ADCs in NSCLC

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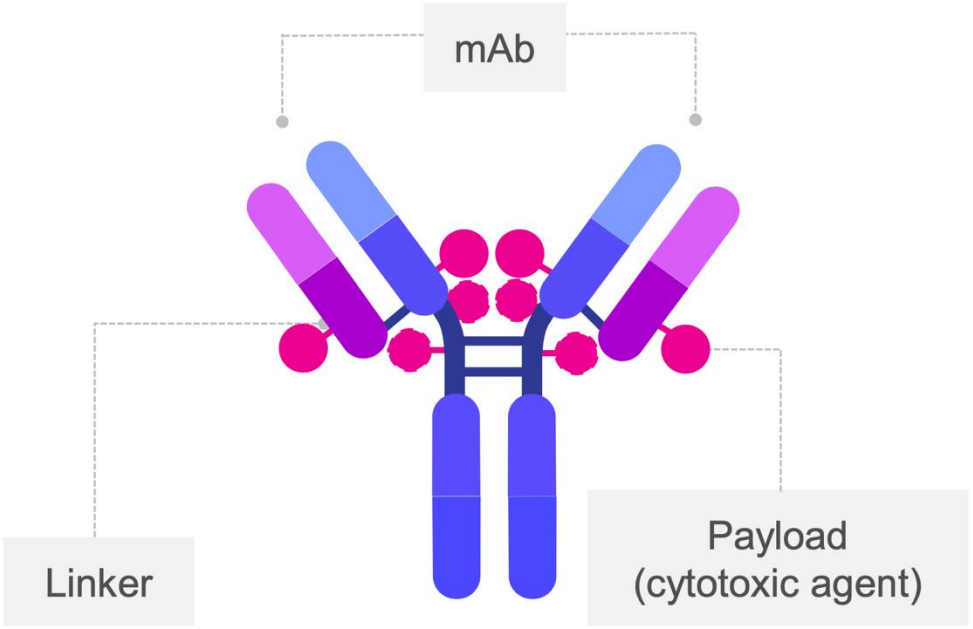
Outline

- The Past
  - ado-trastuzumab emtansine
  - Tusamitamab ravtansine
- The Present
  - fam-trastuzumab deruxtecan
  - Sacituzumab govitecan
  - Datopotamab deruxtecan
- The Future
  - Patritumab Deruxtecan
  - Telisotuzumab Vendotin

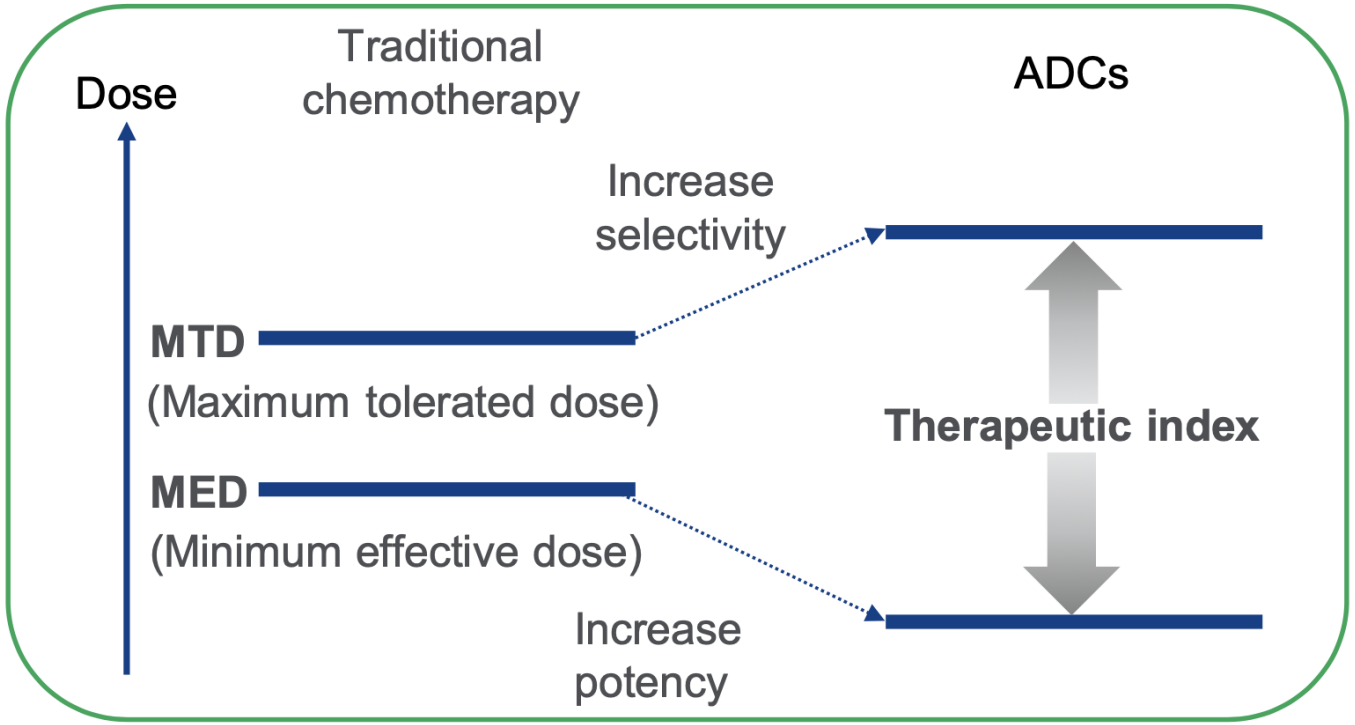
Why ADCs?

Structure of an ADC[1]

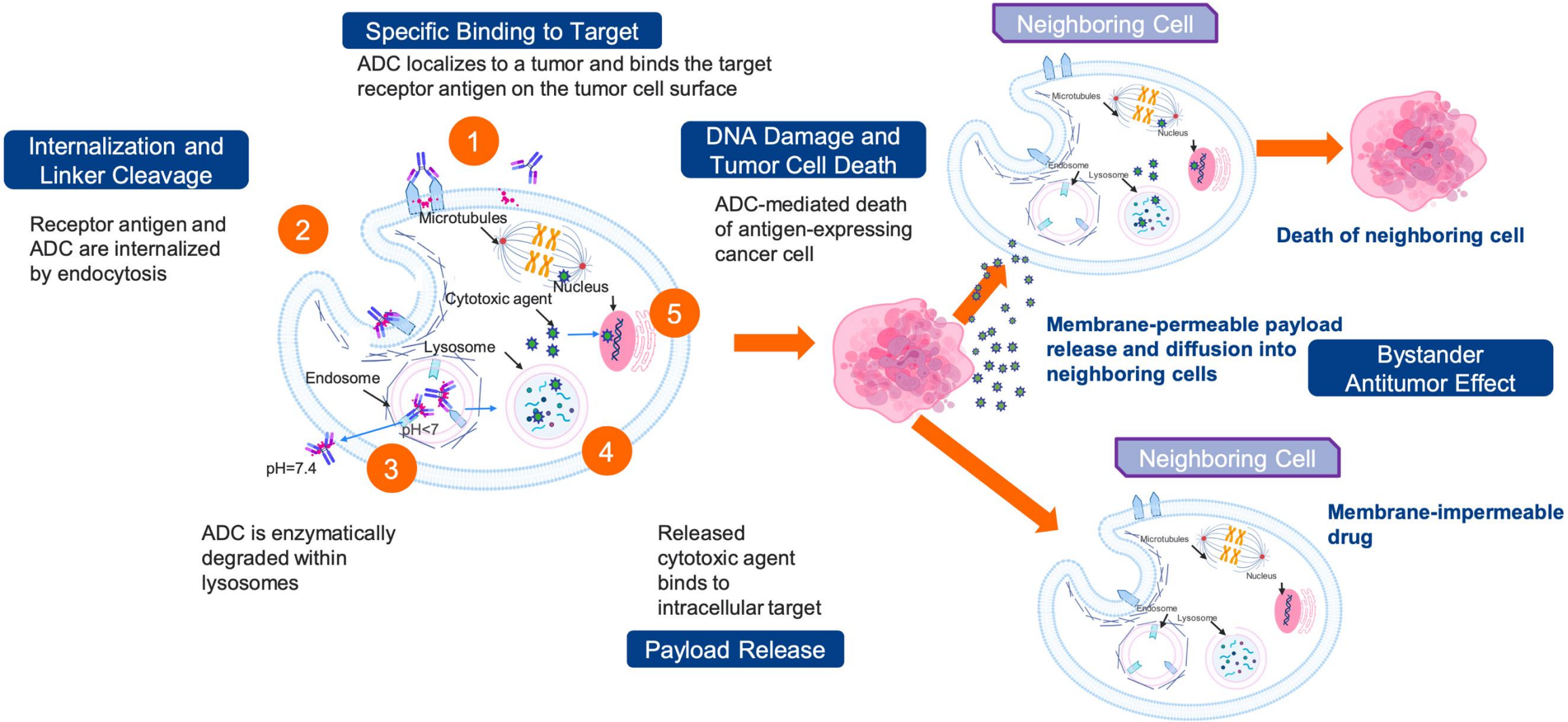


ADCs are designed to have an expanded therapeutic index

The expanded therapeutic index of ADCs vs conventional chemotherapy is a result of efficient and specific drug delivery to antigen-expressing tumor cells.[1,2]



Membrane permeable payloads affect adjacent cells



Trail PA, et al. *Pharmacol Ther.* 2018;181:126-142.

Complexity = more mechanisms for resistance

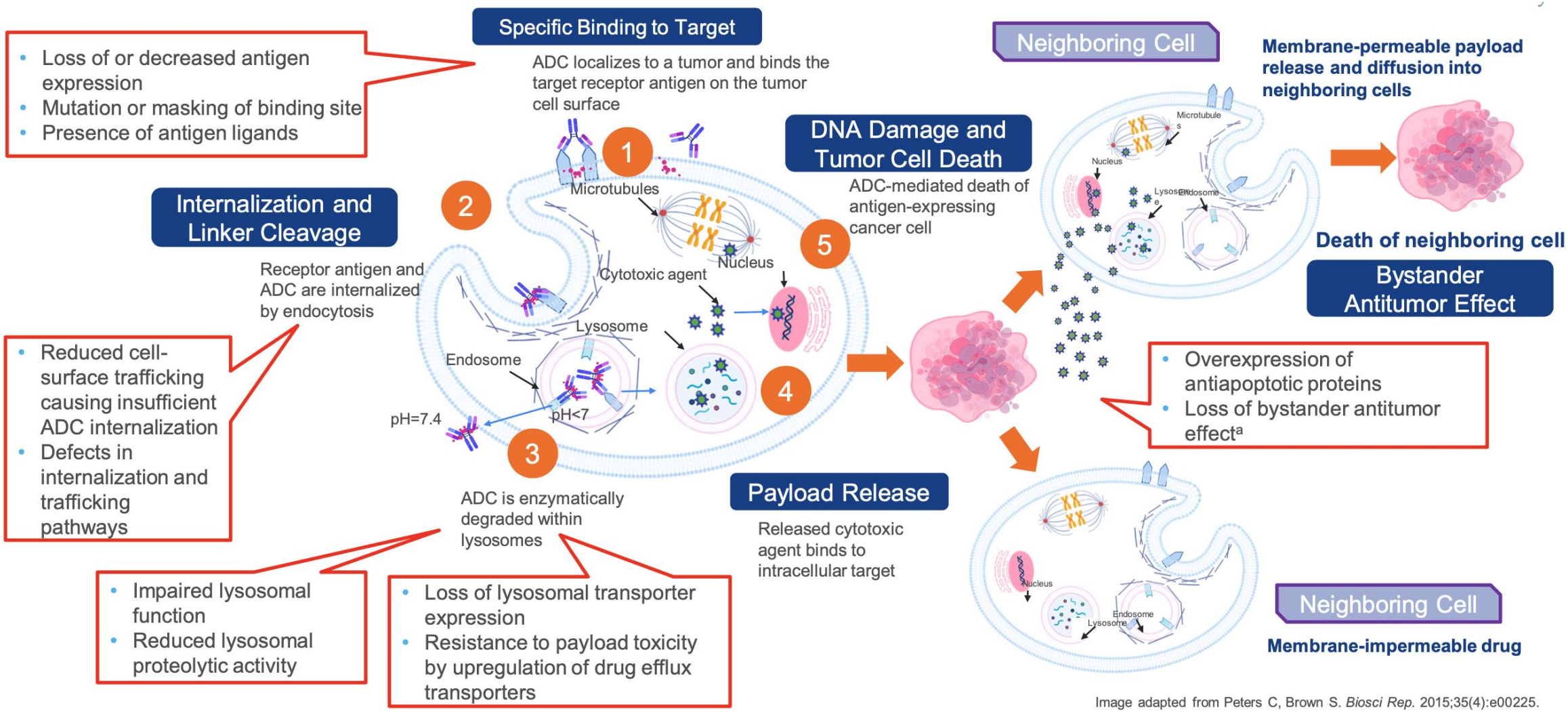
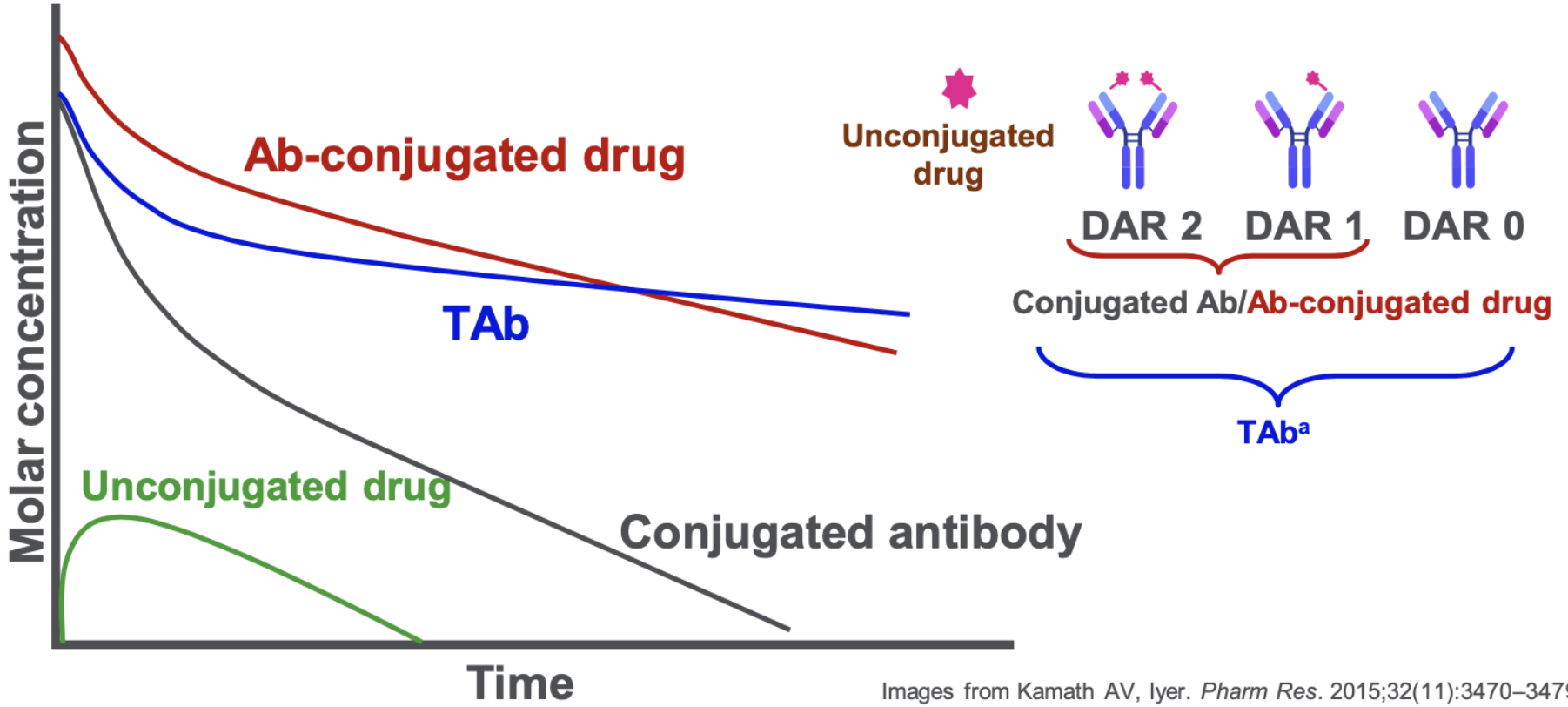


Image adapted from Peters C, Brown S. *Biosci Rep.* 2015;35(4):e00225.

PK Profiles of Different Analytes

Ab-related PK assays	Small-molecule–related PK assays
TAb • Measures the total concentration of Ab (conjugated and unconjugated)	**Ab-conjugated drug** • Measures drug-to-antibody ratio (DAR)
Conjugated Ab • Measures concentration of conjugated Ab only	**Unconjugated drug** • Measures unconjugated drug

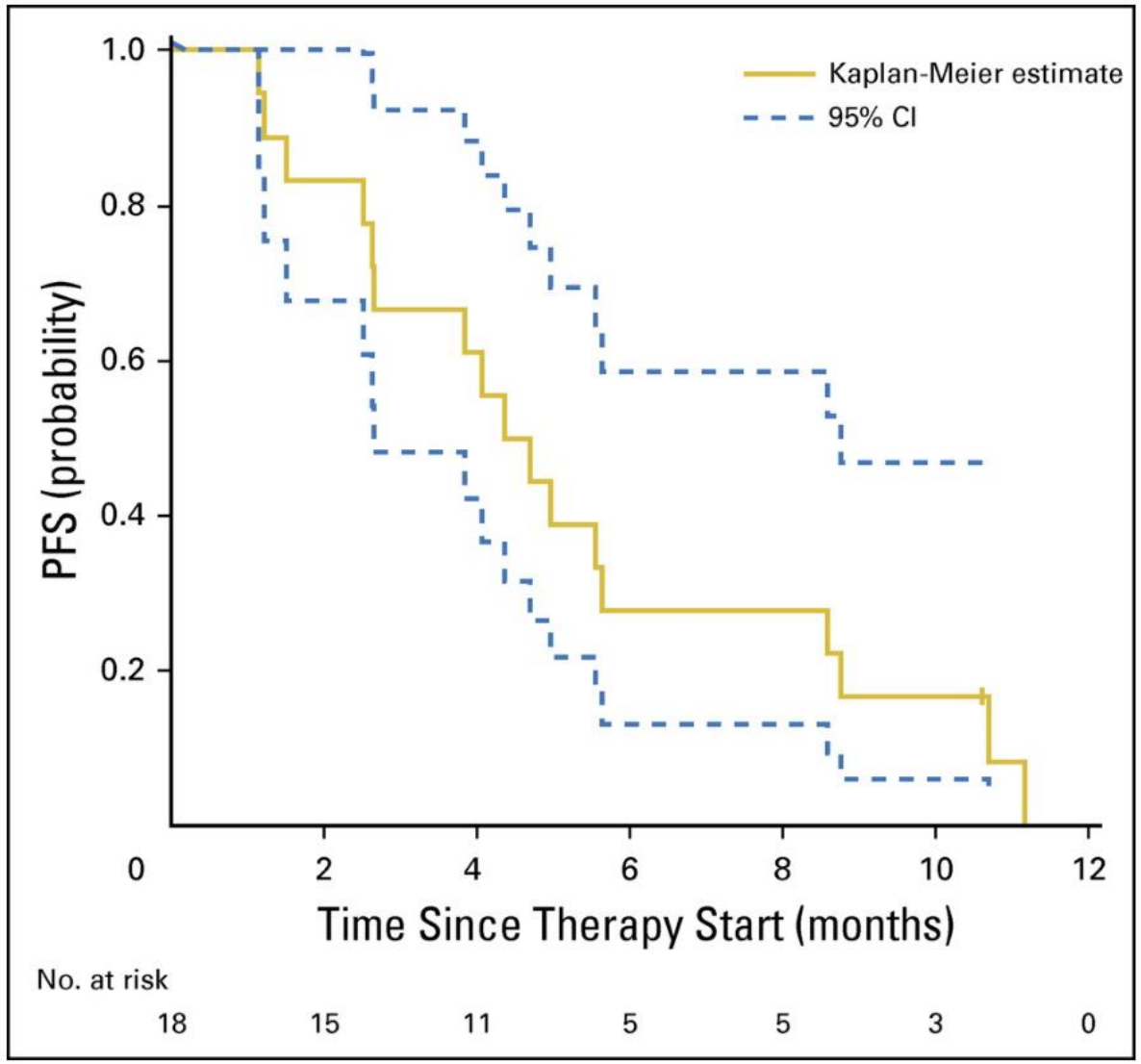


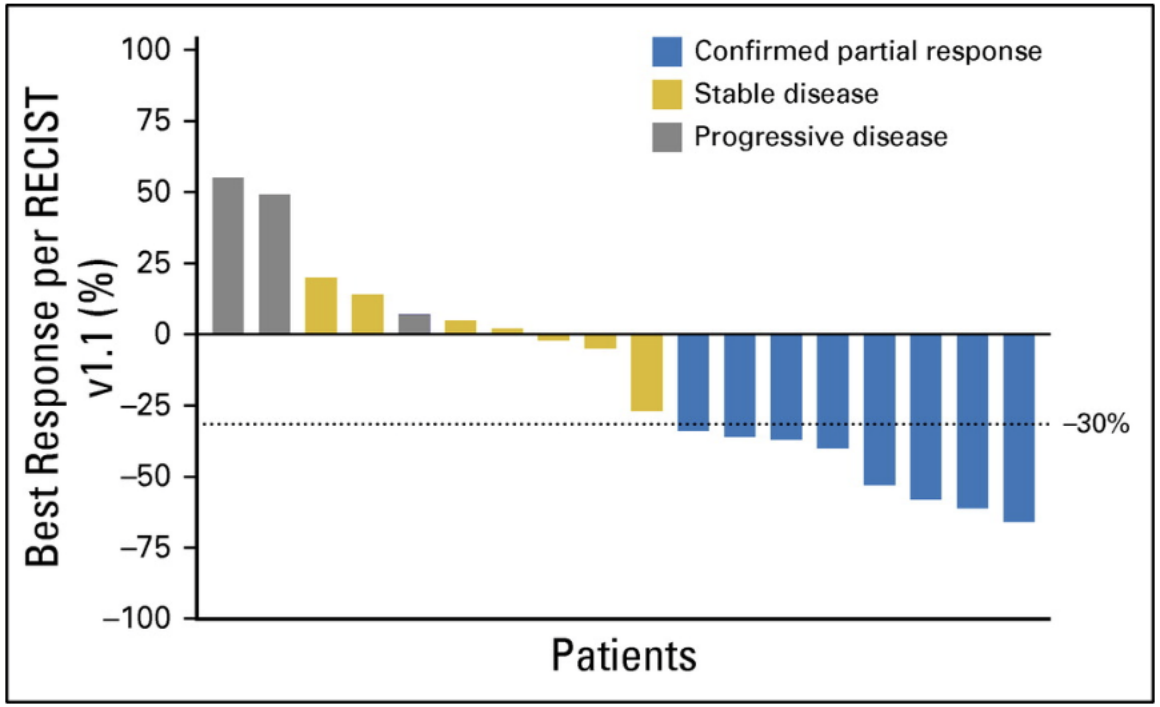
Images from Kamath AV, Iyer. *Pharm Res*. 2015;32(11):3470–3479.

The Past

- Drug antibody Ratio was low (3.5-3.8)
- Payload was not membrane permeable
- Drugs failed or were replaced by better options

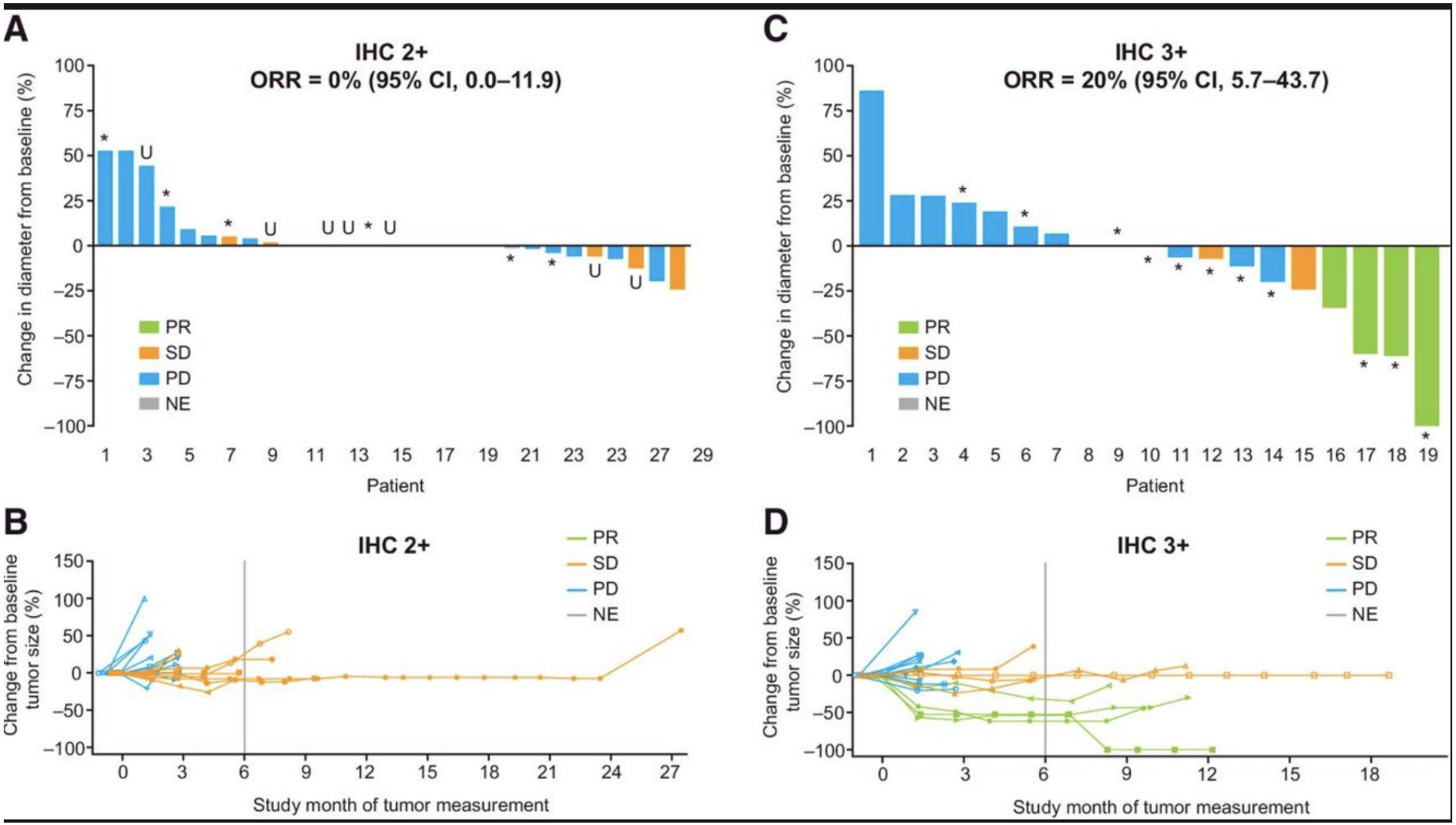
Trastuzumab emtansine in ERBB2 mutated NSCLC





Li et al JCO 2018

Trastuzumab emtansine in ERBB2 overexpressing NSCLC

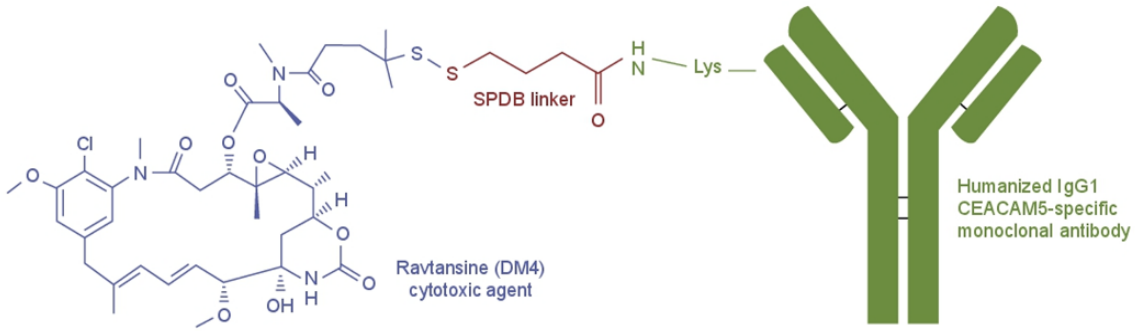


Peters et al Clin Cancer Res 2019

CEACAM5

- CEACAM5: cell-surface glycoprotein selectively expressed on several tumors, including NSCLC.
- Stimulates metastatic spread by promoting cell migration.

Tusamitamab Ravtansine (TUSA)



Drug-to-antibody ratio is 3.8.
CEACAM5, carcinoembryonic antigen-related cell adhesion molecule 5; DM4, ravtansine; IgG1, immunoglobulin G1; SPDB, N-succinimidyl 4-(2-pyridyldithio)butyrate.

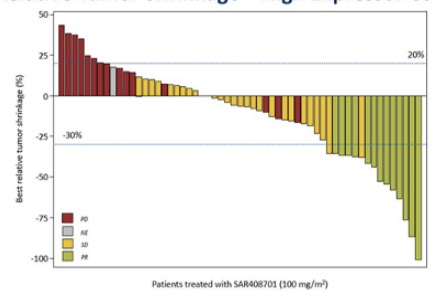
Ricordel et al. ASCO 2022

Best Overall Response

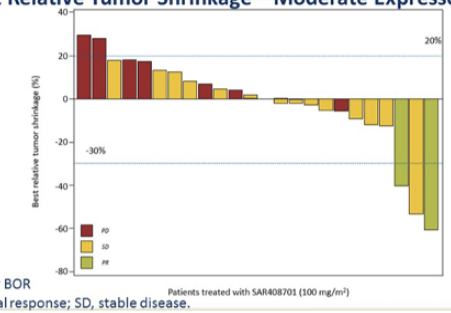
Overall Population

Response, n (%)	High expressors (n = 64)	Moderate expressors (n = 28)
ORR [95% CI]	13 (20.3%) [12.27-31.71]	2 (7.1%) [1.98-22.65]
Confirmed PR	13 (20.3%)	2 (7.1%)
SD	28 (43.8%)	15 (53.6%)
DCR	41 (64.1%)	17 (60.7%)
PD	21 (32.8%)	10 (35.7%)
NE	2 (3.1%)	1 (3.6%)

Best Relative Tumor Shrinkage – High Expressor Cohort



Best Relative Tumor Shrinkage – Moderate Expressor Cohort



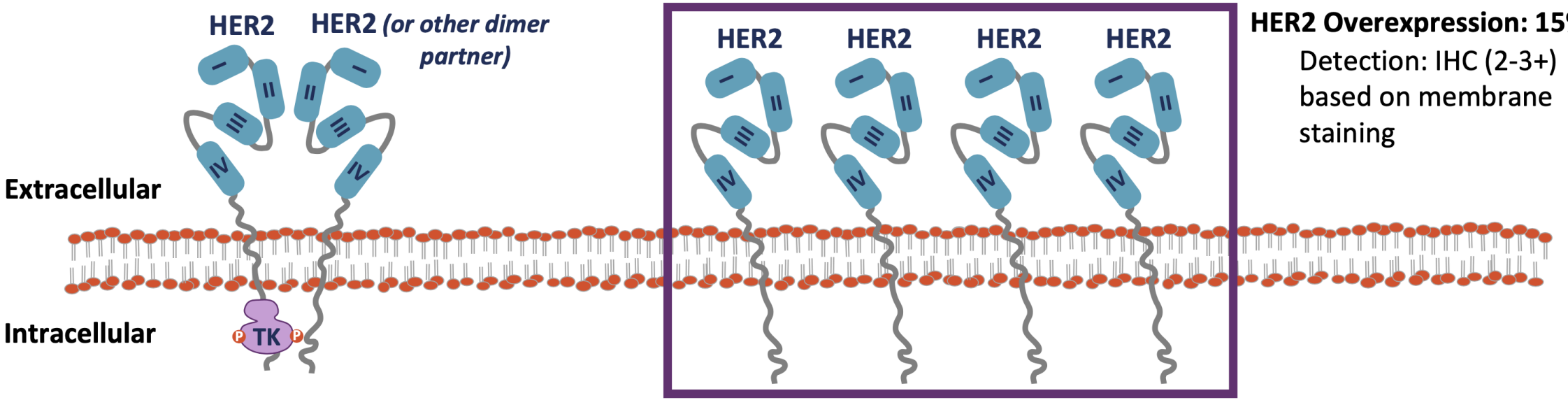
Best relative tumor shrinkage: Patients who had unconfirmed PR (>30% decrease) were counted as SD for BOR
DCR, disease control rate; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease.

Gazzah et al. ASCO 2020

The Present

- Camptothecan payloads – membrane permeable
- Higher DAR

What Is HER2-Positive NSCLC?



HER2 Overexpression: 15%-30%

Detection: IHC (2-3+) based on membrane staining

***HER2* Gene Mutation: 1%-3%**

Detection: NGS (activating *HER2*/*ERBB2* mutation)

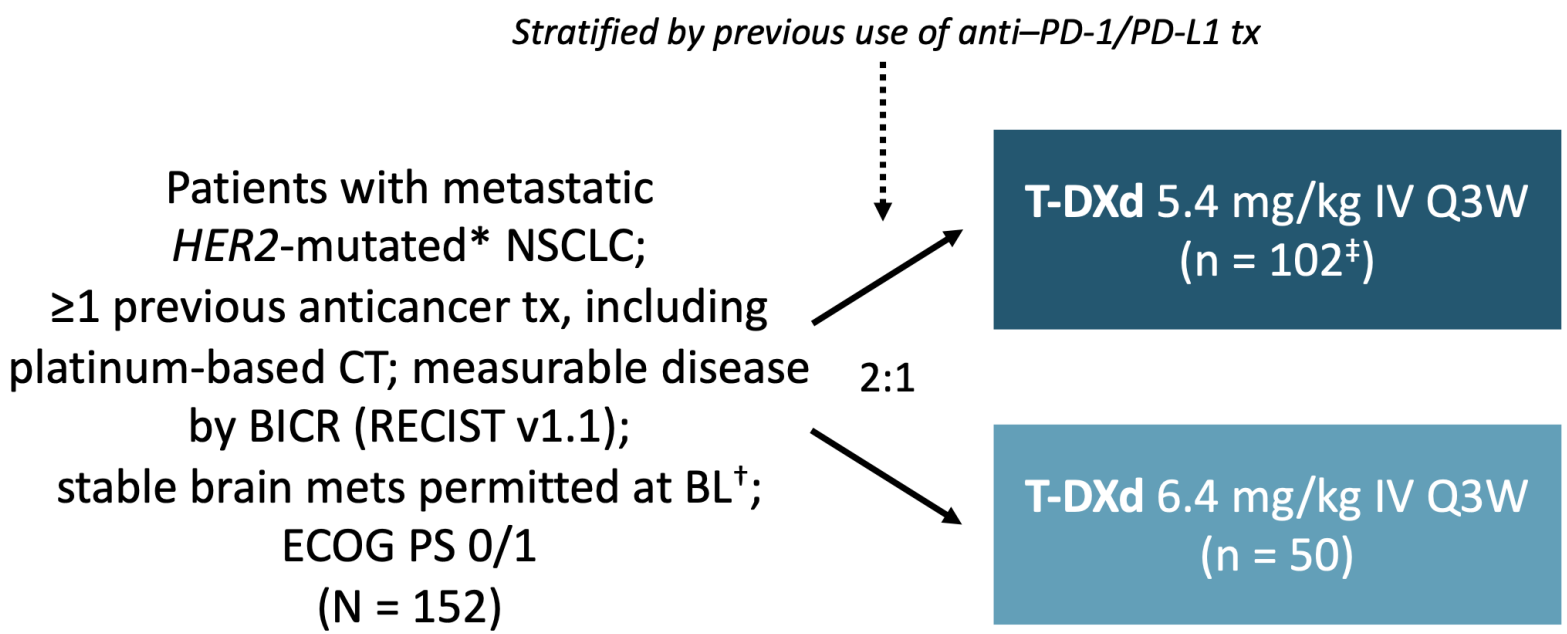
Activating *HER2* mutations are an actionable biomarker for patients with advanced NSCLC based on the accelerated approval of trastuzumab deruxtecan

***HER2* Amplification: 2%-5%**

Detection: FISH (*HER2*/*CEP17* ratio >2 and/or HER2 copy number >6)

DESTINY-Lung02: Trastuzumab Deruxtecan in *HER2*-Mutated NSCLC

- Primary analysis of international, randomized, double-blind, noncomparative phase II trial (data cutoff: December 23, 2022)[1-3]

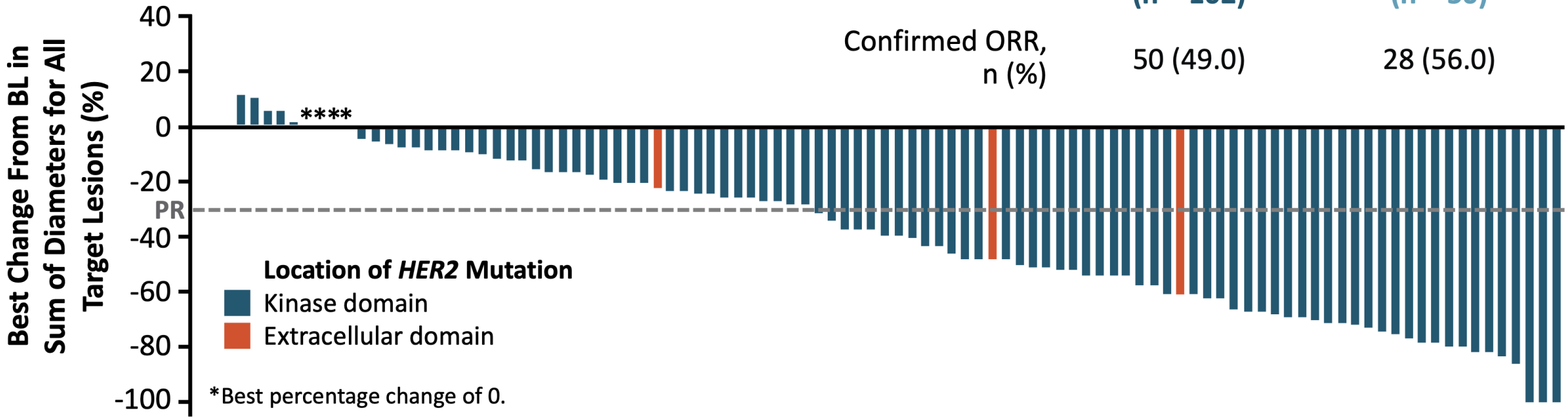


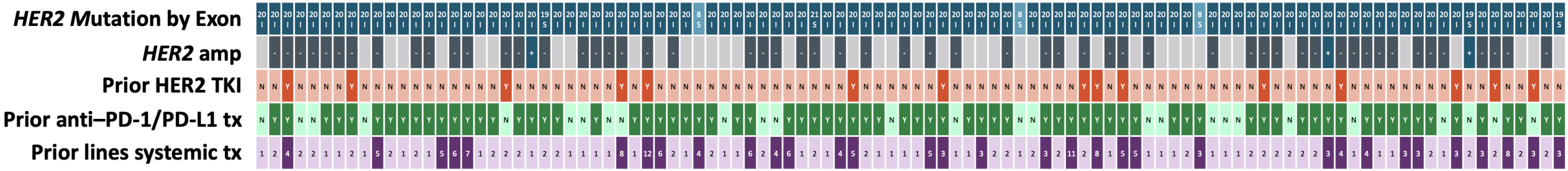
*Identified in fresh/archival tumor tissue. †Must be asymptomatic and not needing corticosteroids or anticonvulsants. ‡n = 1 did not receive treatment.

- **Primary endpoint:** confirmed ORR by BICR[1-3]
  - Hypothesis tested by comparing lower limit of 95% CI for each T-DXd dose vs benchmark ORR of 26.4% (upper limit of ORR 95% CI observed with ramucirumab + docetaxel in REVEL trial)[4]
  - Not statistically powered to compare between arm
- **Secondary endpoints:** ORR by inv; DoR, DCR, and PFS by BICR and inv; OS; safety[1-3]

DESTINY-Lung02: Antitumor Activity With T-DXd 5.4 mg/kg Q3W

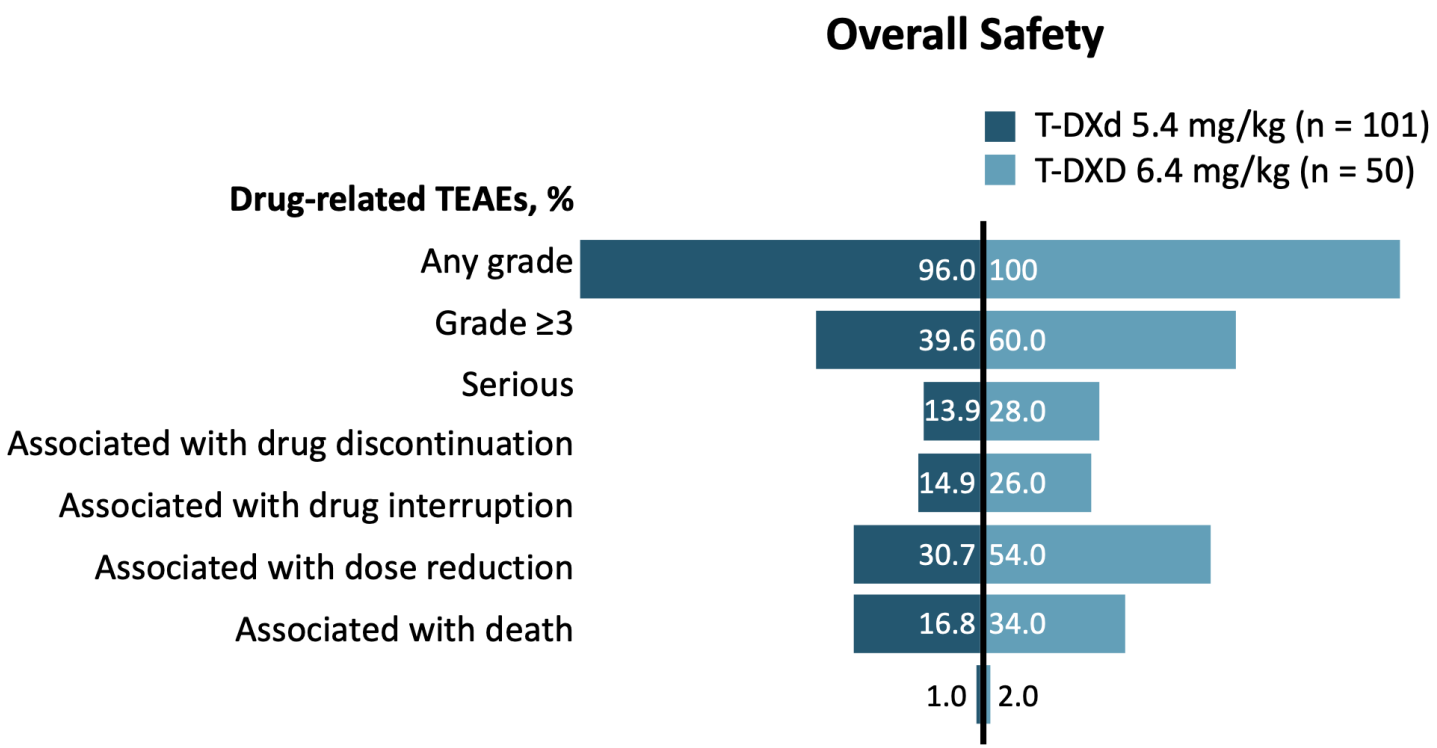
	T-DXd 5.4 mg/kg (n = 102)	T-DXd 6.4 mg/kg (n = 50)
Confirmed ORR, n (%)	50 (49.0)	28 (56.0)





- Responses observed independent of prior tx type, no. of prior lines of tx, or presence of baseline CNS disease

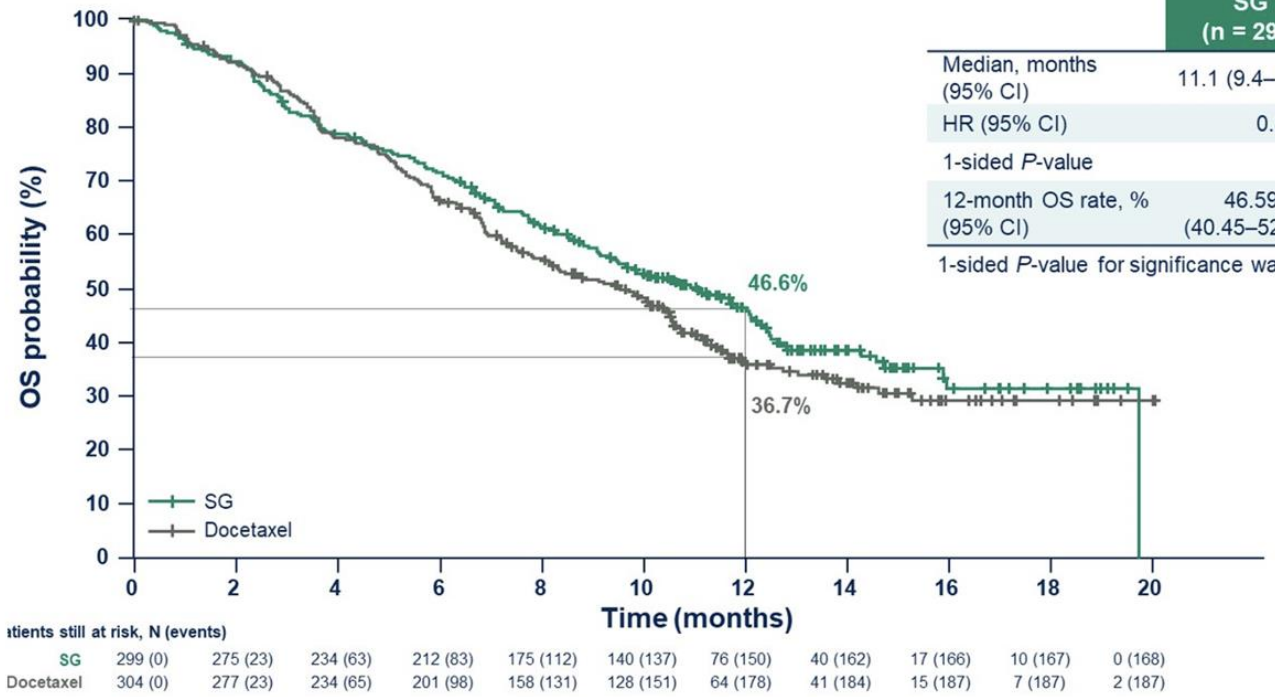
DESTINY-Lung02 Final Analysis: Safety Summary



Safety, %	T-DXd 5.4 mg/kg (n = 102)	T-DXd 6.4 mg/kg (n = 50)
Common drug-related TEAEs	65.3	78.0
▪ Nausea	42.6	56.0
▪ Neutropenia	37.6	46.0
▪ Fatigue	--	46.0
▪ Decreased appetite		
Grade ≥3 hematologic events	18.8	38.0
▪ Neutropenia	11.9	16.0
▪ Anemia	5.9	14.0
▪ Thrombocytopenia	5.9	16.0
▪ Leukopenia		

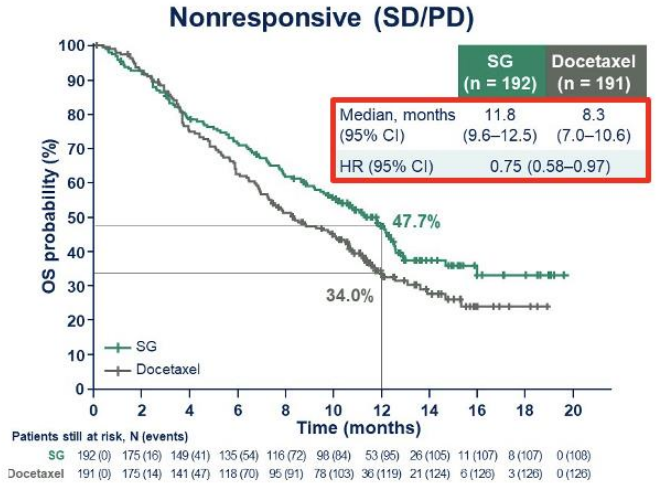
Sacituzumab govitecan

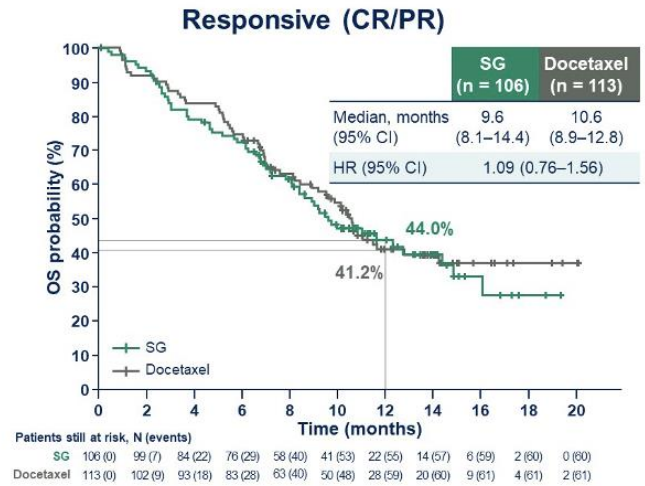
Phase 3 EVOKE-01 Trial – did not meet OS endpoint but potential signal observed in IO nonresponsive (SD/PD) subset



	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 $P \leq 0.0223$



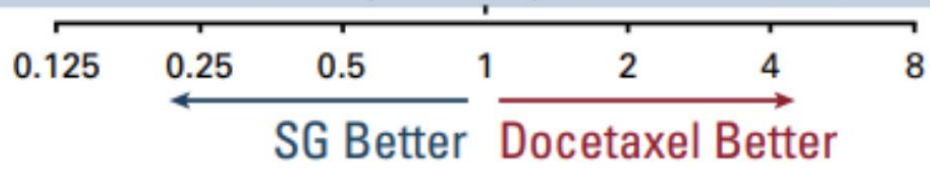


Paz-Ares et al. ASCO 2024

Sacituzumab Govitecan Versus Docetaxel for Previously Treated Advanced or Metastatic Non–Small Cell Lung Cancer: The Randomized, Open-Label Phase III EVOKE-01 Study

B

Subgroup	OS Median, Months (95% CI) SG	Docetaxel	HR (95% CI)
Overall (N = 603)	11.1 (9.4 to 12.3)	9.8 (8.1 to 10.6)	0.84 (0.68 to 1.04)
Histology[a]			
Squamous (n = 164)	10.2 (8.1 to 12.7)	9.2 (6.9 to 11.0)	0.83 (0.56 to 1.22)
Nonsquamous (n = 439)	11.3 (9.4 to 12.6)	9.9 (7.8 to 10.8)	0.87 (0.68 to 1.11)
Response to last anti–PD-(L)1–containing regimen[a]			
Nonresponder (PD/SD) (n = 383)	11.8 (9.6 to 12.5)	8.3 (7.0 to 10.6)	0.75 (0.58 to 0.97)
Responder (CR/PR) (n = 219)	9.6 (8.1 to 14.4)	10.6 (8.9 to 12.8)	1.09 (0.76 to 1.56)
Received previous therapy for actionable genomic alteration[a]			
No (n = 559)	11.0 (9.2 to 12.3)	9.9 (8.1 to 10.7)	0.89 (0.72 to 1.11)
Yes (n = 44)	NR (7.2 to NR)	7.0 (5.2 to 11.6)	0.52 (0.22 to 1.23)
Geographic region			
United States (n = 60)	12.2 (7.9 to NR)	7.4 (5.1 to 14.2)	0.68 (0.36 to 1.27)
Canada/western EU/Australia (n = 455)	10.8 (8.9 to 12.3)	9.8 (7.9 to 10.6)	0.87 (0.69 to 1.10)
Rest of the world (n = 88)	10.2 (7.8 to NR)	12.8 (6.4 to NR)	0.98 (0.53 to 1.83)
Age group, years			
<65 (n = 297)	12.1 (9.7 to 14.7)	10.1 (7.3 to 10.8)	0.80 (0.59 to 1.08)
≥65 (n = 306)	9.9 (8.4 to 12.2)	9.6 (7.6 to 11.2)	0.90 (0.68 to 1.20)
Race			
White (n = 445)	10.7 (8.9 to 12.2)	8.9 (7.3 to 10.6)	0.87 (0.68 to 1.10)
Non-White (n = 65)	12.9 (12.9 to NR)	11.2 (9.3 to 15.3)	0.41 (0.15 to 1.13)
Baseline ECOG status			
0 (n = 190)	12.9 (10.0 to NR)	13.6 (10.4 to NR)	1.06 (0.70 to 1.60)
1 (n = 410)	9.6 (8.1 to 11.9)	7.6 (6.8 to 9.8)	0.81 (0.64 to 1.04)
Sex			
Male (n = 410)	9.5 (8.1 to 12.3)	8.5 (7.3 to 10.2)	0.89 (0.70 to 1.14)
Female (n = 193)	12.1 (10.6 to 16.0)	10.6 (8.2 to 13.9)	0.85 (0.58 to 1.26)



Paz-Ares JCO 2024

Sacituzumab govitecan

- Great DAR of 7
- Soluble payload
- Prior safety in breast cancer
- Target?

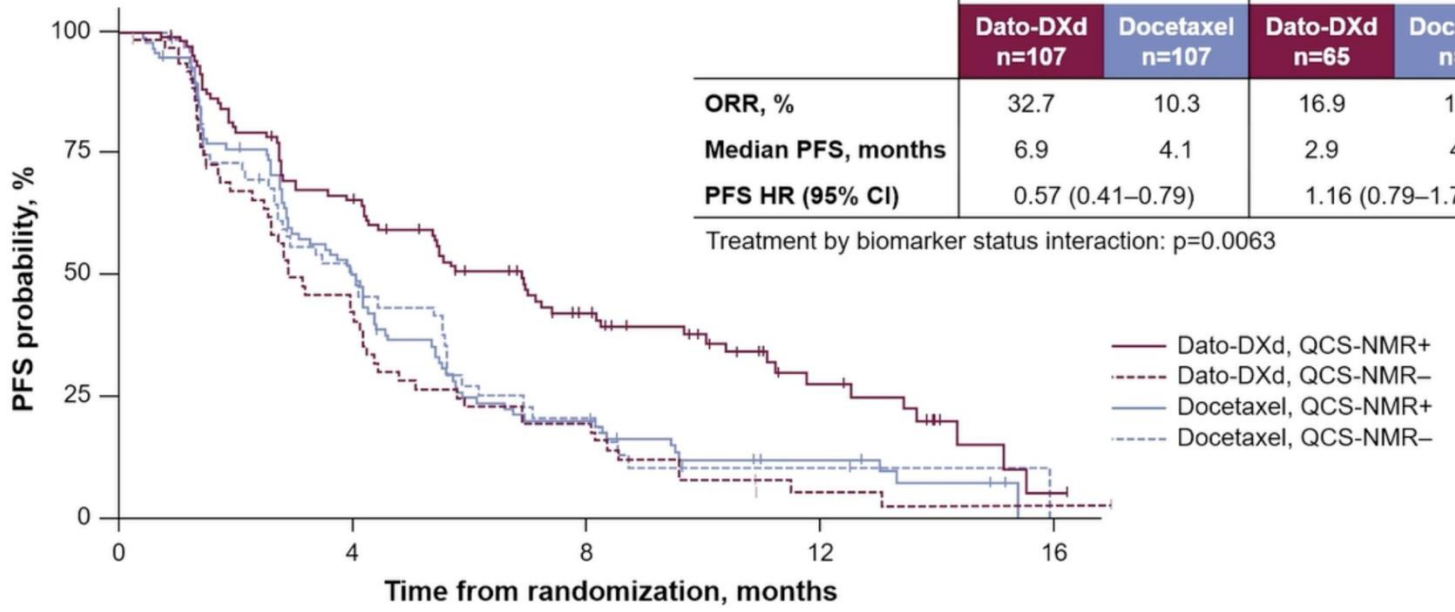
Overall BEP: Efficacy by TROP2 QCS-NMR Status

TROP2 QCS-NMR positivity is predictive for longer PFS with Dato-DXd in the biomarker-evaluable population

Biomarker-evaluable population, n=352

	TROP2 QCS-NMR+		TROP2 QCS-NMR–	
	Dato-DXd n=107	Docetaxel n=107	Dato-DXd n=65	Docetaxel 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)	

Treatment by biomarker status interaction: p=0.0063



Garrassino WCLC 2024

TROPION-Lung01 Study of Dato-DXd vs Docetaxel in Pretreated mNSCLC

Randomized, Phase 3, Open-Label, Global Study (NCT04656652)

Key eligibility criteria

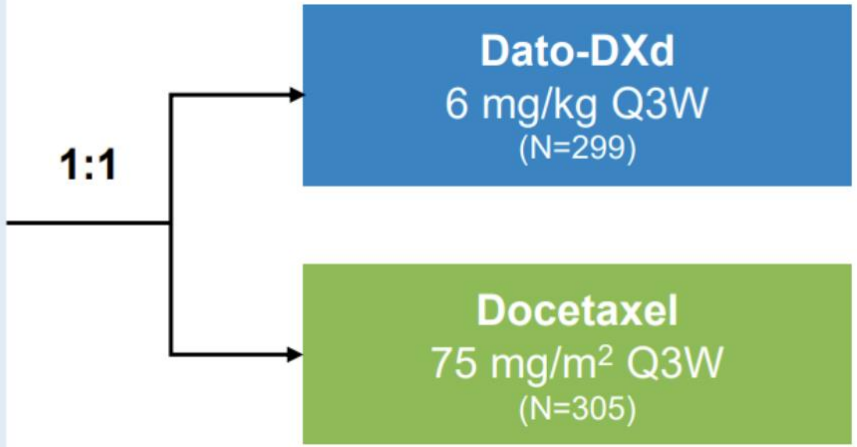
- NSCLC (stage IIIB, IIIC, or IV)
- ECOG PS of 0–1
- No prior docetaxel

Without actionable genomic alterations

- One to two prior lines, including platinum-based 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*
- One to two prior approved targeted therapies + platinum-based CT, and ≤1 anti–PD-(L)1 mAb



Dual primary endpoints

- PFS by BICR[a]
- OS

Secondary endpoints

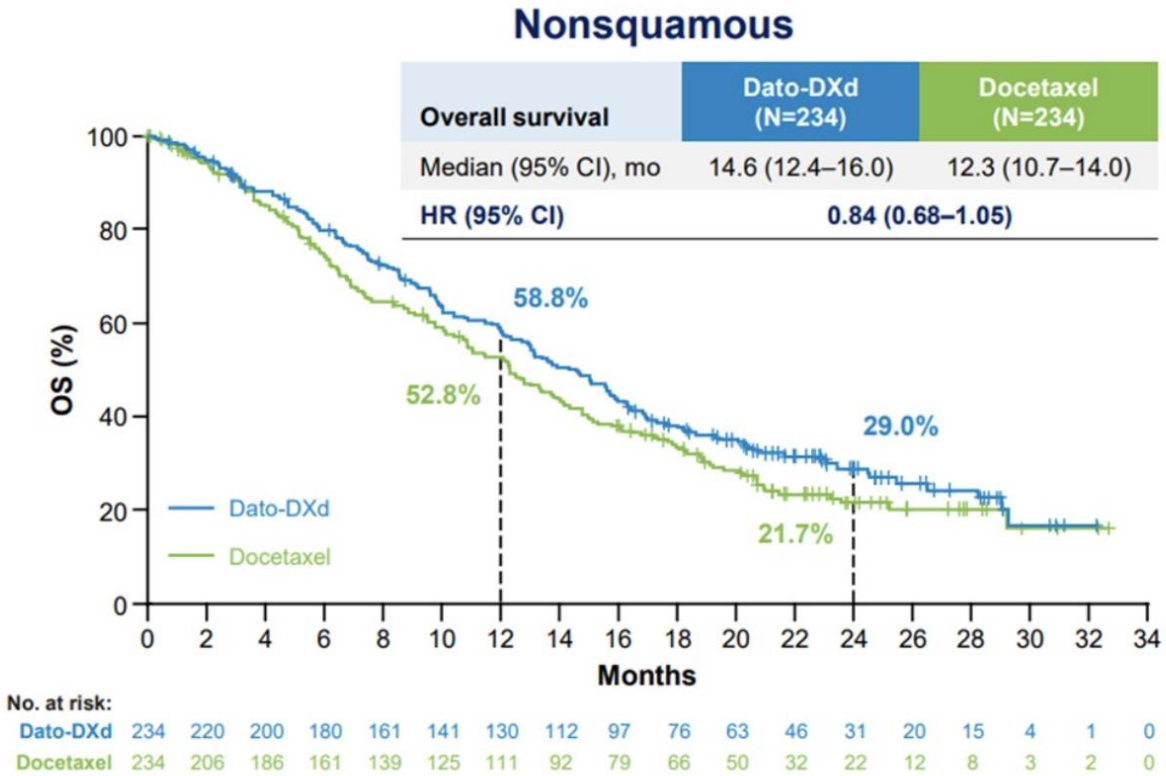
- ORR[a]
- DOR[a]
- Safety and tolerability

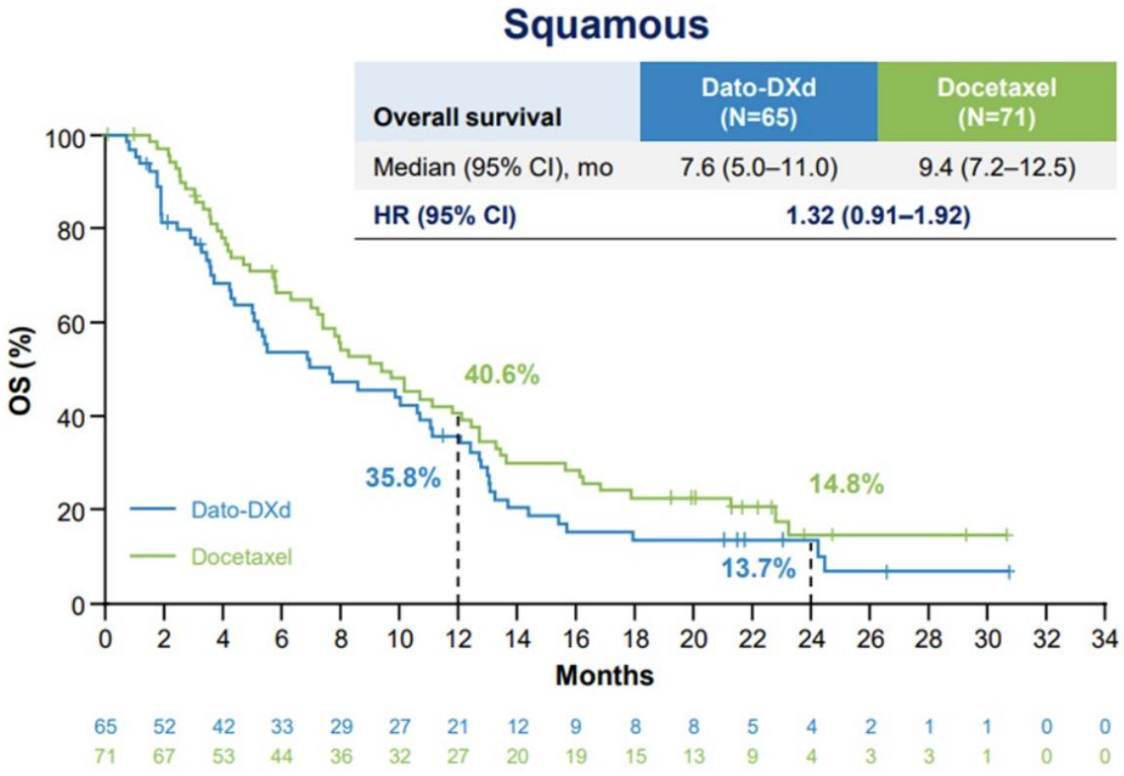
Stratified by histology (nonsquamous vs squamous), actionable genomic alteration status,[b] anti–PD-(L)1 mAb included in most recent prior therapy, and geography[c]

Statistical considerations: Study deemed positive if either of the dual primary endpoints (PFS by BICR or OS) were statistically significant; the pre-specified P-value boundary for the OS analysis was α=0.045

Sands et al WCLC 2024

TROPION LUNG01 - Overall Survival by Histology





- 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 et al WCLC 2024

Phase 3 TROPION-Lung01 Study of Dato-DXd vs Docetaxel in Pretreated mNSCLC ± AGAs: Safety and Tolerability

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

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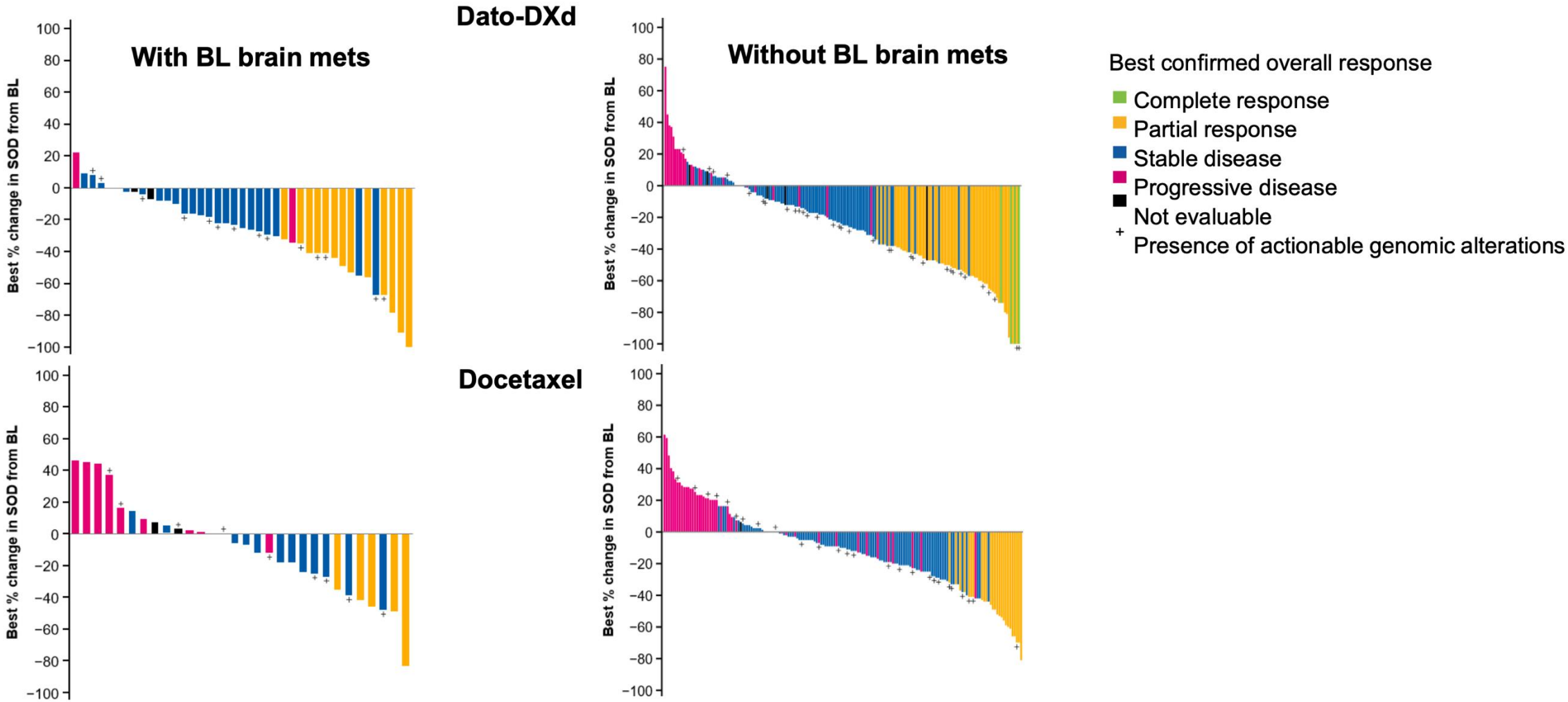
TROPION-Lung01 Brain Mets: Best Change in Sum of Diameters From Baseline

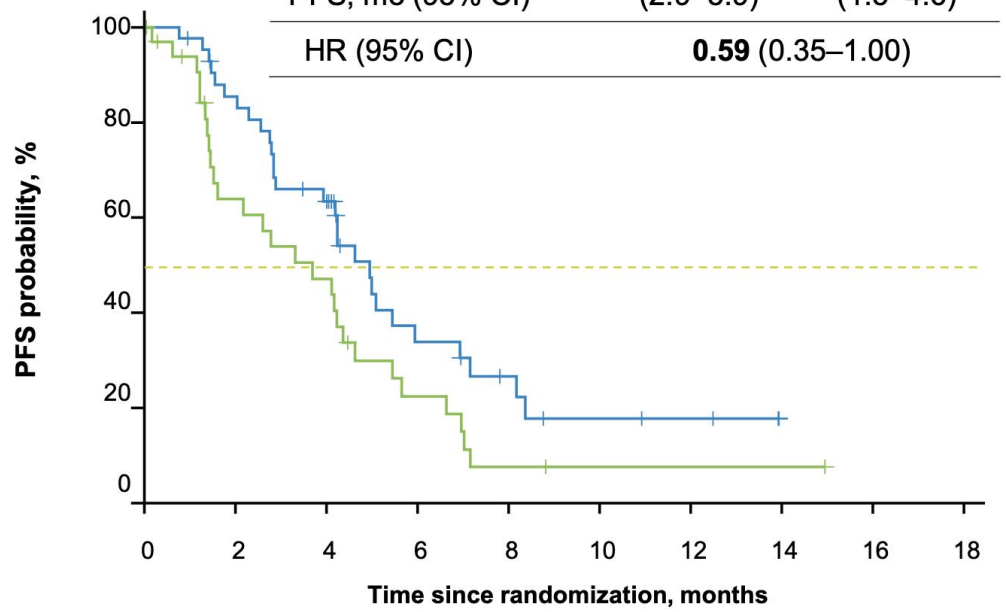


Patients with NSQ histology. Data cutoff: March 29, 2023.
BL, baseline; Dato-DXd, datopotamab deruxtecan; mets, metastases; SOD, sum of diameters.
Pons-Tostivint E, et al. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain. Poster #1312P.

TROPION-Lung01 Brain Mets: Systemic PFS by Brain Mets Status at Baseline

With BL brain mets

	Dato-DXd	Docetaxel
Median systemic PFS, mo (95% CI)	4.9 (2.9–5.9)	3.6 (1.5–4.6)
HR (95% CI)	**0.59** (0.35–1.00)	

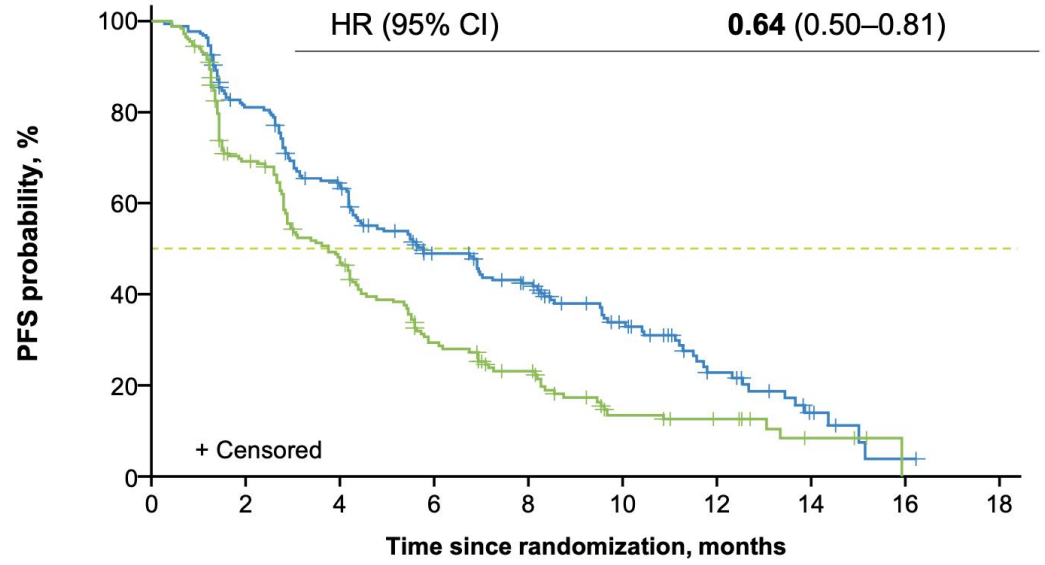


No. at risk

Dato-DXd	43	35	24	10	6	3	2	0	0	0
Docetaxel	41	19	14	6	2	1	1	1	0	0

Without BL brain mets

	Dato-DXd	Docetaxel
Median systemic PFS, mo (95% CI)	5.7 (4.3–7.9)	3.7 (2.8–4.3)
HR (95% CI)	**0.64** (0.50–0.81)	



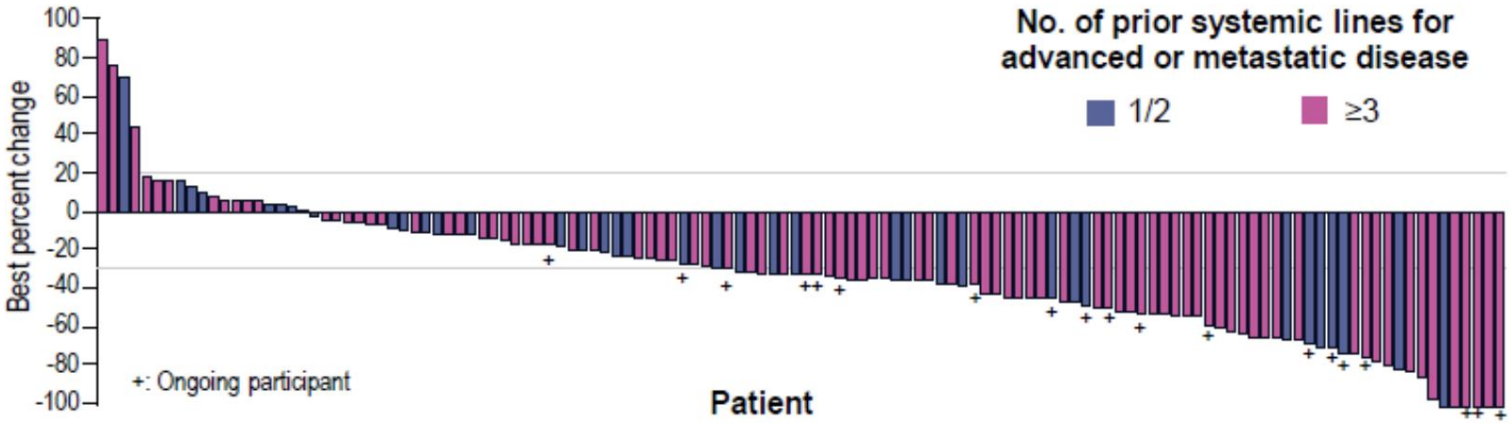
No. at risk

Dato-DXd	191	146	111	76	61	38	18	7	1	0
Docetaxel	193	117	77	44	30	13	9	3	0	0

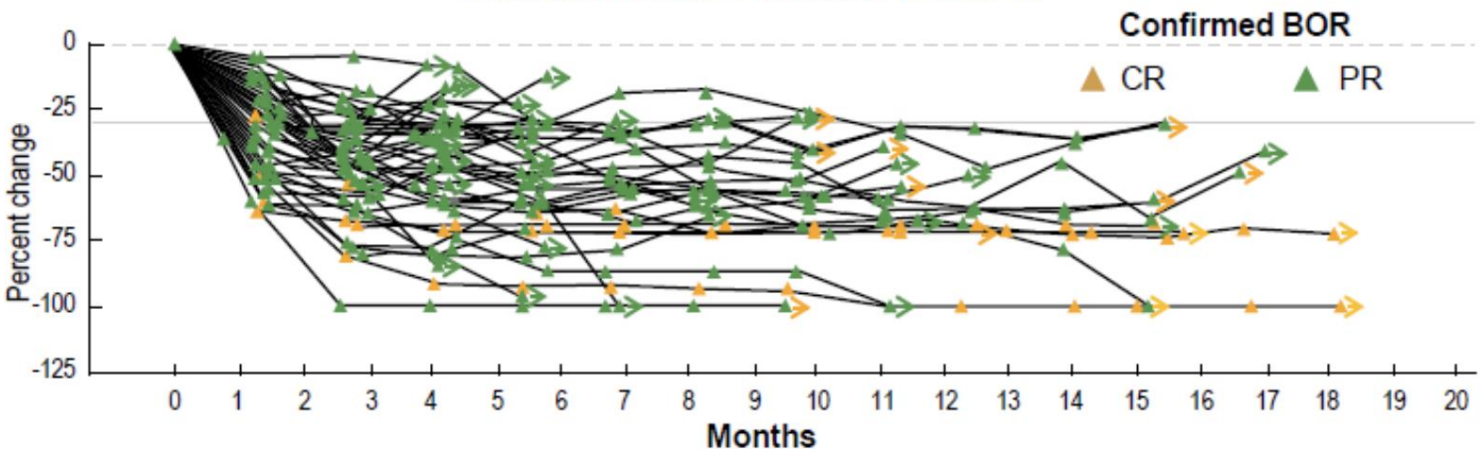
Patients with NSQ histology. Data cutoff: March 29, 2023.
BL, baseline; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; HR, hazard ratio; mets, metastases, mo, months; no, number; NSQ, nonsquamous; PFS, progression-free survival.
Pons-Tostivint E, et al. Presented at: ESMO Congress 2024; September 13-17, 2024; Barcelona, Spain. Poster #1312P.

TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer with actionable genomic alterations

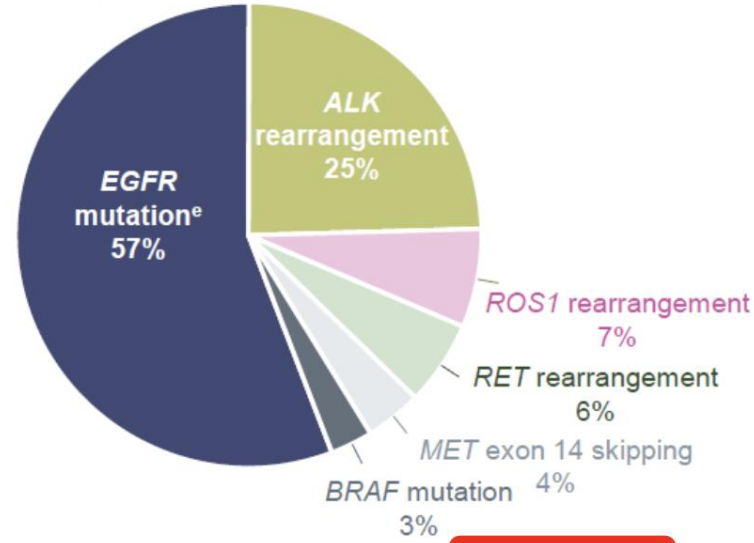
Best Percent Change From Baseline in Sum of Diameters of Target Lesions



Percent Change From Baseline in Sum of Diameters of Target Lesions in Patients With Confirmed CR/PR[c]



Relative Frequency of Genomic Alterations[b-d]



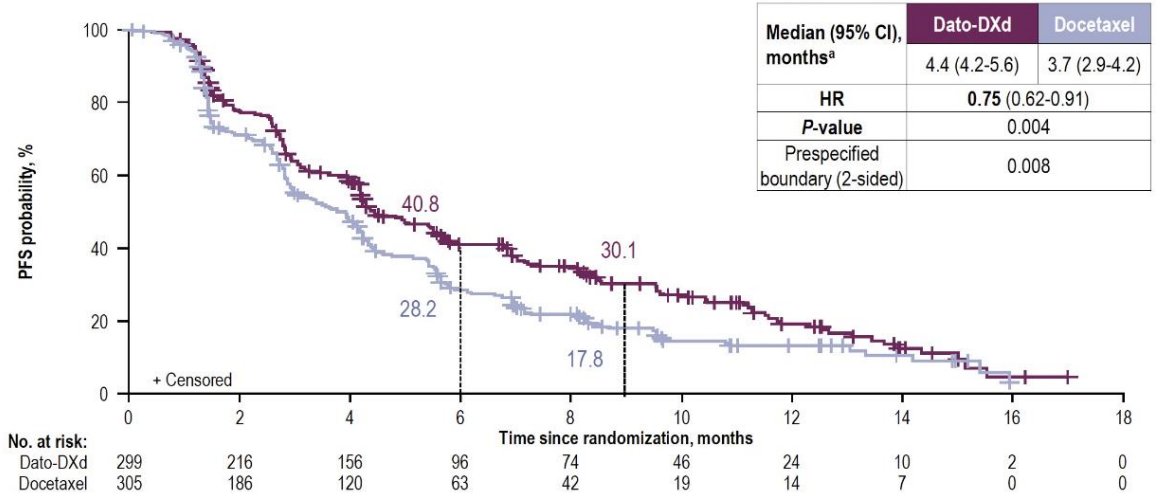
Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI][a]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, 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, (95% CI), months[b]	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 patients (3%) achieved a CR and 45 (33%) achieved a PR

***EGFR* subset:** Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib

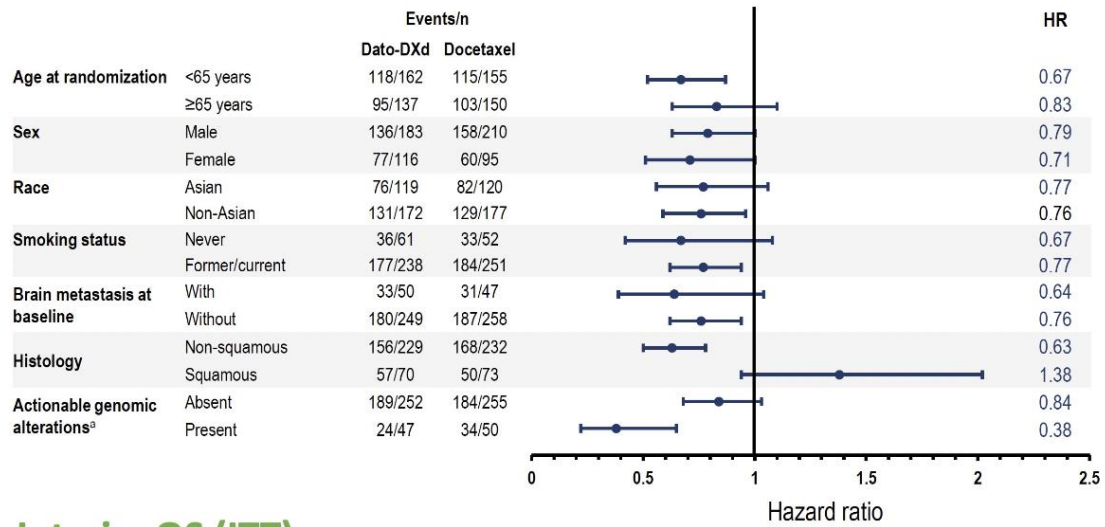
Phase 3 TROPION-Lung01 Study of Dato-DXd vs Docetaxel in Pretreated mNSCLC ± AGAs: Efficacy Outcomes from Interim Analysis

PFS (ITT)



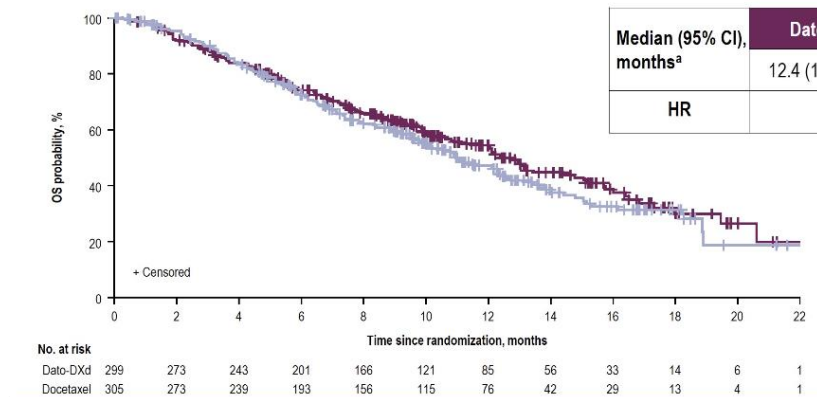
Median (95% CI), months[a]	Dato-DXd	Docetaxel
	4.4 (4.2-5.6)	3.7 (2.9-4.2)
HR	**0.75** (0.62-0.91)	
P-value	0.004	
Prespecified boundary (2-sided)	0.008	

PFS in Key Subgroups



Response	Dato-DXd (n=299)	Docetaxel (n=305)
ORR, % (95% CI)	26.4 (21.5-31.8)	12.8 (9.3-17.1)
Median DOR, months (95% CI)	7.1 (5.6-10.9)	5.6 (5.4-8.1)
Median follow-up, months	13.1	13.0

Interim OS (ITT)



Median (95% CI), months[a]	Dato-DXd	Docetaxel
	12.4 (10.8-14.8)	11.0 (9.8-12.5)
HR	**0.90** (0.72-1.13)	

Information fraction at interim analysis (events/total events required): **74%**.

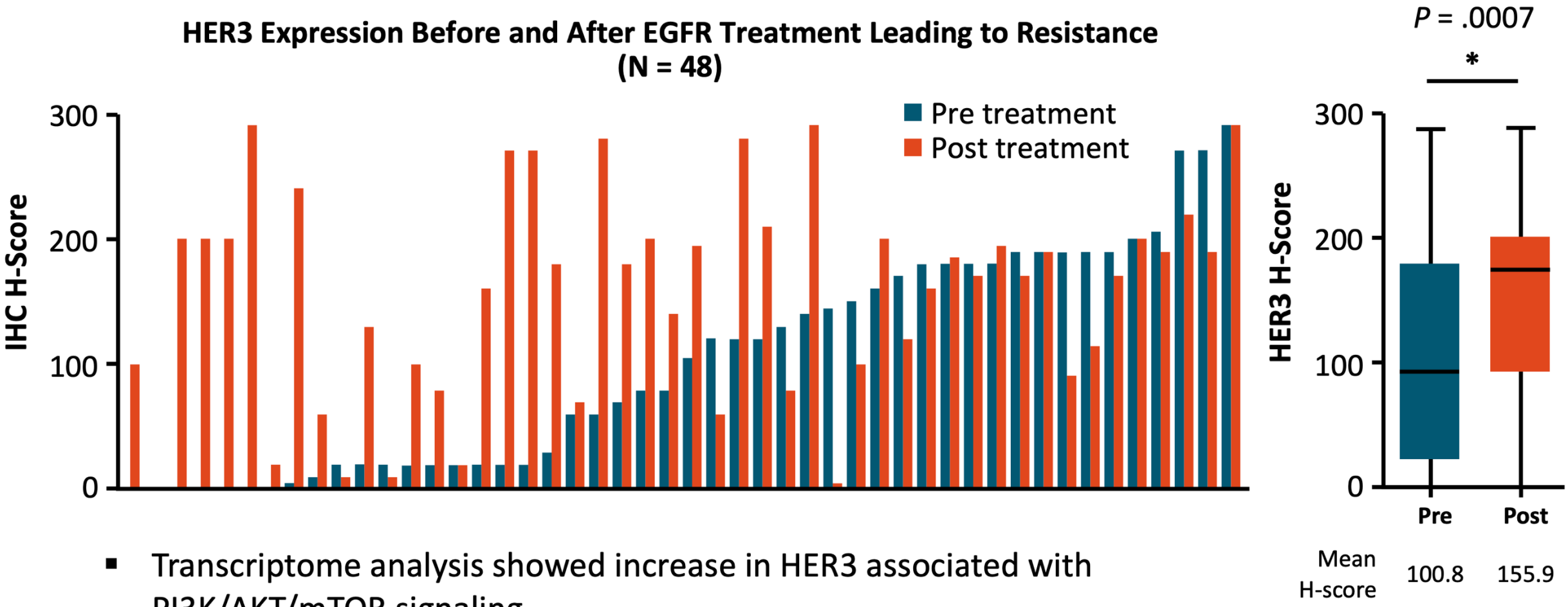
Non-squamous HR (95% CI): **0.77** (0.59-1.01); **Squamous HR** (95% CI): **1.32** (0.87-2.00)

Lisberg AE, et al. ESMO 2023. Abstract LBA12.

The Future

- Better Selection of Clinical Scenario
- Membrane permeable payloads
- High DAR

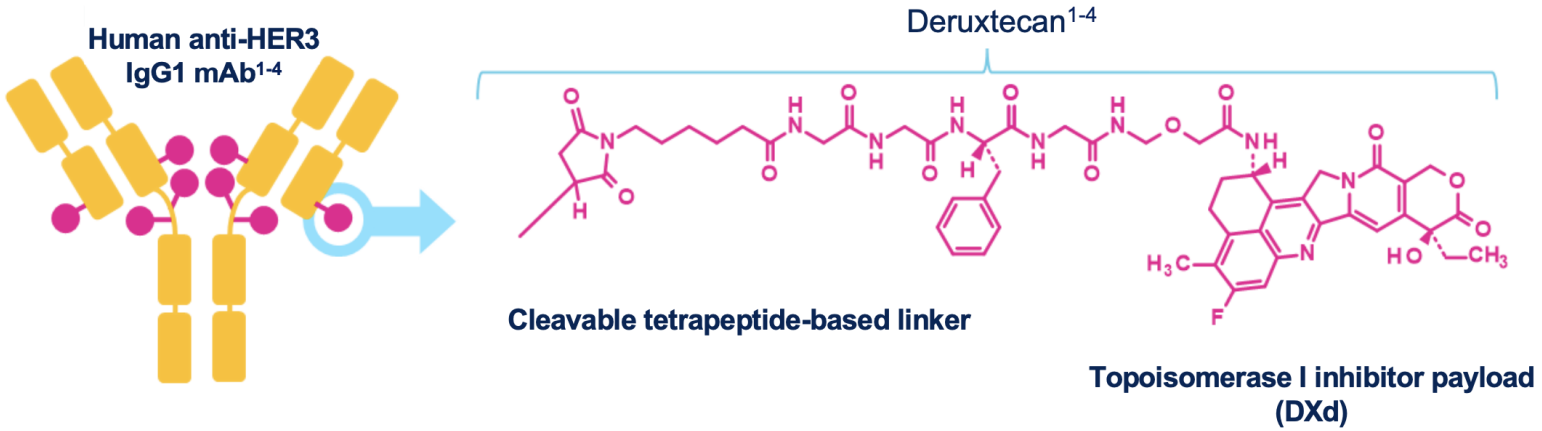
HER3 Expression Increases With Acquired EGFR TKI Resistance



- Transcriptome analysis showed increase in HER3 associated with PI3K/AKT/mTOR signaling

Patritumab Deruxtecan

- HER3-DXd is an ADC composed of 3 parts[1-4]:
  - A fully human anti-HER3 IgG1 mAb (patritumab)
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker that covalently bonds the other 2 components

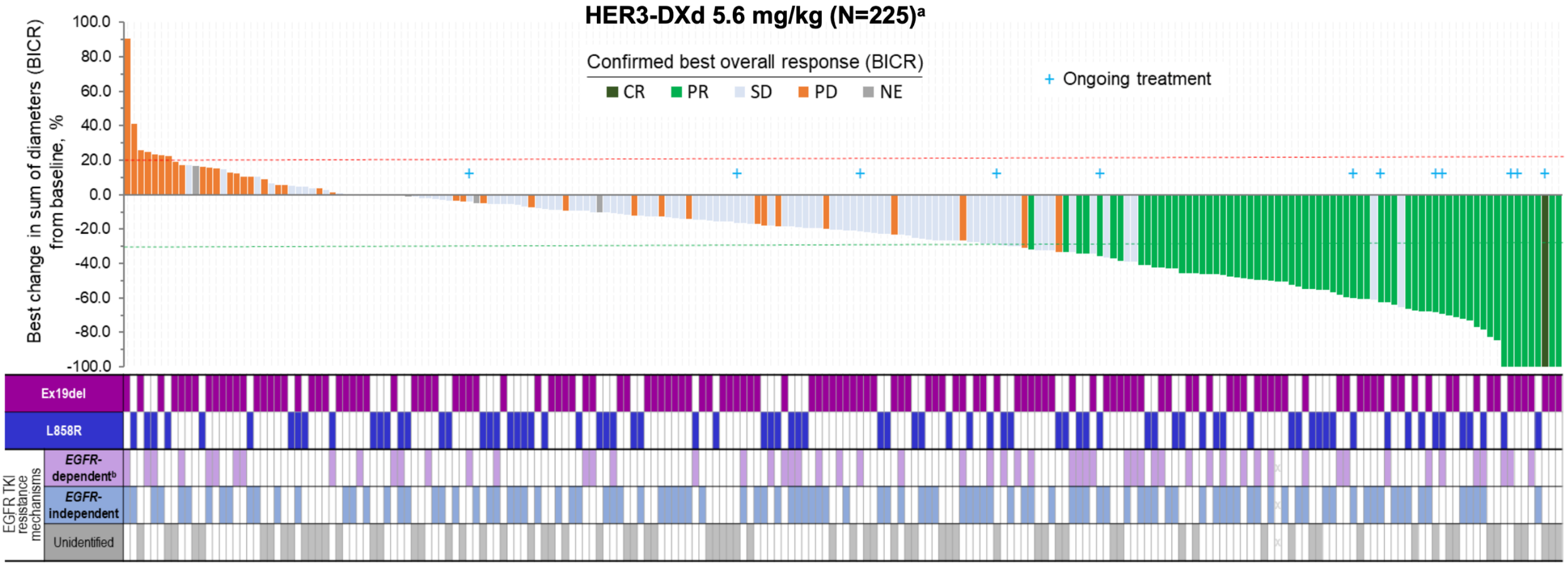


7 Key Attributes of HER3-DXd

Payload mechanism of action: topoisomerase I inhibitor[1-4,a]
High potency of payload[1-4,a]
High drug-to-antibody ratio ≈8[1,2,a]
Payload with short systemic half-life[2,3,a,b]
Stable linker-payload[2-4,a]
Tumor-selective cleavable linker[1-5,a]
Bystander antitumor effect[2,6,a]

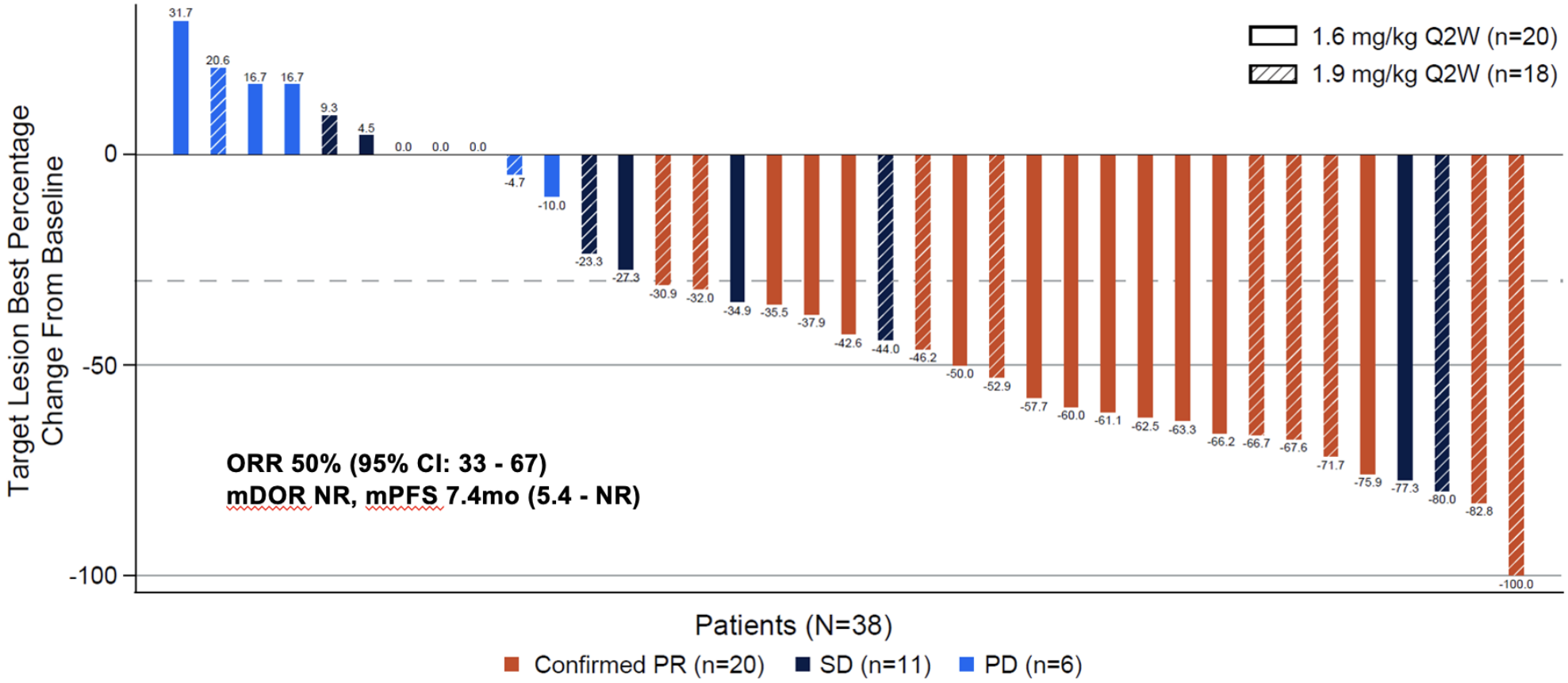
ADC, antibody-drug conjugate; HER, human epidermal growth factor receptor; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
[a] The clinical relevance of these features is under investigation. [b] Based on animal data.
1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res.* 2016;22(20):5097-5108.
4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci.* 2016;107(7):1039-1046.

Patritumab Deruxtecan in EGFRm NSCLC



Telisotuzumab vedotin (Teliso-V):

Promising efficacy of Teliso-V + osimertinib after osimertinib failure in *EGFR*m NSCLC with c-MET overexpression



Horinchini et al. ESMO Asia 2024

Thank you!