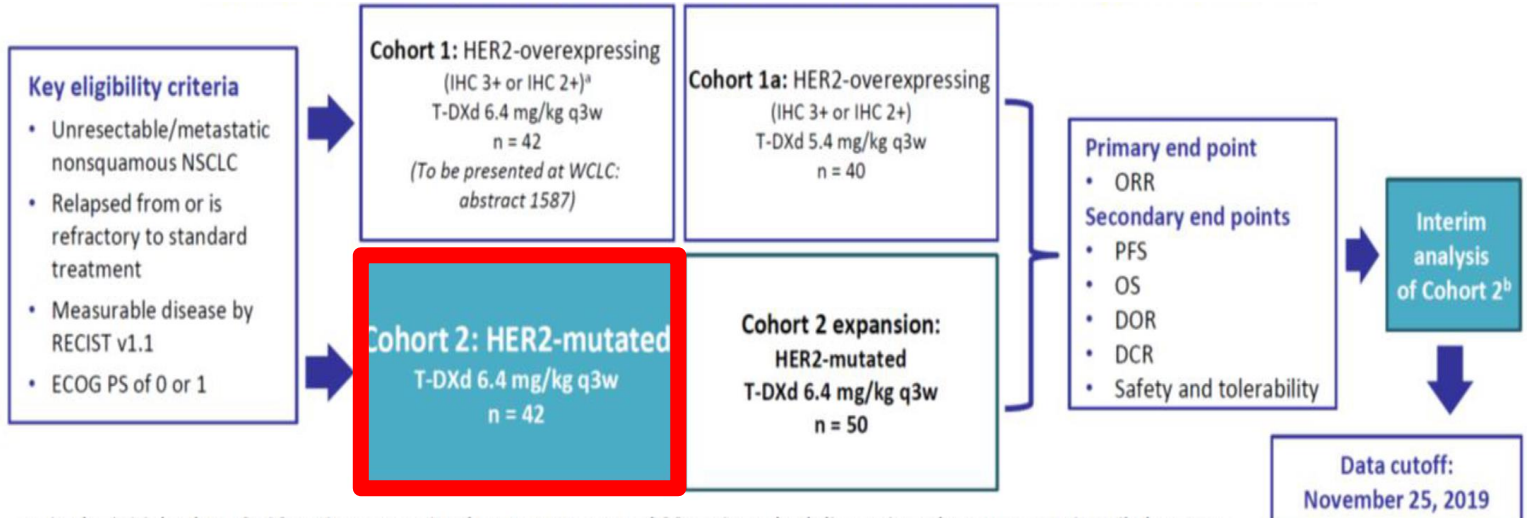
FDA Accelerated Approval 4/2024:
- Advanced HER2+ solid tumors

First drug approved for HER-mutant NSCLC.

https://www.adcreview.com/trastuzumab-deruxtecan-drug-description/

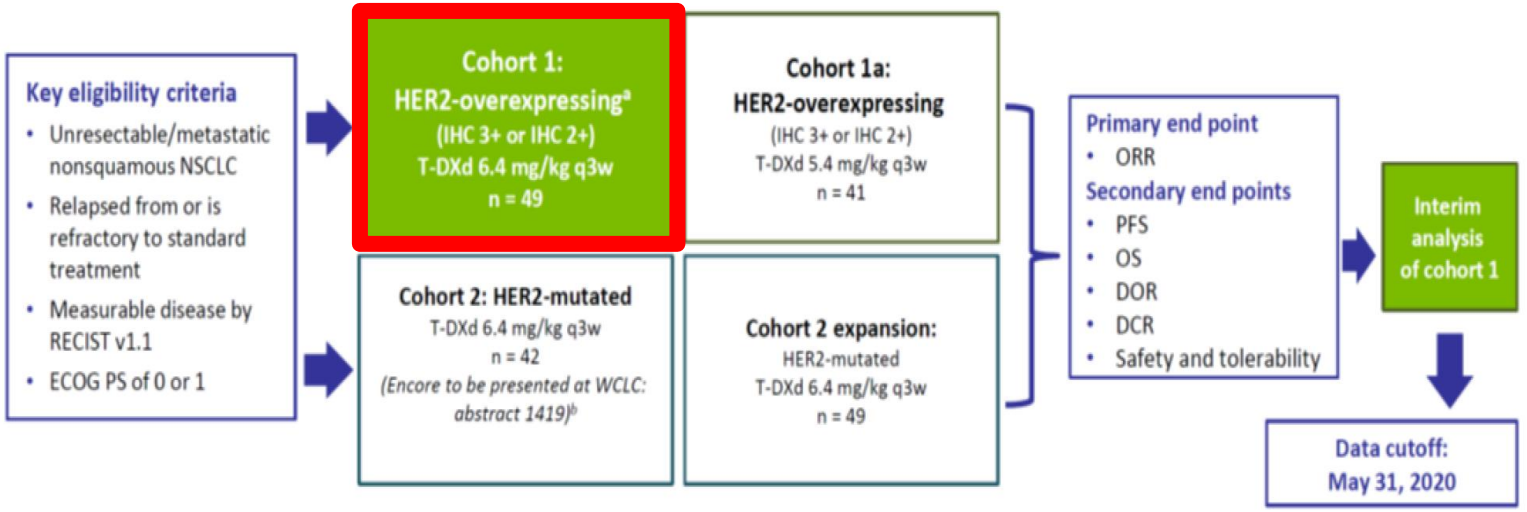
Ellisen LW, ESMO 2024

Trastuzumab Deruxtecan in NSCLC: Destiny Lung 01



Response Assessment by ICR	Patients (N = 42)
Confirmed ORR n (95% CI)	**61.9%** 26 (45.6-76.4)
CR, n (%)	1 (2.4%)
PR, n (%)	25 (59.5%)
SD, n (%)	12 (28.6%)
PD, n (%)	2 (4.8%)
Not evaluable, n (%)	2 (4.8%)
DCR n (95% CI)	**90.5%** 38 (77.4-97.3)
Median DOR, months (95% CI)	NE (5.3-NE)
Median PFS, months (95% CI)	14 (6.4-14.0)
Median OS, months (95% CI)	NE (11.8-NE)

Adapted from Smit E et al, WCLC 2020

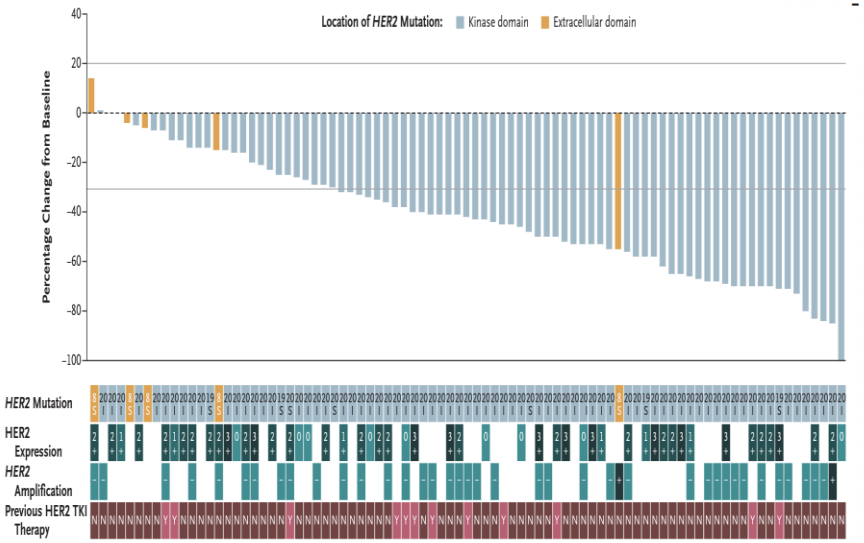


Response Assessment by ICR	IHC 3+ (n = 10)	IHC 2+ (n = 39)	Overall (N = 49)
Confirmed ORR, n (95% CI)	**20.0%** 2 (2.5-55.6)	**25.6%%** 10 (13.0-42.1)	**24.5%** 12 (13.3-38.9)
CR, n (%)	0	1 (2.6%)	1 (2.0%)
PR, n (%)	2 (20.0%)	9 (23.1%)	11 (22.4%)
SD, n (%)	6 (60.0%)	16 (41.0%)	22 (44.9%)
PD, n (%)	1 (10.0%)	10 (25.6%)	11 (22.4%)
Not evaluable, n (%)	1 (10.0%)	3 (7.7%)	4 (8.2%)
DCR, n (95% CI)	**80.0%** 8 (44.4-97.5)	**66.7%** 26 (49.8-80.9)	**69.4%** 34 (54.6-81.8)
Median DOR, months (95% CI)	**6.0 (NE-NE)**	**5.8 (3.2-NE)**	**6.0 (3.2-NE)**

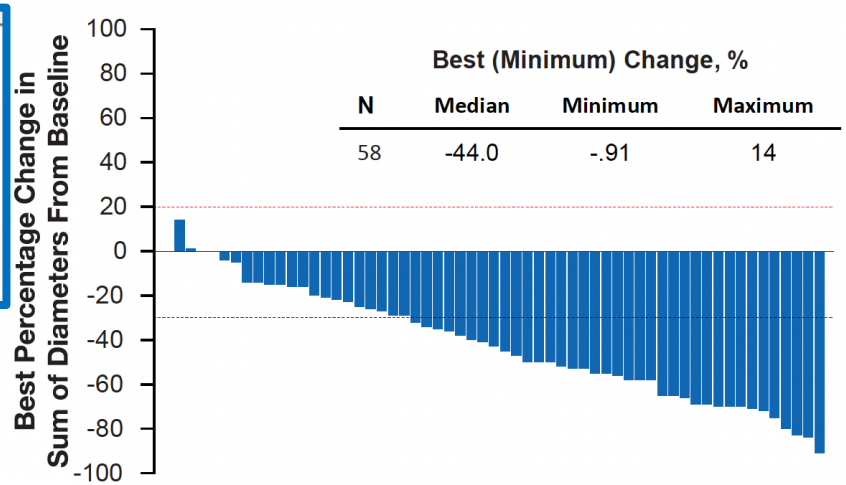
Adapted from Nakagawa K et al, WCLC 2020

Trastuzumab Deruxtecan in NSCLC: Destiny Lung 01

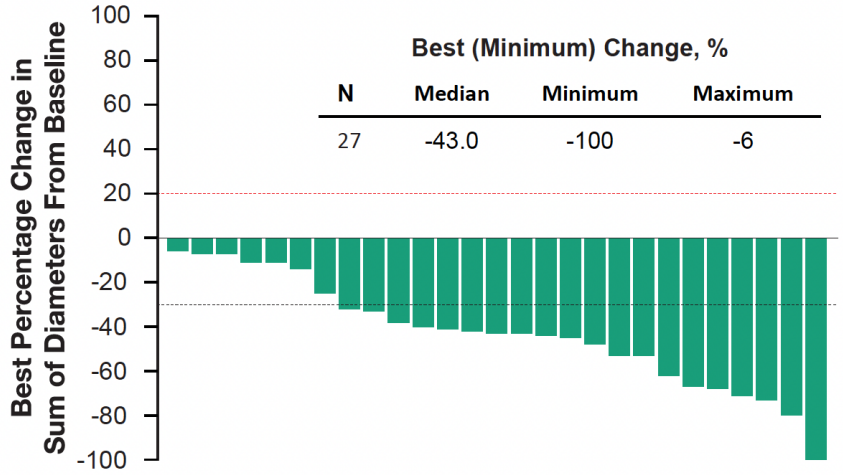
Response Assessment	Patients (N=91)
Confirmed objective response*	
No. of patients	50
Percentage of patients (95% CI)	55 (44–65)



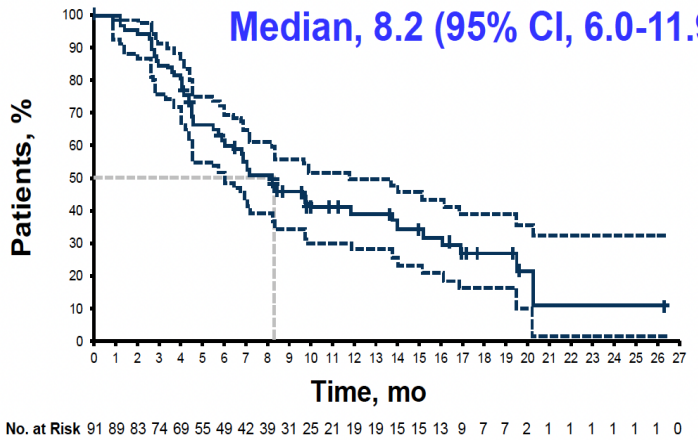
Patients With ≤2 Prior Lines of Therapy at Baseline



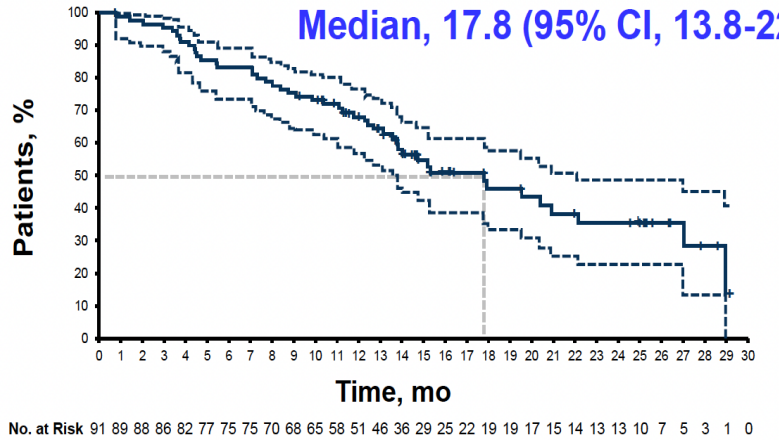
Patients With >2 Prior Lines of Therapy at Baseline



PFS



OS



Li T et al, NEJM 2021

Trastuzumab Deruxtecan in NSCLC: Destiny Lung 02

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

Patients and investigators were blinded to the dose level

R 2:1

N = 152

T-DXd 5.4 mg/kg Q3W N = 102[c]

T-DXd 6.4 mg/kg Q3W N = 50

Final analysis data cutoff: August 25, 2023

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

Exploratory Endpoints
- PROs:
  - EQ-5D-5L
  - EORTC QLQ-C30
  - EORTC QLQ-LC13
  - NSCLC-SAQ

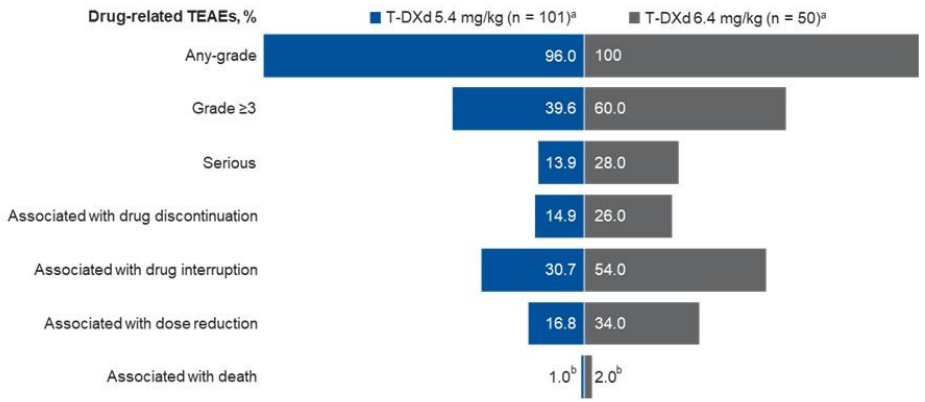
Efficacy

Efficacy summary	T-DXd 5.4 mg/kg n = 102	T-DXd 6.4 mg/kg n = 50
cORR,[a,b] n (% [95% CI])	51 (50.0 [39.9-60.1])	28 (56.0 [41.3-70.0])
CR | PR	3 (2.9) | 48 (47.1)	4 (8.0) | 24 (48.0)
SD | PD	44 (43.1) | 4 (3.9)	18 (36.0) | 2 (4.0)
Non-evaluable	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])
DoR,[b] median (95%CI), months	12.6 (6.4 to NE)	12.2 (7.0 to NE)
PFS, median (95% CI), months	10.0 (7.7-15.2)	12.9 (7.2-16.7)
OS, median (95% CI), months	19.0 (14.7 to NE)	17.3 (13.8 to NE)
Follow-up, median (range), months	15.8 (1.1-28.6)	16.5 (0.6-28.7)

Statistical considerations

- Statistical hypothesis testing for the primary analysis was performed by comparing the lower limit of the 95% Clopper-Pearson CI of cORR with the benchmark ORR of 26.4%[3,7]
- **This study was not powered to statistically compare between treatment arms**

Overall safety



Adjudicated drug-related ILD/pneumonitis

Adjudicated as drug-related ILD/pneumonitis, n (%)	T-DXd 5.4 mg/kg n = 101[a]	T-DXd 6.4 mg/kg n = 50[a]
Total	15 (14.9)	16 (32.0)
Grade 1	4 (4.0)	3 (6.0)
Grade 2	9 (8.9)	11 (22.0)
Grade 3	1 (1.0)	1 (2.0)
Grade 4	0	0
Grade 5	1 (1.0)	1 (2.0)

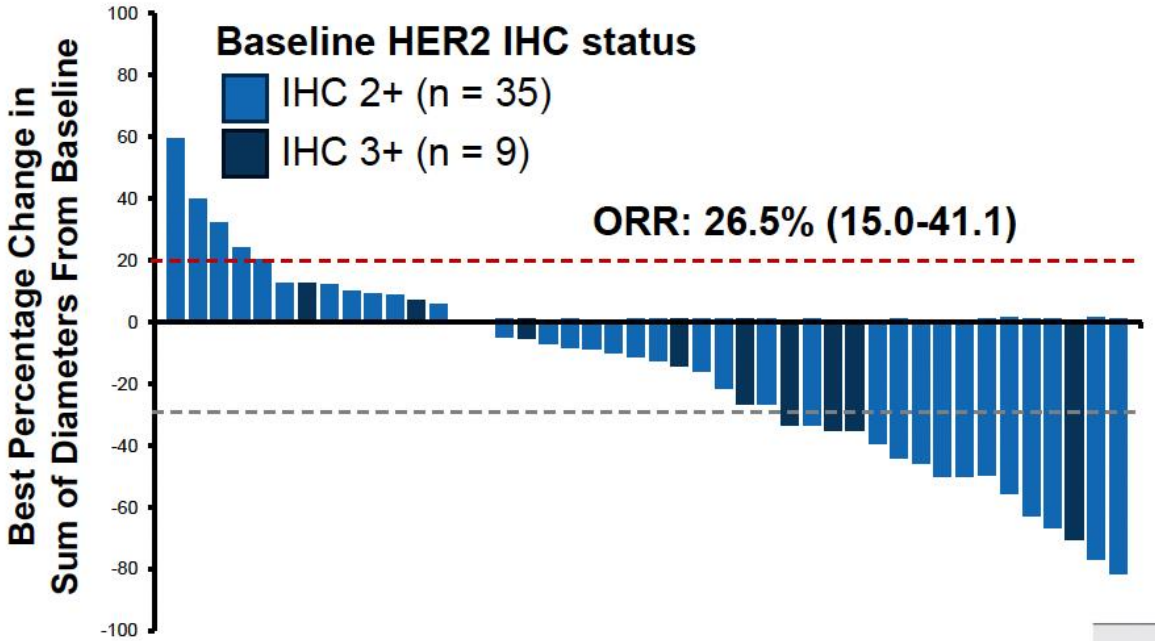
Adjudicated drug-related ILD/pneumonitis, n/N (%)	T-DXd 5.4 mg/kg	T-DXd 6.4 mg/kg
Time since prior anti–PD-(L)1 therapy[c]		
>3 months	5/44 (11.4)	10/28 (35.7)
≤3 months	6/30 (20.0)	3/11 (27.3)
No prior therapy	2/27 (14.8)	3/11 (27.3)

Janne P et al, ASCO 2024

TDXd in NSCLC Overexpressing HER2

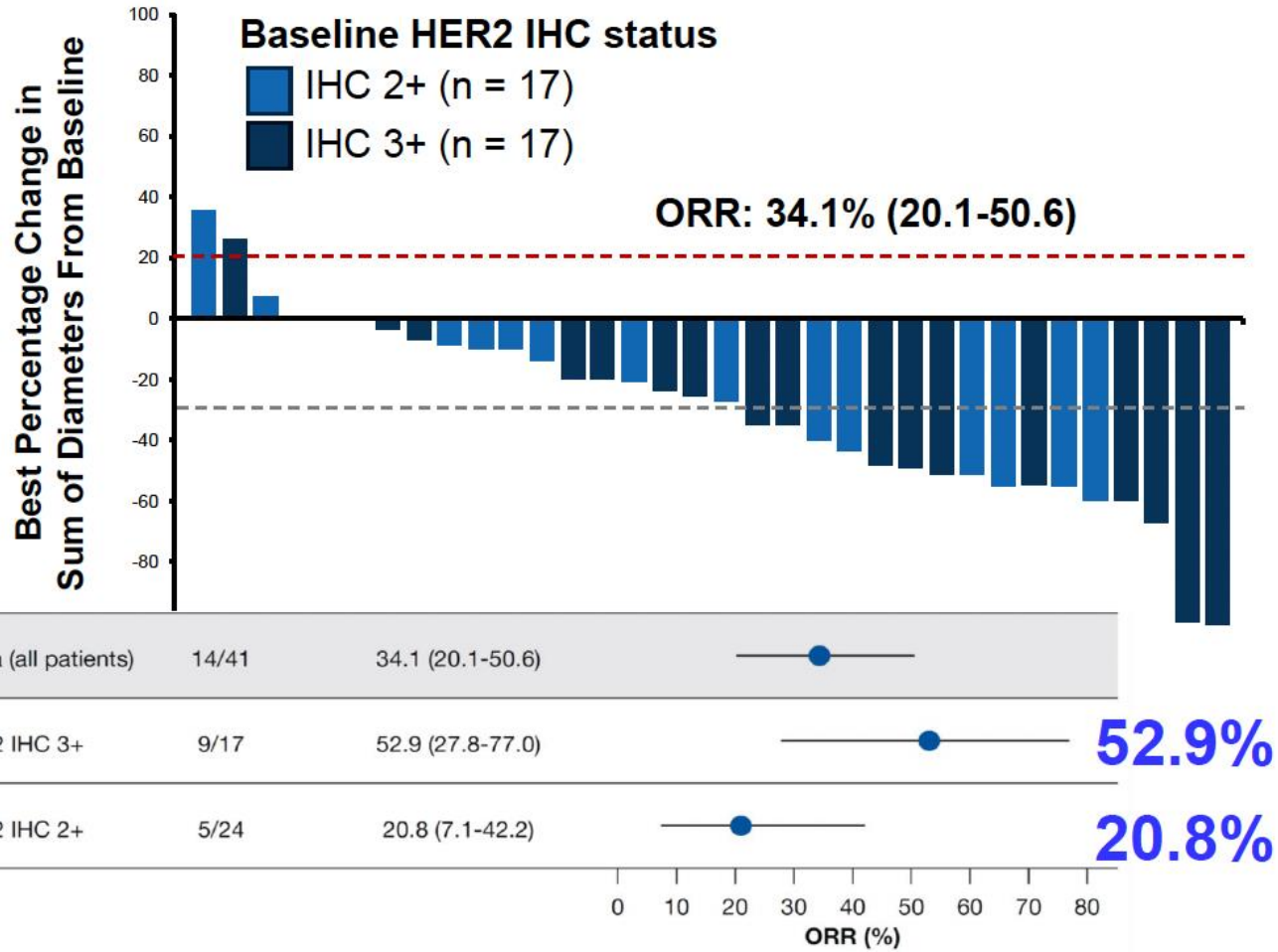
Cohort 1

Trastuzumab Deruxtecan 6.4 mg/kg (n = 49)



Cohort 1a

Trastuzumab Deruxtecan 5.4 mg/kg (n = 41)



52.9%

20.8%

1. Smit EF et al. *Lancet Oncol*. 2024;25:439-454.

Courtesy of Planchard D, ESMO 2024

TDXd in NSCLC Overexpressing HER2: Destiny Lung03

Patient population

- Aged ≥18 years
- **Centrally assessed HER2-OE (IHC 3+/2+)* unresectable, locally advanced or metastatic nonsquamous NSCLC**
- Measurable disease per RECIST v1.1
- WHO/ECOG performance status 0–1
- Patients in Part 1 had 1 or 2 prior lines of therapy; patients with therapy-targetable alterations must have had prior appropriate targeted therapy

Part 1: dose escalation† (enrollment complete)

Arm 1A: T-DXd + durvalumab + cisplatin Q3W
Arm 1B: T-DXd + durvalumab + carboplatin Q3W

Part 1: fixed-dose monotherapy (enrollment complete)

Arm 1D: T-DXd 5.4 mg/kg IV Q3W (N=36)

Part 3: dose confirmation and expansion (currently recruiting)

T-DXd + volrustomig ± carboplatin

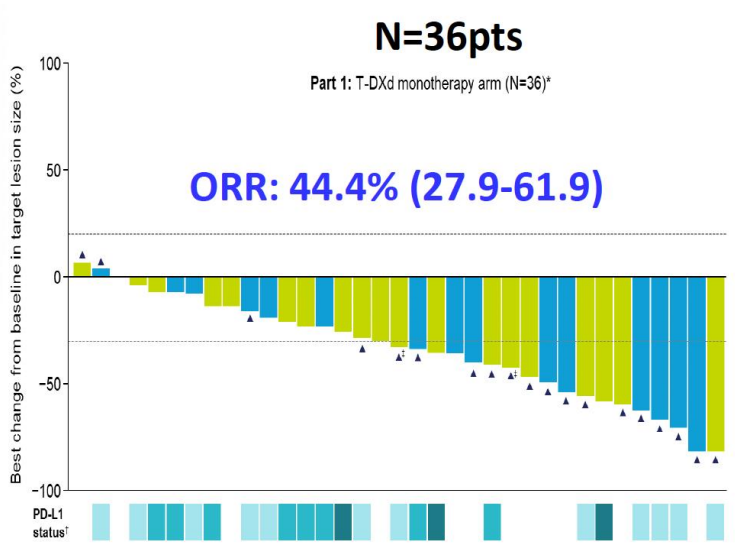
Part 4: safety run-in and expansion (currently recruiting)

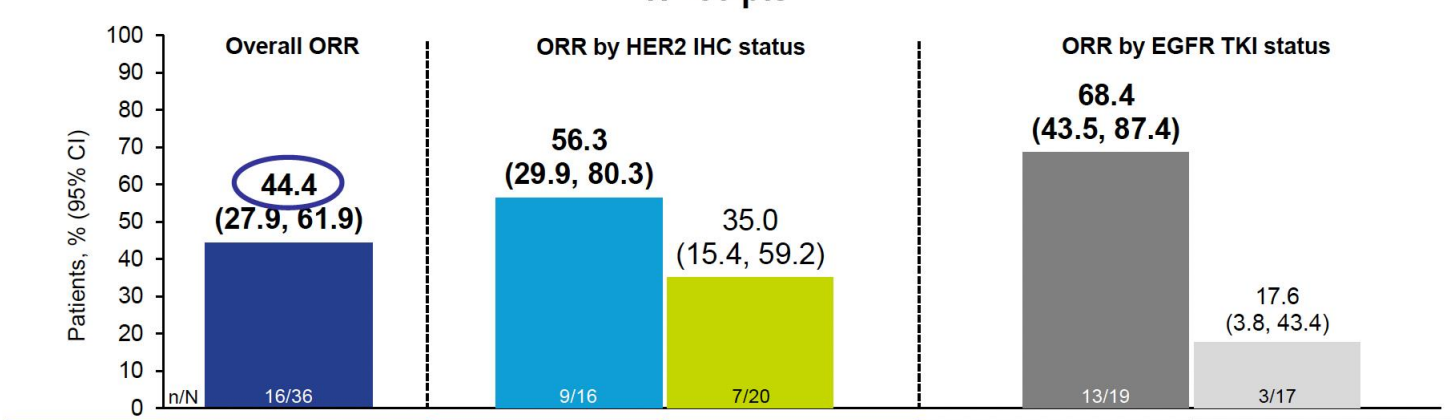
T-DXd + rilvegostomig ± carboplatin

Key endpoints for the T-DXd monotherapy arm

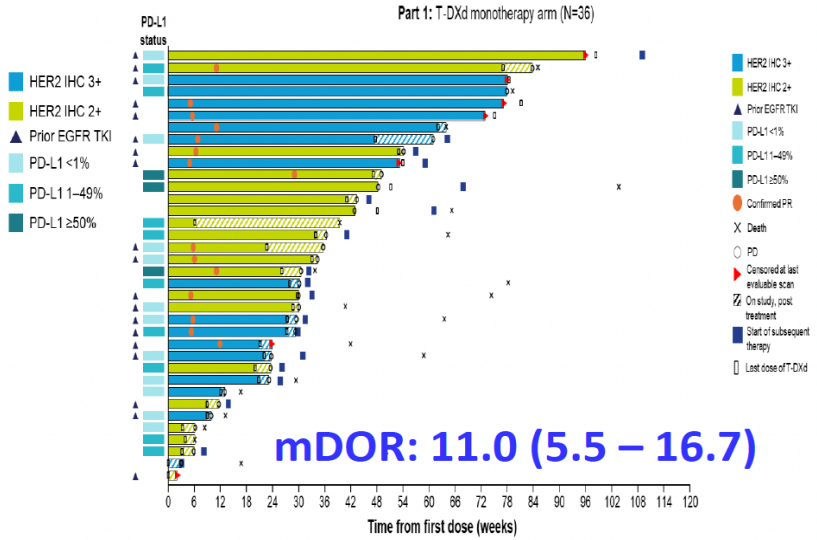
- ORR, DOR, PFS (Investigator assessed)
- OS
- Safety and tolerability

Data cutoff for the Part 1 T-DXd monotherapy arm results: April 1, 2024‡





	Overall	HER2 IHC 3+	HER2 IHC 2+	Prior EGFR TKI	EGFR TKI naïve
Median DOR, months (95% CI)	**11.0 (5.5, 16.7)**	**12.5 (5.5, NE)**	6.6 (4.5, 11.0)	**11.7 (5.5, NE)**	4.6 (4.5, NE)
DCR at 12 weeks, % (95% CI)	77.8 (60.9, 89.9)	81.3 (54.4, 96.0)	75.0 (50.9, 91.3)	84.2 (60.4, 96.6)	70.6 (44.0, 89.7)

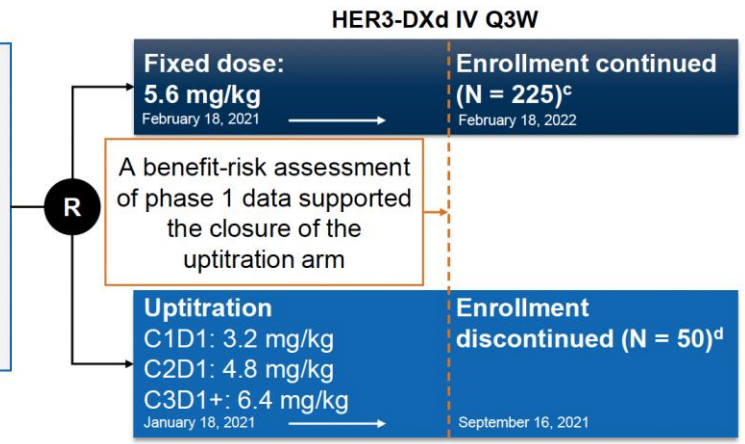


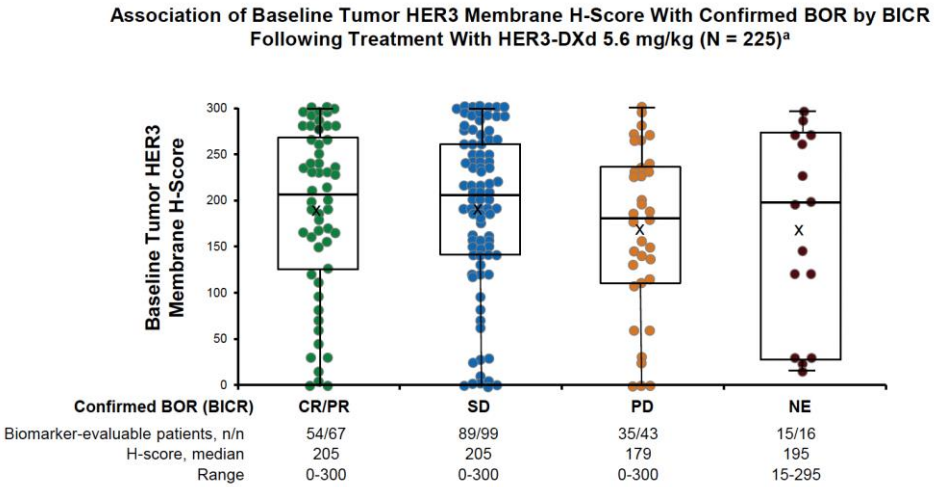
Planchard D et al, WCLC 2024

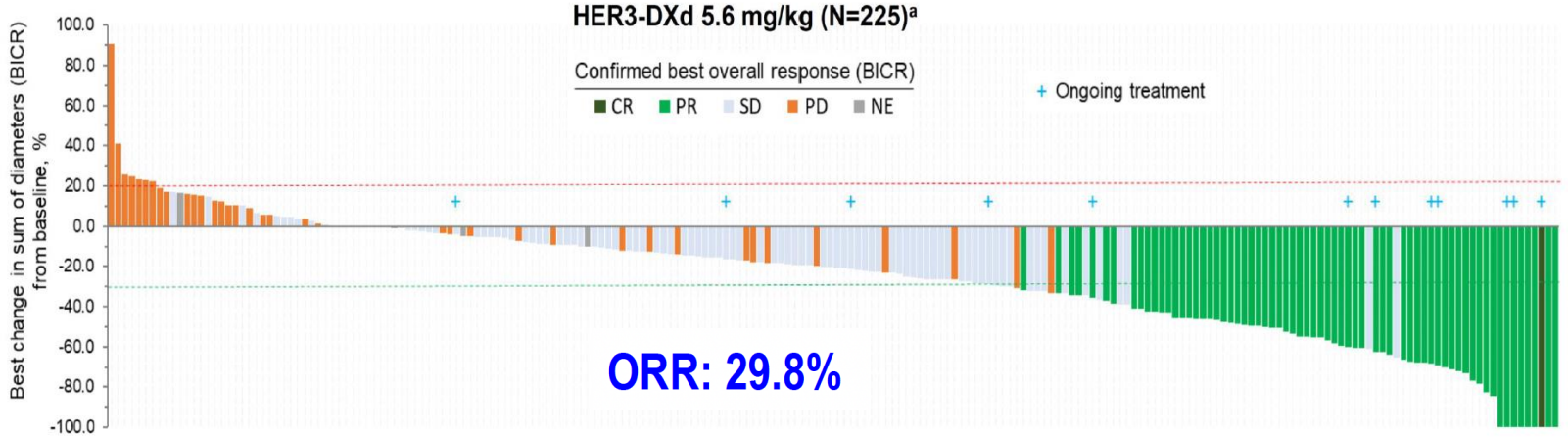
HER3-DXd for EGFRm+: HERTENA-Lung01

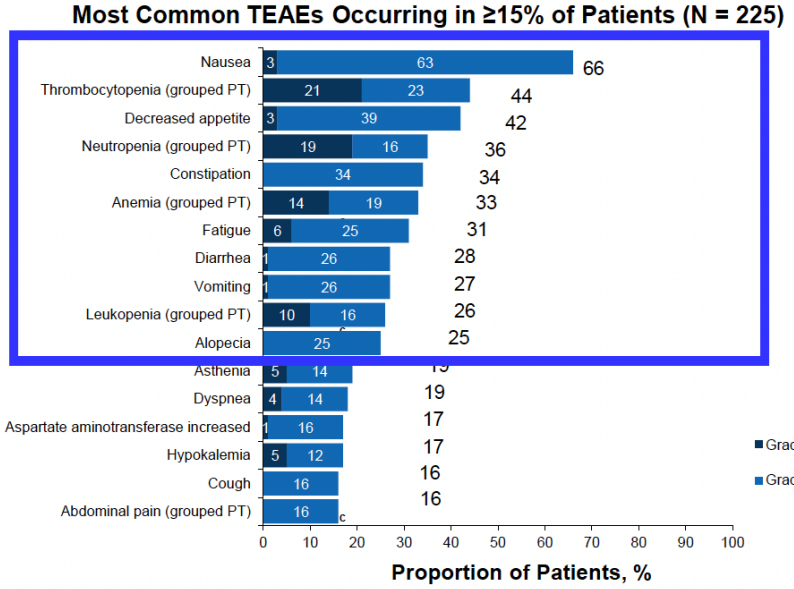
- Advanced *EGFR*-mutated NSCLC
- Progression on most recent systemic therapy
- Prior EGFR TKI and platinum-based chemotherapy (amended protocol required prior osimertinib)
- Inactive or previously treated asymptomatic brain metastases allowed
- Pretreatment tumor tissue required[b]

- **Primary endpoint:** cORR by BICR
- **Key secondary endpoint:** DOR by BICR







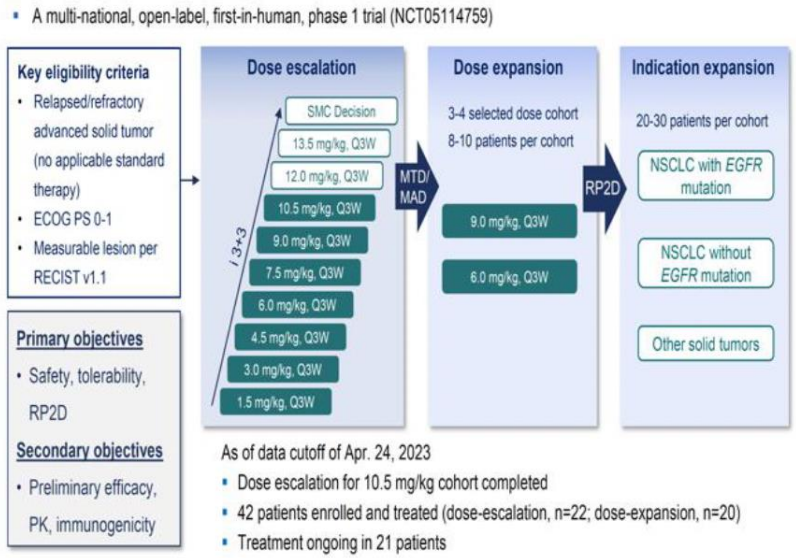


	Type of EGFR TKI resistance mechanism			
	EGFR-dependent, only (n=34)	*EGFR*-independent, only (n=81)	Both *EGFR*-dependent and -independent (n=32)	None identified (n=77)
Confirmed ORR (95% CI), %	32.4 (17.4-50.5)	27.2 (17.9-38.2)	37.5 (21.1-56.3)	27.3 (17.7-38.6)

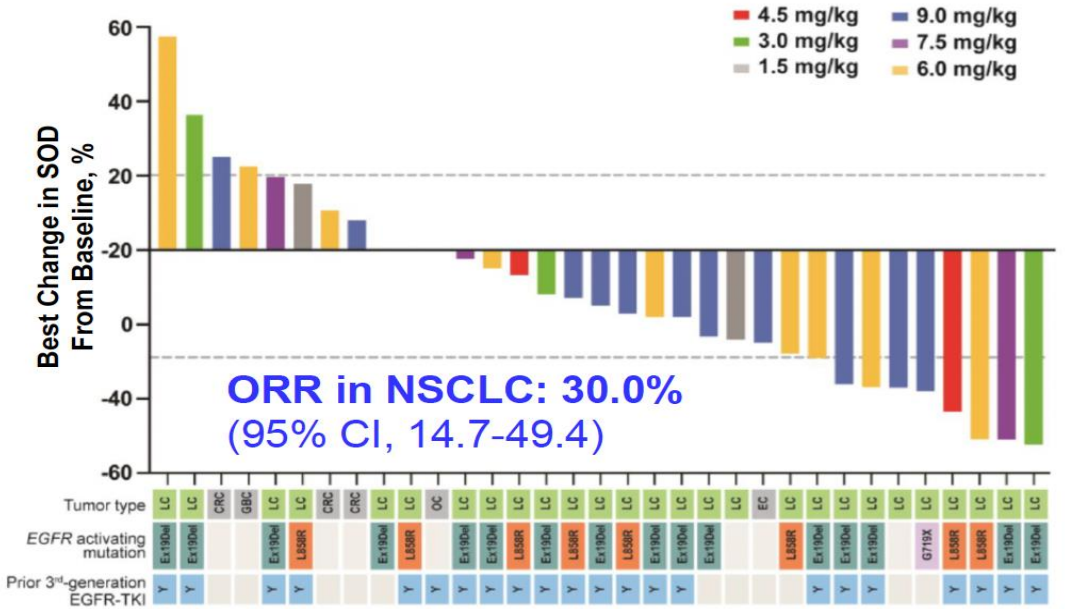
32.4% **37.2%**

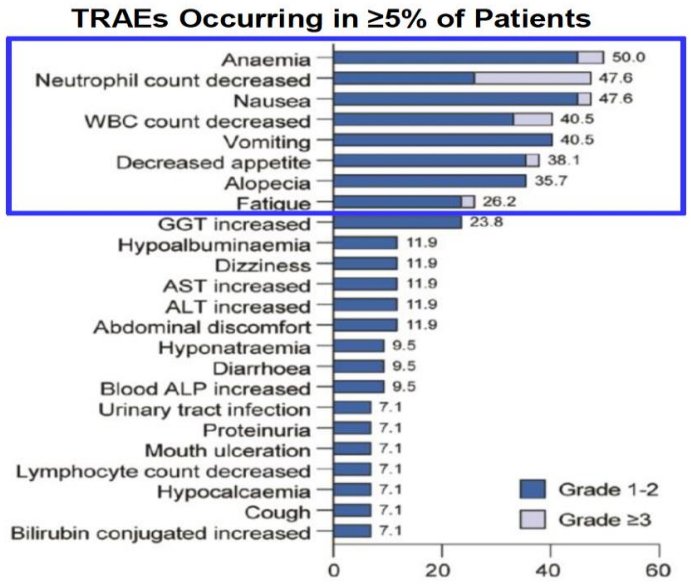
Yu H et al, J Clin Oncol 2023

SHR-A2009 (fully-human anti-HER3IgG1mAb)



Parameter	All Patients (N = 42)	NSCLC Patients (n = 36)
Median age (y) (range)	59 (42-68)	59 (42-68)
Female, n (%)	27 (64.3)	22 (61.1)
Asian, n (%)	42 (100)	36 (100)
ECOG PS 1, n (%)	35 (83.3)	35 (97.2)
Tumor type, n (%)		
NSCLC	36 (85.7)	36 (100)
Others	6 (14.3)	0 (0)
Tumor stage IV, n (%)	42 (100)	36 (100)
Site of metastasis, n (%)		
Bone	19 (45.2)	17 (47.2)
Brain	12 (28.6)	11 (30.6)
Liver	11 (26.2)	8 (22.2)
***EGFR* activating mutation, n (%)**	34 (81.0)	34 (94.4)
Ex19Del	17 (40.5)	17 (47.2)
L858R	15 (35.7)	15 (41.7)
G719X	2 (4.8)	2 (5.6)
Median prior lines of systemic therapy, range	3 (1-11)	3 (1-61)
Prior 3rd-generation EGFR TKI, n (%)	29 (69.0)	29 (80.6)





Wu Y-L et al, ESMO 2023

BL-B01D1-101 (bispecific anti-EGFR-HER3)

Dose Escalation

Key Inclusion Criteria:
- Locally advanced or metastatic NSCLC or other solid tumors
- ECOG PS 0-1
- Measurable disease per RECIST v1.1
- Failed standard therapy or without feasible treatment

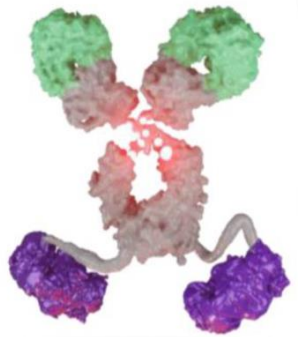
QW 4-week cycle
0.27, 1.5, 3.0 mg/kg

D1D8 Q3W
2.5, 3.0, 3.5 mg/kg

D1 Q3W
4.5, 5.0, 6.0 mg/kg

Dose Expansion

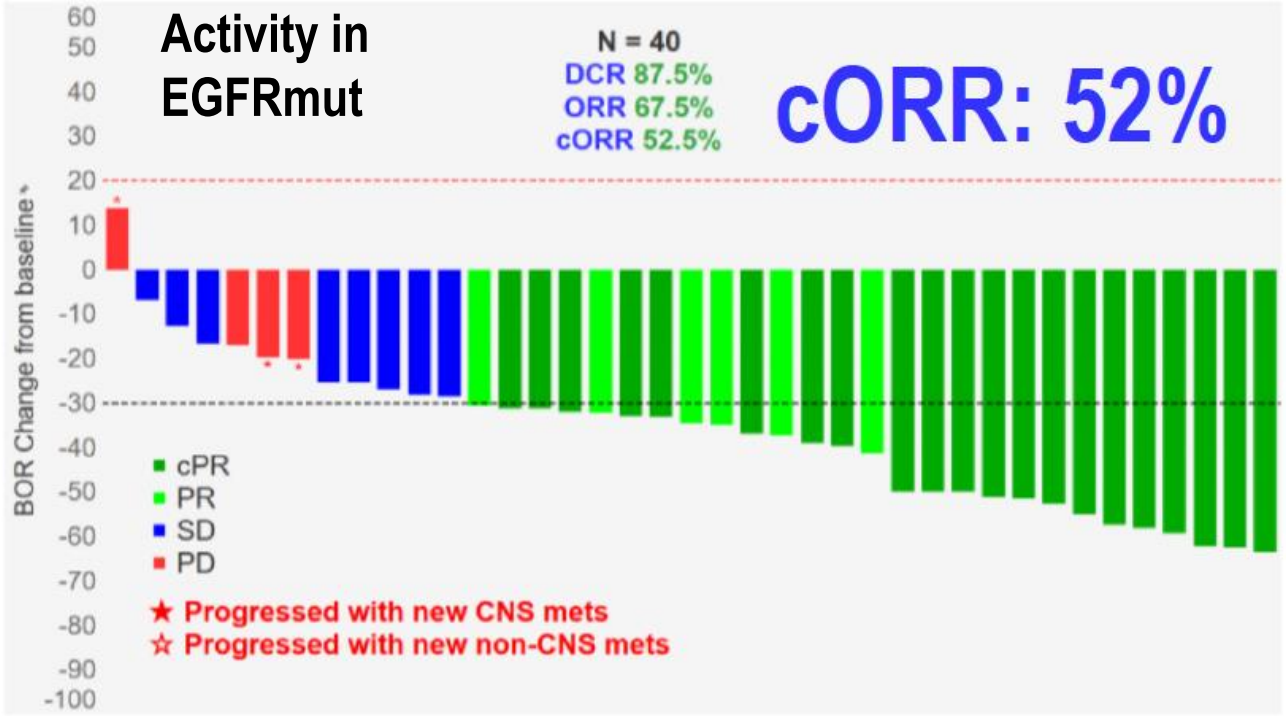
NSCLC (EGFRmt and EGFRwt)	D1D8 Q3W + D1 Q3W
NPC previously treated	D1D8 Q3W + D1 Q3W
SCLC previously treated	D1D8 Q3W + D1 Q3W
HNSCC previously treated	D1D8 Q3W + D1 Q3W



- BL-B01D1 is a first-in-class (FIC) ADC consisting of an EGFRxHER3 bispecific antibody bounded to a novel topoisomerase I inhibitor payload via a cleavable linker.
- Here, we update its safety, tolerability in patients with solid tumor and preliminary efficacy in NSCLC patient cohort in a first-in-human (FIH) trial (BL-B01D1-101).

	NSCLC EGFRmt	NSCLC EGFRmt with treated/no CNS mets (target dose)[1]
Enrolled	N = 40	N = 13
Prior systemic chemo line		
0	25% (10/40)	8% (1/13)
1	50% (20/40)	46% (6/13)
2+	25% (10/40)	46% (6/13)
DCR (95%CI), %	87.5 (73.2, 95.8)	92.3 (64.0, 99.8)
ORR (95%CI), %	67.5 (50.9, 81.4)	69.2 (38.6, 90.9)
cORR (95%CI), %	52.5 (36.1, 68.5)	61.5 (31.6, 86.1)
mDOR (95%CI), mo	8.5 (2.8, NR)	12.3 (2.7, NR)
mPFS (95%CI), mo	5.6 (3.9, 9.7)	15.0 (4.3, NR)

[1] 2.5mg/kg D1D8Q3W and 4.5mg/kg D1Q3W



Yuxiang MA et al, Lancet Oncol 2024

Targeting CEACAM5: SAR408701 (Tusamitamab Ravtansine)

CARMEN-LC03:

- Patients with nonsq NSCLC with prior platinum-based CT and ICI treatment
- CEACAM5 expression (≥2+ intensity in ≥50% of tumor cells assessed by IHC)
- ≥1 measurable lesion by RECIST v1.1
- ECOG PS 0 or 1

R 1:1

- Tusa rav 100 mg/m² Q2W* (N=225)
- Docetaxel 75 mg/m² Q3W* (N=225)

Dual primary endpoints#
- PFS as per IRC
- OS

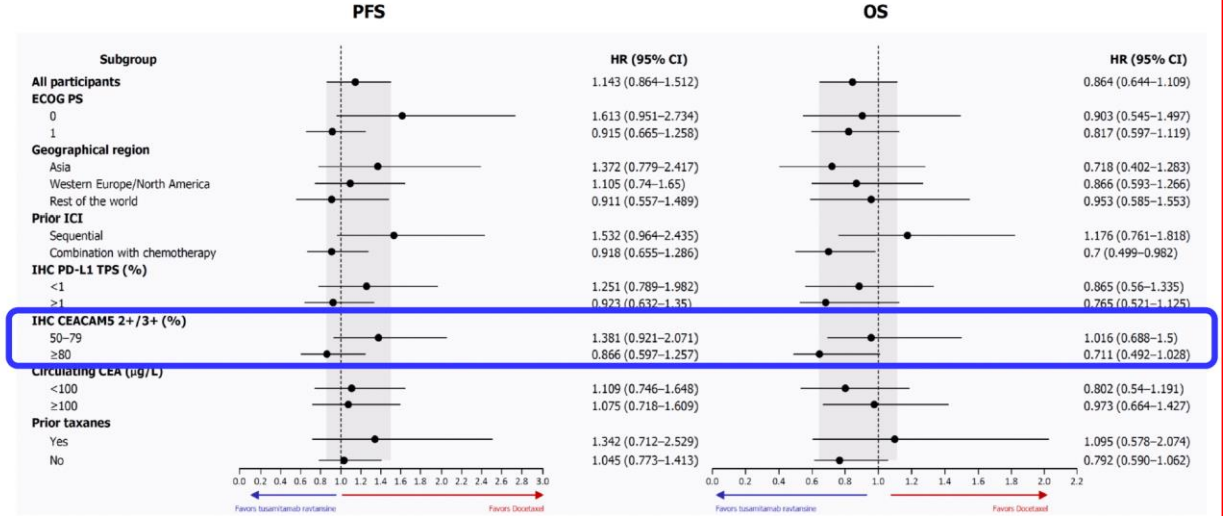
Secondary endpoints
- ORR
- HRQoL
- Safety
- DoR

Stratified by: ECOG (0 vs 1), geographical region (Asia vs Western Europe + Australia + NA vs ROW), and prior ICI treatment (sequential vs combination with chemotherapy)

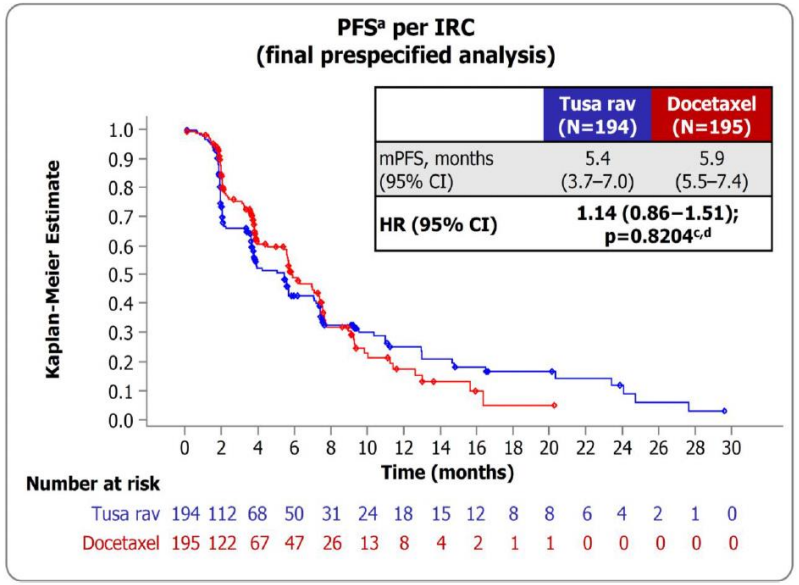
The final PFS and interim OS results are presented, with early study termination

- **Final PFS/IA1 of OS**: When either ~210 deaths (~58% of IF) or ~221 PFS events were observed, whichever occurred first
- **IA2 OS**: When ~290 deaths (~80% IF) were observed (OS HR critical value of 0.745 if PFS not significant)
- **Final OS analysis:** When ~363 OS events were observed (OS HR critical value of 0.792 if PFS not significant)

Patients with ≥80% CEACAM5 expression on tusa rav had improved PFS and OS

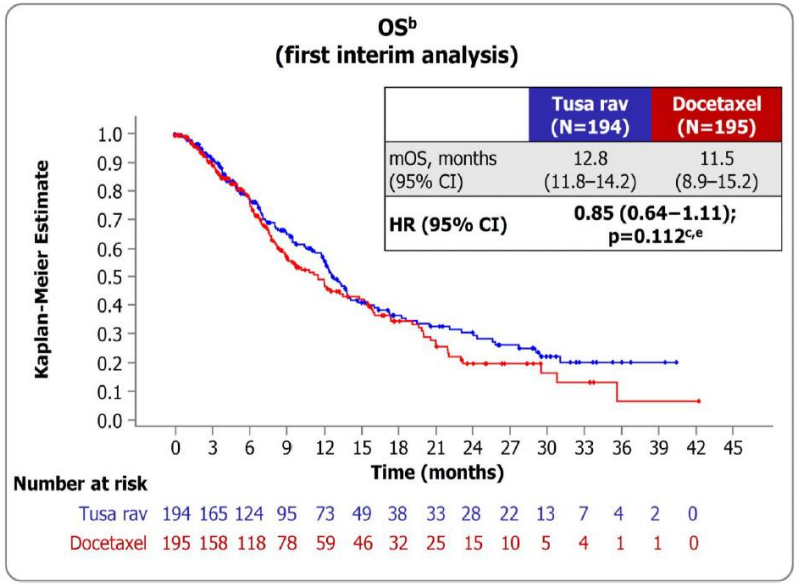


PFS[a] per IRC (final prespecified analysis)



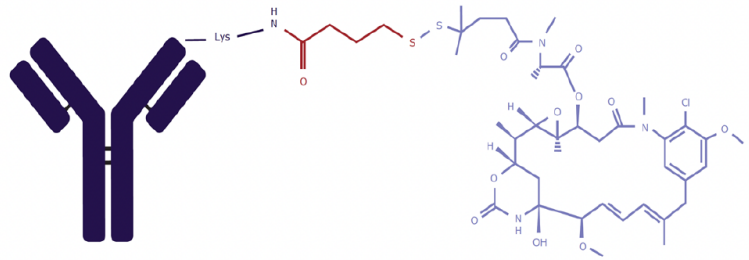
	Tusa rav (N=194)	Docetaxel (N=195)
mPFS, months (95% CI)	5.4 (3.7–7.0)	5.9 (5.5–7.4)
HR (95% CI)	1.14 (0.86–1.51); p=0.8204[c,d]	

OS[b] (first interim analysis)



	Tusa rav (N=194)	Docetaxel (N=195)
mOS, months (95% CI)	12.8 (11.8–14.2)	11.5 (8.9–15.2)
HR (95% CI)	0.85 (0.64–1.11); p=0.112[c,e]	

tusamitamab ravtansine

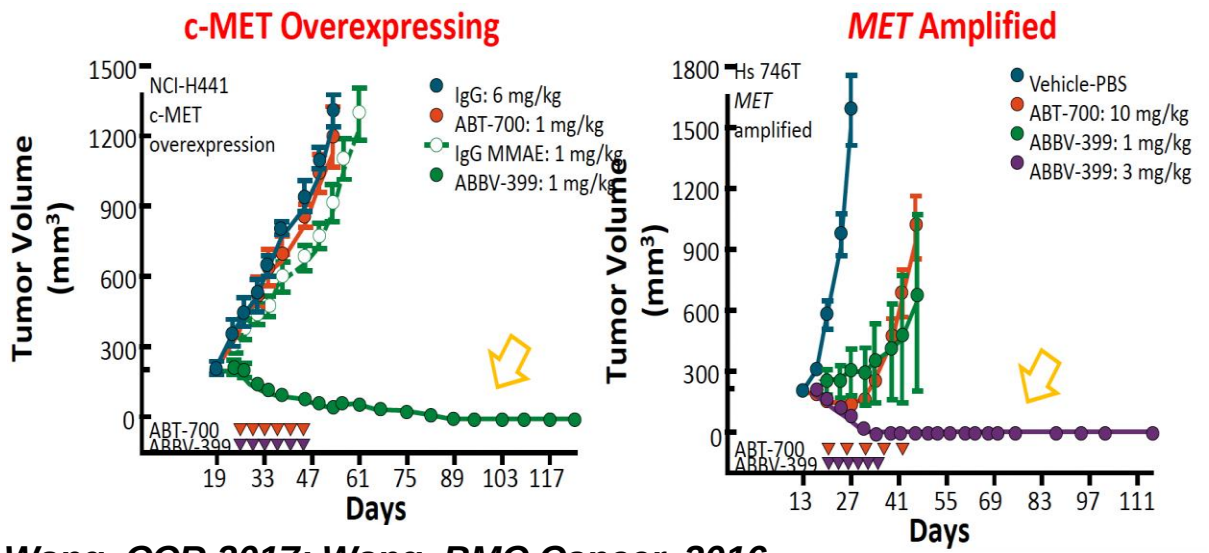


HUMANIZED ANTIBODY[3]	SPDB LINKER[4]	CYTOTOXIC AGENT[3]
• Specific for the A3-B3 domain of CEACAM5 • No cross-reactivity with CEACAM1, CEACAM6, or CEACAM8	• Cleavable inside cells • Stable in plasma and aqueous formulation	• Maytansinoid (DM4) • Inhibits tubulin polymerization

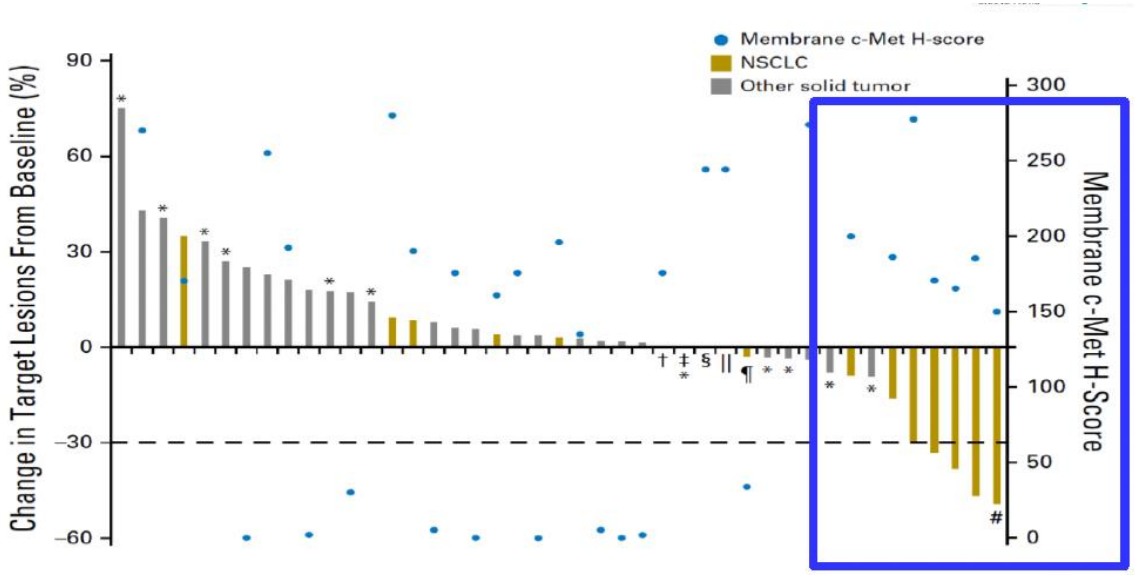
Average Drug Antibody Ratio (DAR) of 3.8

Yuxiang MA et al, Lancet Oncol 2024

Targeting MET-Amplified and c-Met–Overexpressing Tumors: Telisotuzumab Vedotin (ABBV-399)



Wang, CCR 2017; Wang, BMC Cancer, 2016



StricklerJH et al, J Clin Oncol 2018

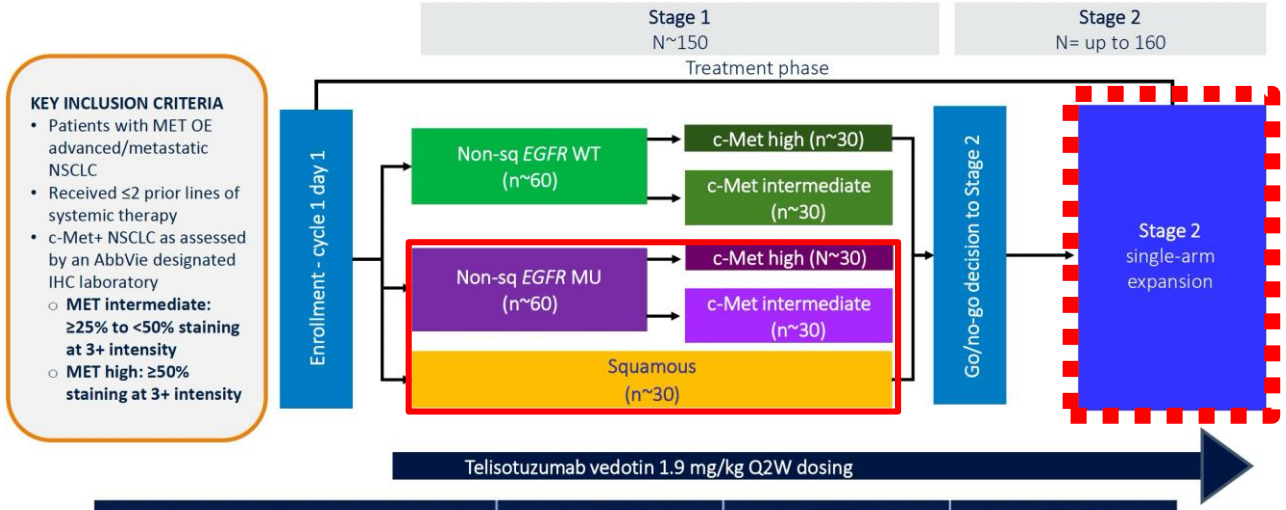
Activity seen almost only in **NSCLC**
c-Met–overexpressing tumors (H-score≥150)

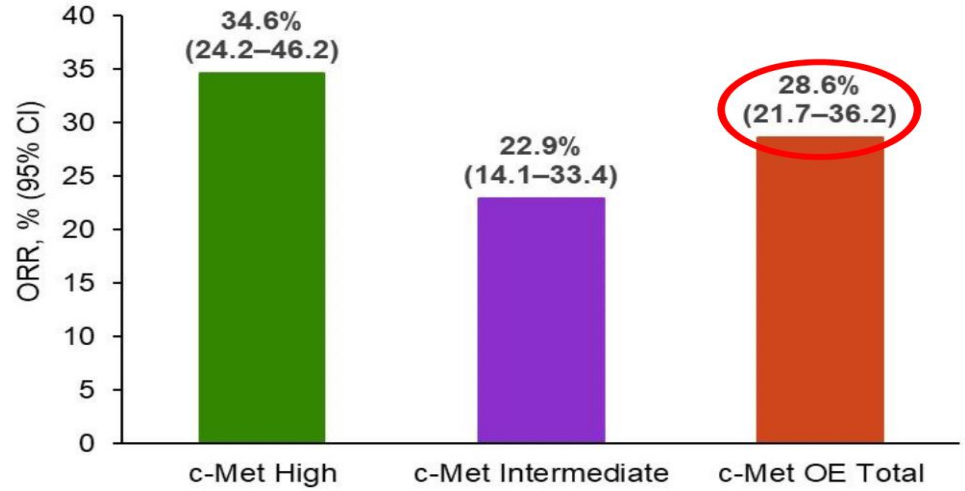
Histology matters

Antibody ratio of approximately (DAR) 3

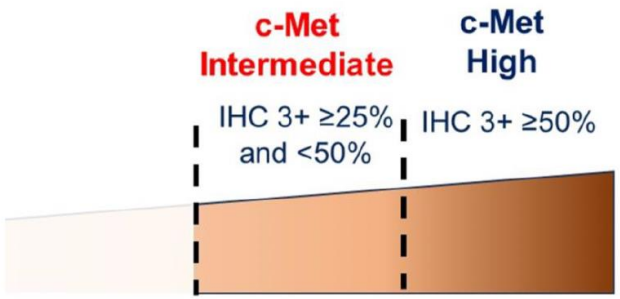
Courtesy of Planchard D, ESMO 2024

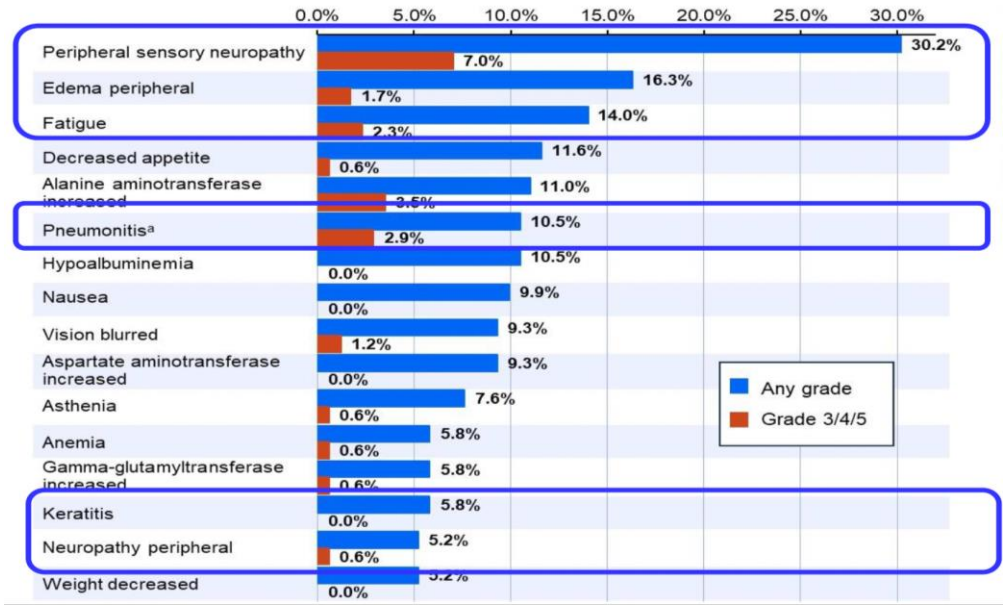
Teliso-V in NSQ EGFRwt c-Met expressing (LUMINOSITY stage 2)





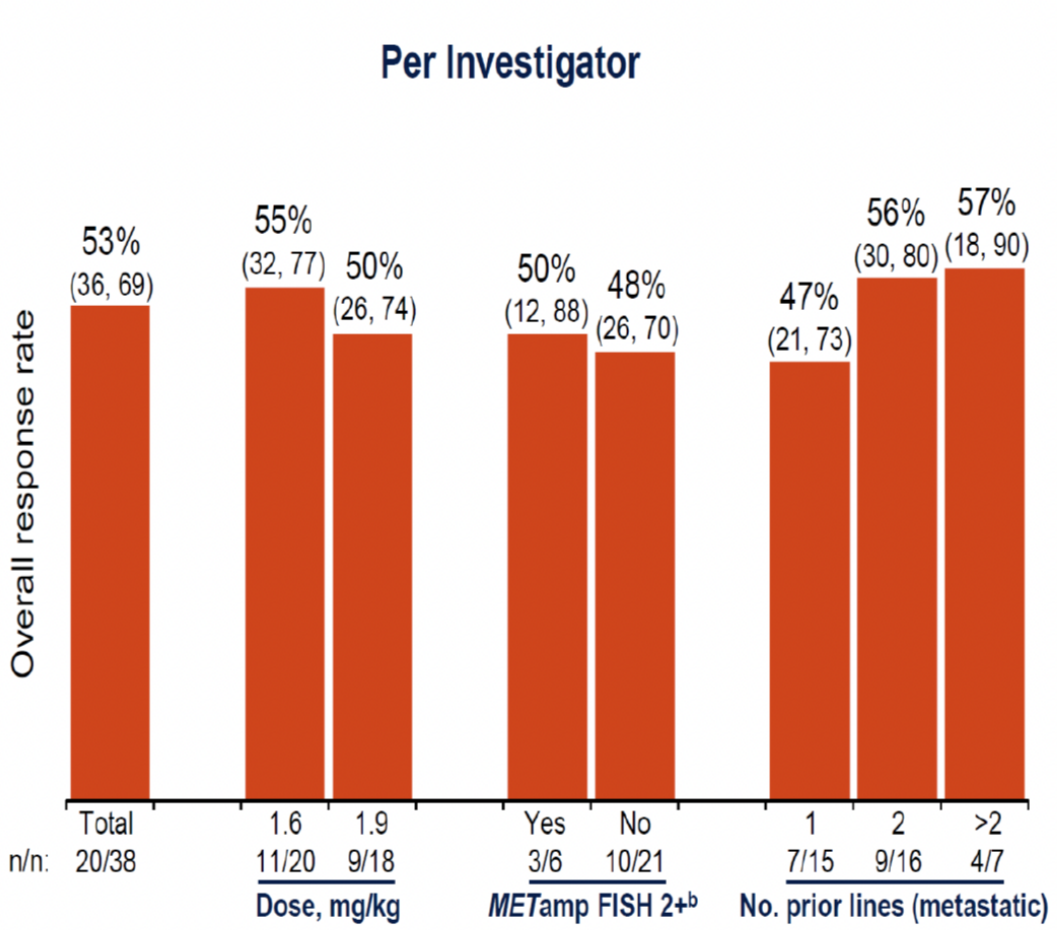
	c-Met High (n=78)	c-Met Intermediate (n=83)	c-Met OE Total (N=161)
Number of responders	27	19	46
Median DOR, months [95% CI]	9.0 [4.2, 13.0]	7.2 [5.3, 11.5]	8.3 [5.6, 11.3]
DOR ≥6 months, n (%)	17 (63.0)	9 (47.4)	26 (56.5)

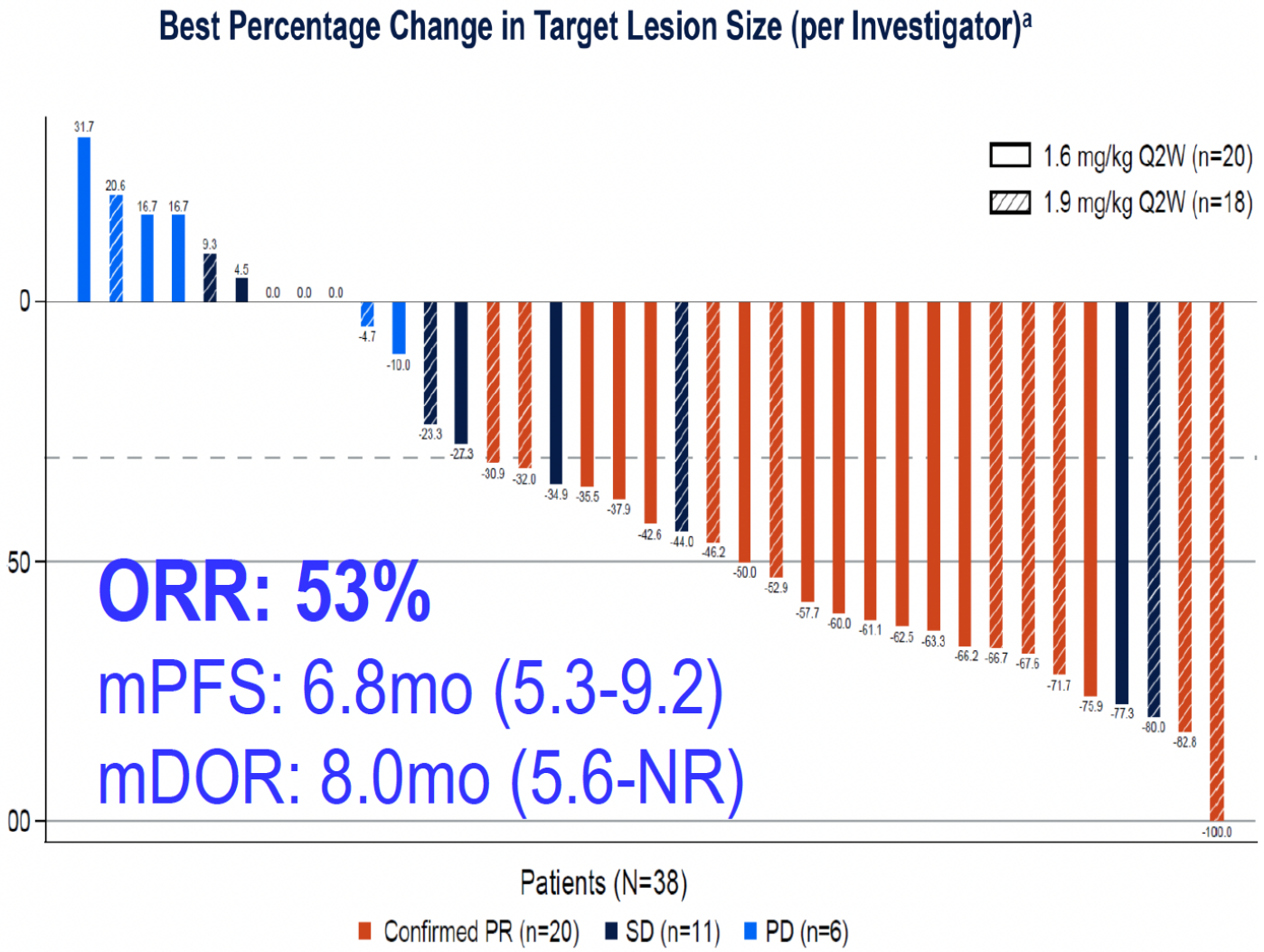




Camidge R et al, ASCO 2024

Teliso-V in NSQ EGFRmut, c-MET+: Phase 1





Horinouchi H et al, ESMO Asia 2023

Buonarroti M, 'La Pietà (Vaticana)', 1497-1499, Basilica di San Pietro, Vaticano

Buonarroti M, 'La Pietà Rondanini', 1552-1564, Museo Civico Castello Sforzesco, Milano

Salem M, 'A Palestinian Woman Embraces the Body of Her Niece', Pietà di Gaza, World Press Photo, Prize 2024