ADCs in Lung Cancer

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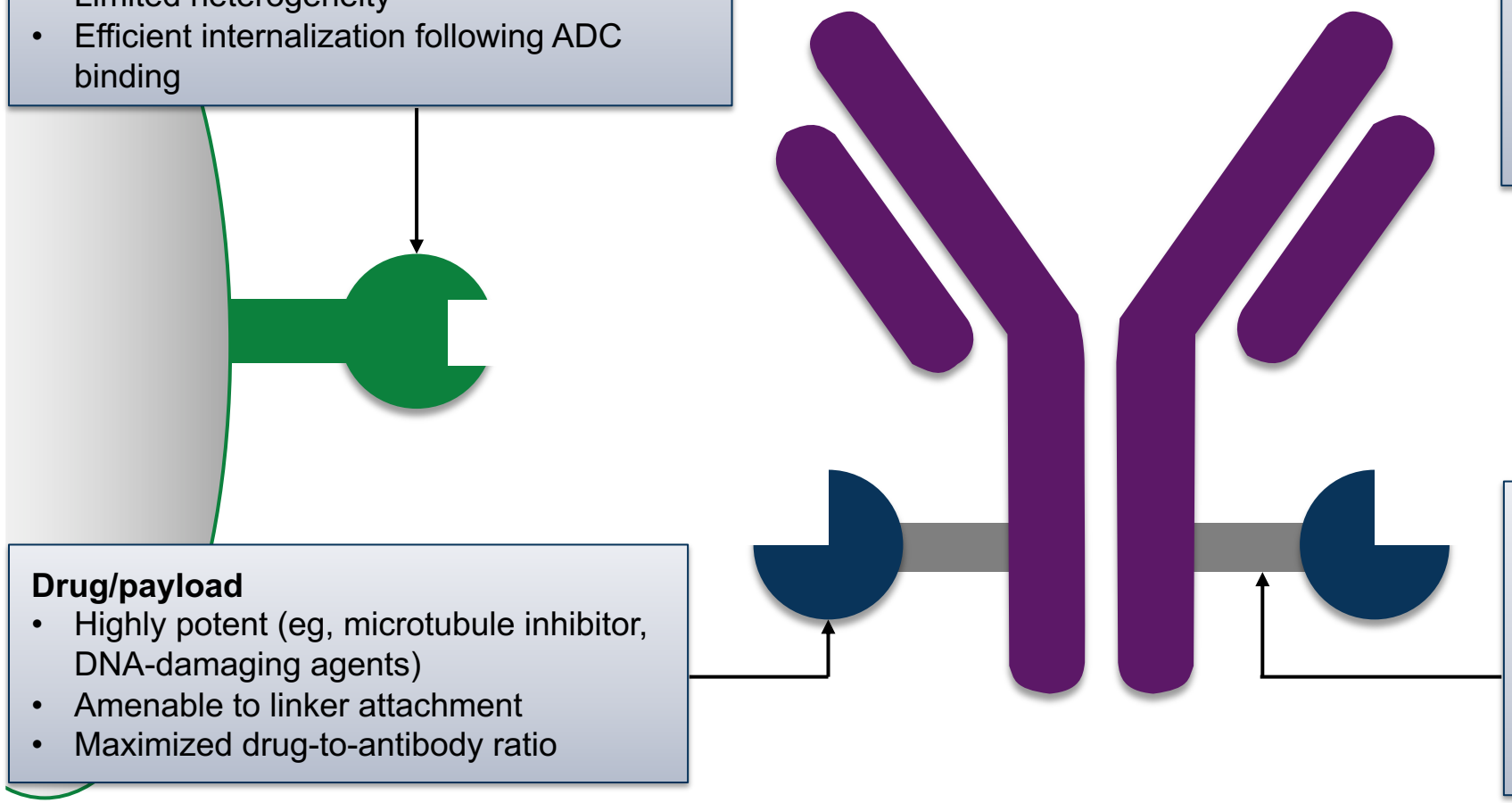
ADCs: Understanding Their Composition and Structure[1]

Antigen target/receptor
- High homogeneous expression in tumor
- Limited/absent expression in normal tissue
- Limited heterogeneity
- Efficient internalization following ADC binding

Antibody
- High affinity and avidity for target antigen
- Long half-life
- Conjugation sites with minimal impact on ADC stability, internalization, and PK (eg, cysteine, lysine)
- Chimeric or humanized (decreasing immunogenicity)



Drug/payload
- Highly potent (eg, microtubule inhibitor, DNA-damaging agents)
- Amenable to linker attachment
- Maximized drug-to-antibody ratio

Linker
- Controlled release of payload
  - Noncleavable (eg, lysosomal degradation of mAb)
  - Cleavable (eg, acid/redox/lysosomal sensitive)

1. Marks S, Naidoo J. *Lung Cancer*. 2022;163:59-68.

ADC in Development in Cancer

Drug		Target	Linker	Payload	DAR
Trastuzumab emtansine	**T-DM1**	HER2	Noncleavable	DM1	3.5
Trastuzumab deruxtecan	**T-DXd**	HER2	Cleavable	DXd	8
A166		HER2	Cleavable	Duostatin-5	-
Sacituzumab govitecan	**SG**	TROP 2	Cleavable	SN-38	7.6
Datopotamab-deruxtecan	**Dato-DXd**	TROP 2	Cleavable	DXd	4
Telisotuzumab vedotin	**Teliso-V**	MET	Cleavable	MMAE	3.1
Cofetuzumab pelidotin		PTK7	Cleavable	Aur0101	4
Anetumab ravtansine		Mesothelin	Cleavable	DM4	3.2
MGC018		B7-H3	Cleavable	Duocarmycin	2.7
Tisotumab vedotin		Tissue Factor	Cleavable	MMAE	4.1
Enapotamab vedotin	**EnaV**	AXL	Cleavable	MMAE	4
MRG003		EGFR	Cleavable	MMAE	-
Patritumab deruxtecan	**HER3-DXd**	HER3	Cleavable	DXd	8
XMT-1536		NaPi2B	Cleavable	AF-HPA	10-15
Tusamitamab Ravtansine	**CEACAM5-DM4**	CEACAM5	Cleavable	MaytansinoidDM4	-

Focus on ADCs in wild type mNSCLC

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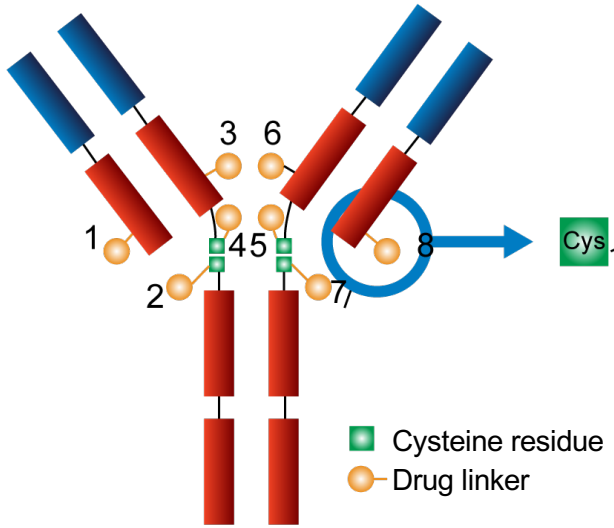
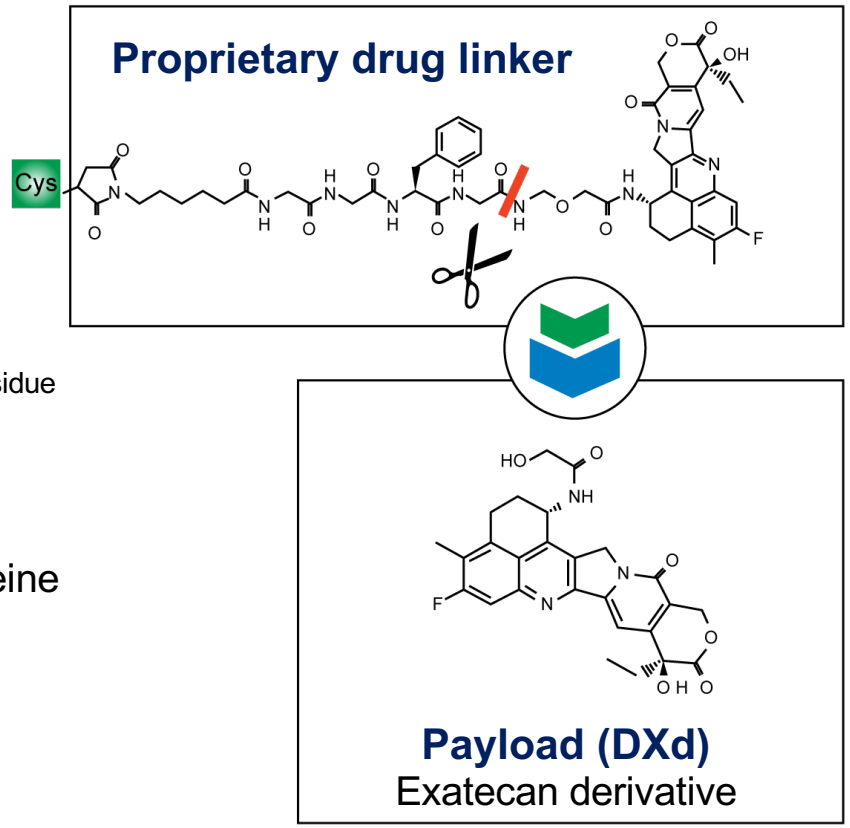
MGC018		B7-H3	Cleavable	Duocarmycin	2.7
Tisotumab vedotin		Tissue Factor	Cleavable	MMAE	4.1
Enapotamab vedotin	**EnaV**	AXL	Cleavable	MMAE	4
MRG003		EGFR	Cleavable	MMAE	-
Patritumab deruxtecan	**HER3-DXd**	HER3	Cleavable	DXd	8
XMT-1536		NaPi2B	Cleavable	AF-HPA	10-15
Tusamitamab Ravtansine	**CEACAM5-DM4**	CEACAM5	Cleavable	MaytansinoidDM4	-

Her 2 ADC

Trastuzumab Deruxtecan (T-DXd)[1-4]



Conjugation Chemistry
The linker is connected to cysteine residue of the antibody



- ADC composed of three components
  - Humanized HER2-targeted mAb
  - Topoisomerase I inhibitor "payload"
  - Tetrapeptide-based cleavable linker

- High drug-to-antibody ratio (~8:1)
- High potency payload that is membrane permeable → nearby cells in tumor targeted regardless of HER2 expression ("bystander antitumor effect")

1. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185. 2. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-5108.
3. Trail PA et al. *Pharmacol Ther*. 2018;181:126-142. 4. Ogitani Y et al. *Cancer Sci*. 2016;107:1039-1046.

DESTINY-Lung01: Study Design[1,2]

- Unresectable/metastatic nonsquamous NSCLC
- Relapsed/refractory to standard treatment
- Measurable disease by RECIST v1.1
- Asymptomatic CNS metastases at baseline[a]
- ECOG PS 0 or 1
- Locally reported *HER2* mutation (cohort 2)[b]

→ **Cohort 1[c]** (n = 49)
HER2 overexpressing
(IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg Q3W

Cohort 1a[c] (n = 41)
HER2 overexpressing
(IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg Q3W

→ **Cohort 2** (n = 42)
***HER2* mutated**
T-DXd 6.4 mg/kg Q3W

Cohort 2 (n = 49)
***HER2* mutated**
T-DXd 6.4 mg/kg Q3W

- **Primary endpoint:** confirmed ORR by ICR[d]
- **Secondary endpoints:** DOR, PFS, OS, DCR, and safety
- **Exploratory endpoint:** biomarkers of response

[a] Patients with asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy were allowed to enroll. [b] *HER2* mutation documented solely from a liquid biopsy could not be used for enrollment. [c] HER2 overexpression without known *HER2* mutation was assessed by local assessment of archival tissue and centrally confirmed.
[d] Per RECIST v1.1.

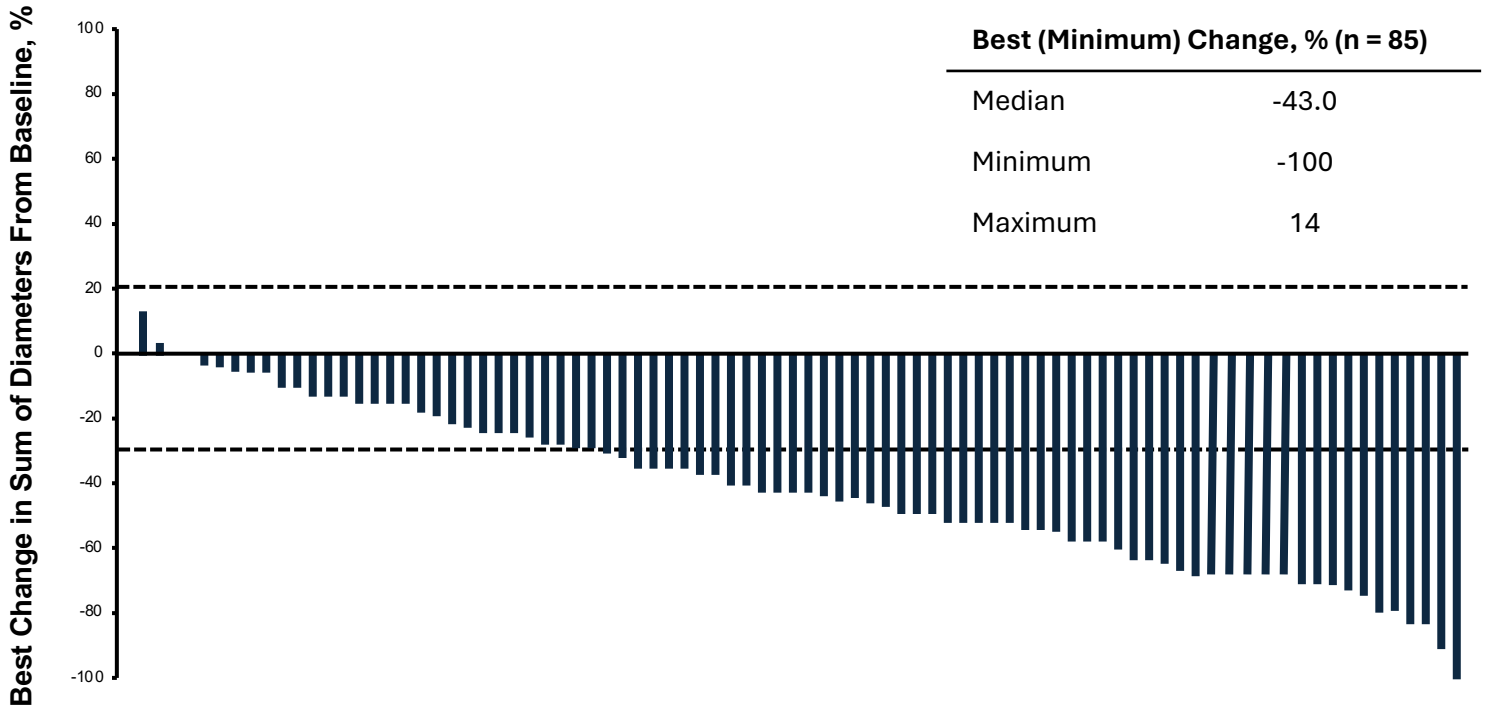
1. https://clinicaltrials.gov/ct2/show/NCT03505710. 2. Li BT et al. *N Engl J Med*. 2022;386:241-251.

DESTINY-Lung01 Cohort 2 (*HER2*-Mutated NSCLC): Updated Efficacy Results[1]

Updated data: 7 mo additional follow-up

- Confirmed ORR by ICR in overall population: 54.9% (95% CI, 44.2%-65.4%)
- Median DOR in overall population: 10.6 mo
- Median DOR 14.1 mo (95% CI, 5.9-NE mo) with ≤2 prior lines of therapy vs 5.8 mo (95% CI, 4.2-12.0 mo) with >2 prior lines

Best Percentage Change From Baseline in Target Lesions by ICR for the Overall NSCLC *HER2*m Population (DCO December 3, 2021)



1. Li B et al. ESMO 2022. Abstract 976P.

DESTINY-Lung01 Cohort 2 (*HER2*-Mutated NSCLC): Updated Safety Results[1]

Safety Summary of T-DXd in the Overall *HER2*mut NSCLC Population (DCO December 3, 2021)

n, %	Overall Population (N = 91)
Any-grade TEAEs	91 (100)
Drug-related TEAEs	88 (96.7)
Drug-related grade ≥3 TEAEs	42 (46.2)
Serious drug-related TEAEs	18 (19.8)
Drug-related TEAEs associated with	
Drug discontinuation	24 (26.4)
Dose reduction	33 (36.3)
Drug interruption	31 (34.1)
Drug-related TEAEs associated with an outcome of death	2 (2.2)

Adjudicated Drug-Related ILD in the Overall *HER2*mut NSCLC Population (DCO December 3, 2021)

	Overall Population (N = 91)
Any grade, n (%)	25 (27.5)
Grade 1	3 (3.3)
Grade 2	16 (17.6)
Grade 3	4 (4.4)
Grade 4	0
Grade 5	2 (2.2)
Median time to first onset, days (range)	125 (14-461)
Median duration, days (95% CI)	43 (29-94)
Outcome of event as reported by investigator, n (%)	
Fatal	1 (4)
Not recovered/not resolved	8 (32)
Recovering/resolved	1 (4)
Recovered/resolved with sequelae	2 (8)
Recovered/resolved	13 (52)

1. Li B et al. ESMO 2022. Abstract 976P.

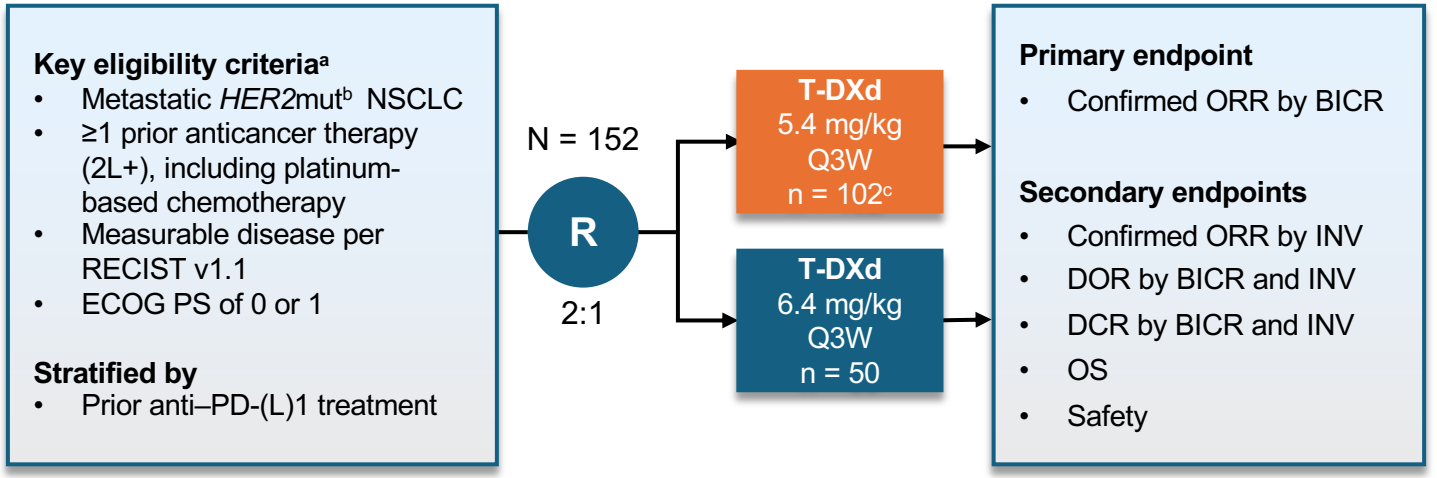
DESTINY-Lung02: Study Design[1-4]

A 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*mut mNSCLC
- DESTINY-Lung02 assessed the efficacy and safety of T-DXd 5.4 mg/kg and 6.4 mg/kg in patients with *HER2*mut mNSCLC
  - In the interim analysis, T-DXd showed deep and durable responses and an acceptable and generally manageable safety profile[3]
- Following are the **primary analysis results** of DESTINY-Lung02

Study Design

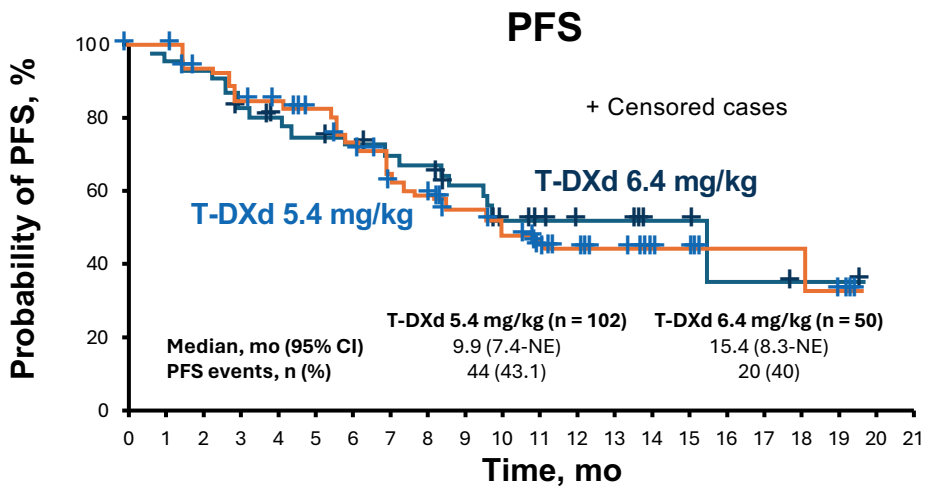


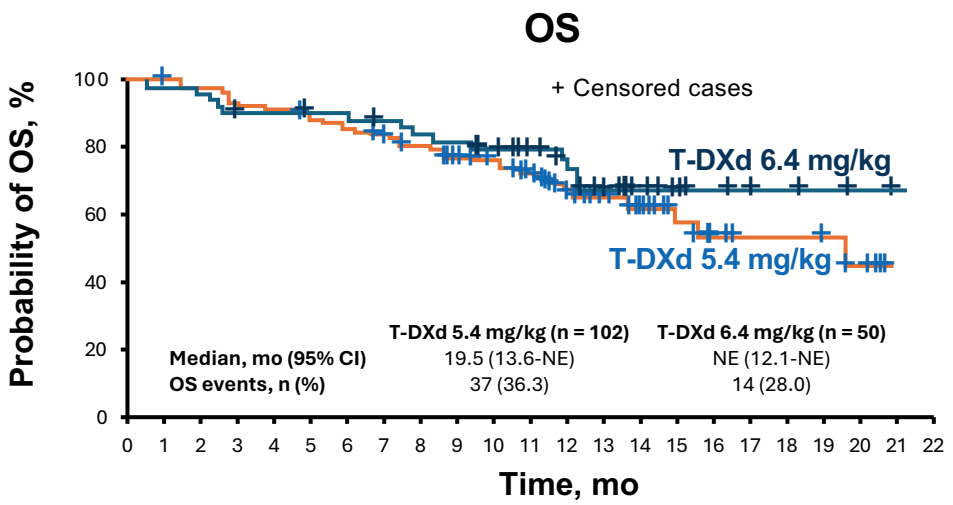
Statistical considerations

- 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 a benchmark ORR of 26.4% (upper limit of the ORR 95% CI in the ramucirumab plus docetaxel arm of the REVEL trial)[4]
- The study was not powered to statistically compare between arms

DESTINY-Lung02: Baseline Characteristics and Efficacy Summary[1,2]

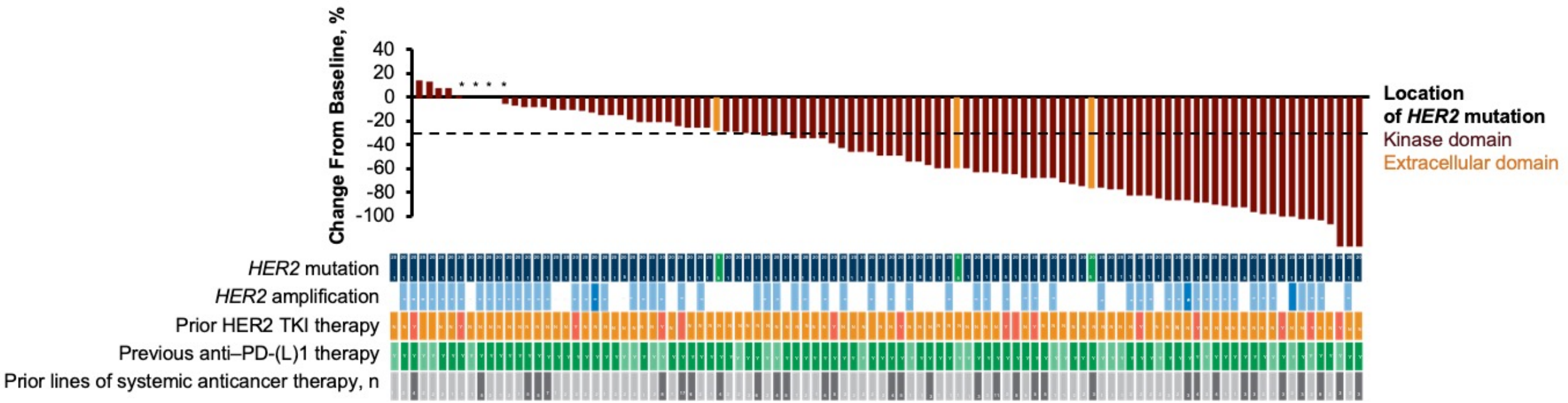
Response Assessed by BICR	T-DXd 5.4 mg/kg (n = 102)	T-DXd 6.4 mg/kg (n = 50)
Confirmed ORR, n (%) [95% CI]	50 (49.0) [39.0-59.1]	28 (56.0) [41.3-70.0]
CR	1 (1.0)	2 (4.0)
SD	45 (44.1)	18 (36.0)
Nonevaluable	3 (2.9)	2 (4.0)
DCR, n (%) [95% CI]	95 (93.1) [86.4-97.2]	46 (92.0) [80.8-97.8]
Median DOR, mo(95% CI)	16.8 (6.4-NE)	NE (8.3-NE)
Median TTIR, mo (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Median Follow-up, mo (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)





1. Jänne P et al. WCLC 2023. Abstract MA13.10. 2. Goto K et al. *J Clin Oncol.* 2023;41:4852-4863.

DESTINY-Lung02: Best Percentage Change in Tumor Size by BICR With T-DXd 5.4 mg/kg (N = 102)[1,2]

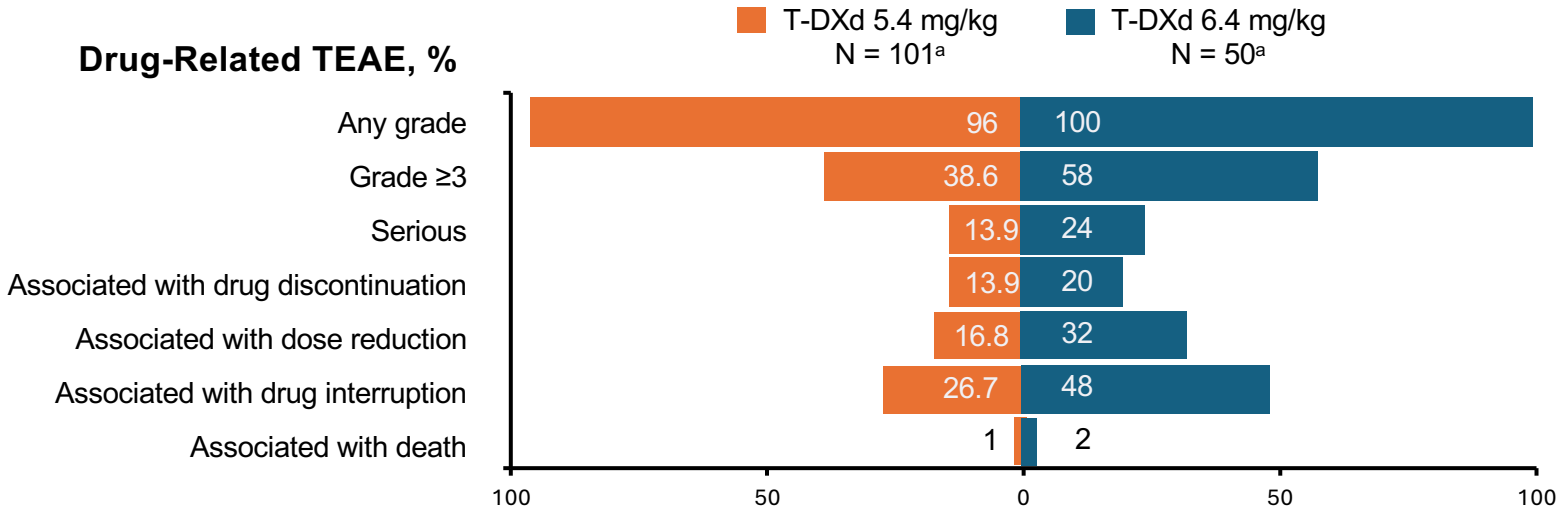


Responses were observed regardless of *HER2* mutation type, *HER2* amplification status, and number or type of prior therapies

1. Jänne P et al. WCLC 2023. Abstract MA13.10. 2. Goto K et al. *J Clin Oncol.* 2023;41:4852-4863.

DESTINY-Lung02: Overall Safety Summary[1,2]

Overall Safety



Adjudicated Drug-Related ILD

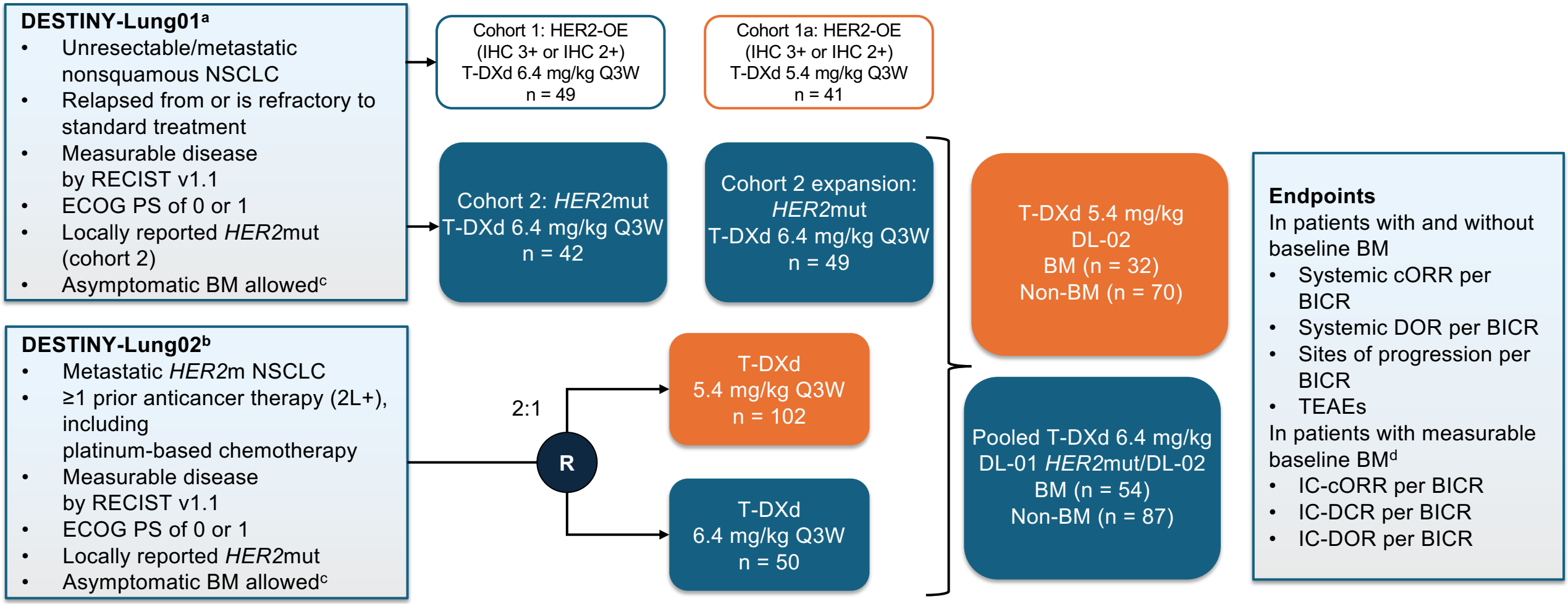
Adjudicated as Drug-Related ILD	T-DXd 5.4 mg/kg (n = 101[a])	T-DXd 6.4 mg/kg (n = 50[a])
Any grade, n (%)	**13 (12.9)**	**14 (28)**
Grade 1	4 (4)	4 (8)
Grade 2	7 (6.9)	9 (18)
Grade 3	1 (1)	0
Grade 4	0	0
Grade 5	1 (1)	1 (2)

- **Median treatment duration** was 7.7 mo (range, 0.7-20.8) with T-DXd 5.4 mg/kg and 8.3 mo (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%)

[a] The safety analysis set included all randomly assigned patients who received ≥1 dose of study drug.

1. Jänne P et al. WCLC 2023. Abstract MA13.10. 2. Goto K et al. *J Clin Oncol.* 2023;41:4852-4863.

Exploratory Pooled Brain Metastases Analyses[1] of DESTINY-Lung01[2,3] and DESTINY-Lung02[4]



[a] Data cutoff: December 3, 2021. [b] Data cutoff: December 23, 2022. [c] CT or MRI of the brain was required at screening; patients with asymptomatic BM at baseline were eligible if they did not need ongoing corticosteroid or anticonvulsant treatments had recovered from acute radiotherapy toxicity, and ≥2 weeks had passed since WBRT. [d] BM were considered measurable if they were ≥10 mm in 1 dimension on CT or MRI. 14/32 patients with baseline BM in DL-01 and 30/54 in DL-02 had BM that were measurable. IC responses were evaluated in measurable baseline BM per RECIST v1.1 based on CT or MRI scans every 6 wk from cycle 1 day 1; no additional scans were required for those without baseline BM unless clinically indicated.

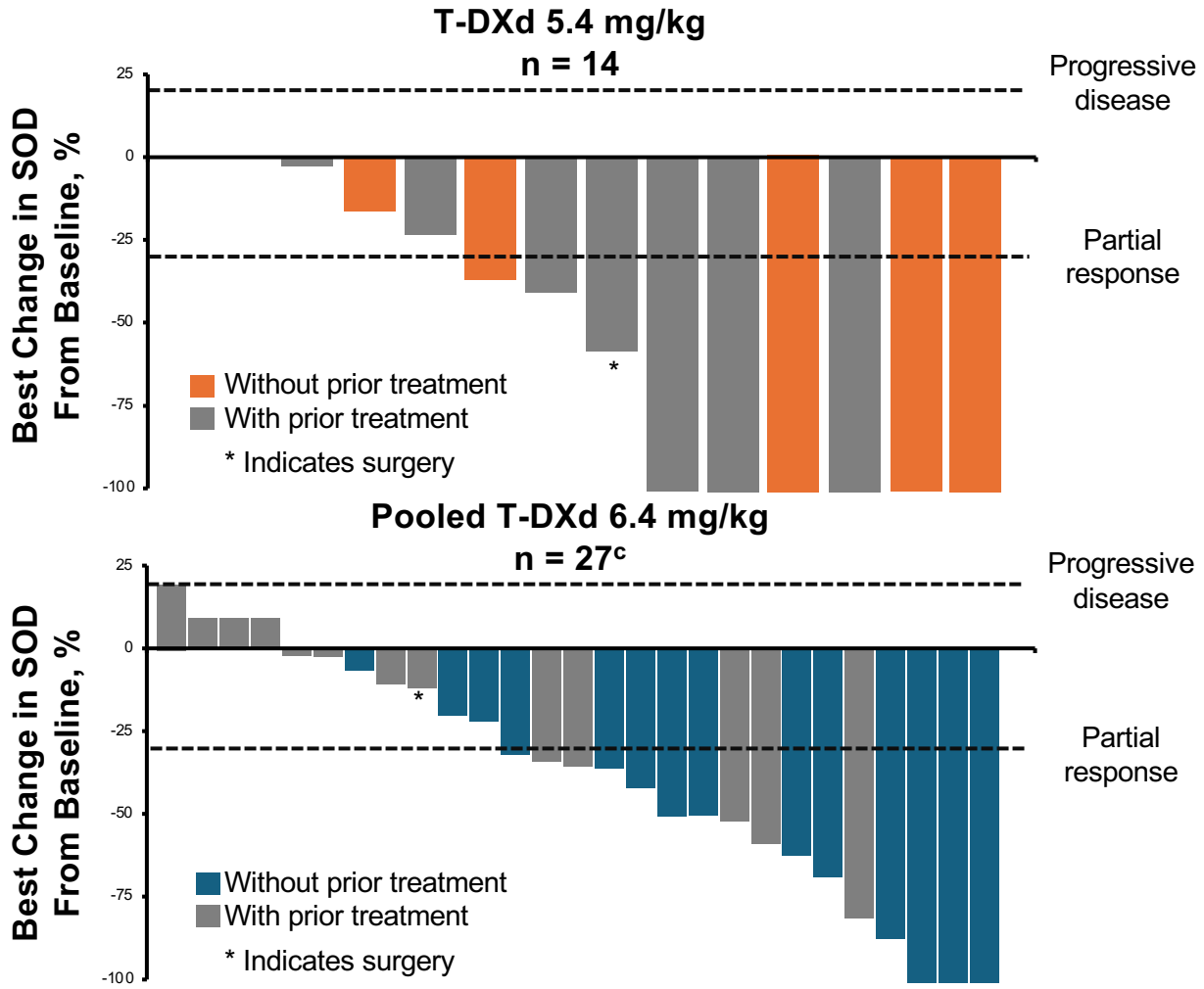
1. Li BT et al. ESMO 2023. Abstract 1321MO. 2. Li BT et al. *N Engl J Med*. 2022;386:241-251. 3. Li BT et al. ESMO 2022.

DESTINY-Lung01 and DESTINY-Lung02: IC Objective Response Rates and Best Overall Response (BICR)[1]

Measurable BM at Baseline

IC-cORR, n (%)[a]	**7 (50)**	**9 (30)**
95% CI[b]	23-77	14.7-49.4
CR	3 (21.4)	0
PR	4 (28.6)	9 (30)
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, mo[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

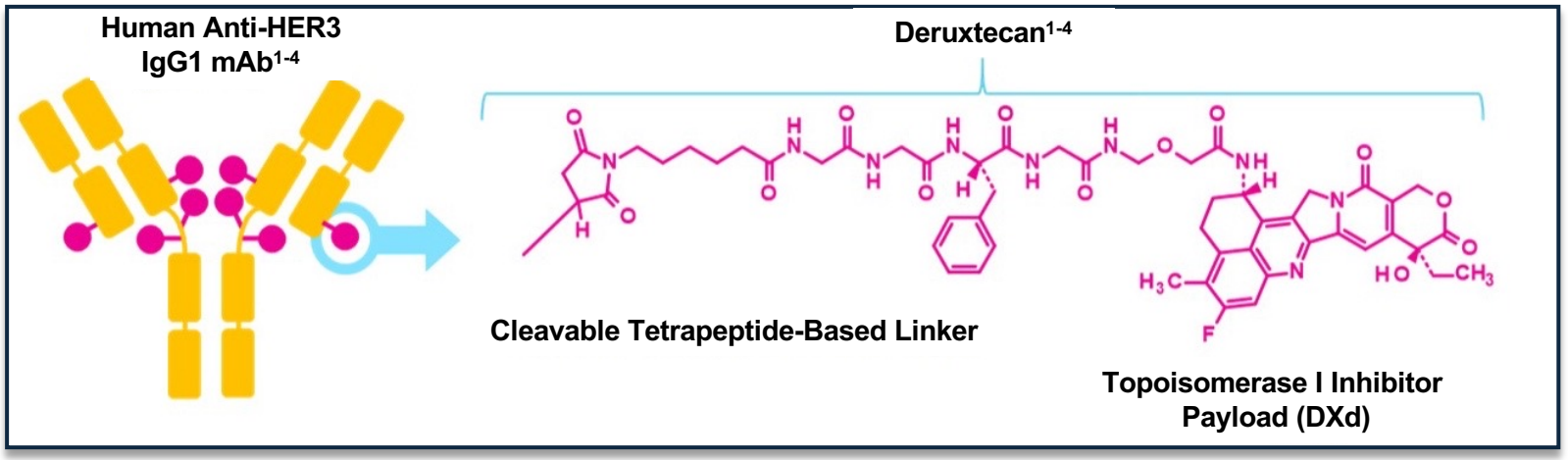


[a] Denominator for percentage is the number of patients in the full analysis set who have at least 1 target lesion at baseline per BICR. [b] Based on the Clopper–Pearson method for single proportion. [c] For 1 patient deemed NE in the 6.4 mg/kg group, it was not possible to derive objective response due to missing data of 1 target lesion; the patient's best overall response however was calculated from available target lesion assessments and included in 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.

Her 3 ADCs

Patritumab Deruxtecan (HER3-DXd): Targeting HER3 May Address Multiple EGFR TKI Resistance Mechanisms

- HER3-DXd is an ADC with 3 components[1-6]
  - A fully human anti-HER3 IgG1 mAb (patritumab)
  - A topoisomerase I inhibitor payload (an exatecan derivative, DXd)
  - A tetrapeptide-based cleavable linker
- HER3-DXd is in clinical evaluation for NSCLC, metastatic breast cancer, and colorectal cancer

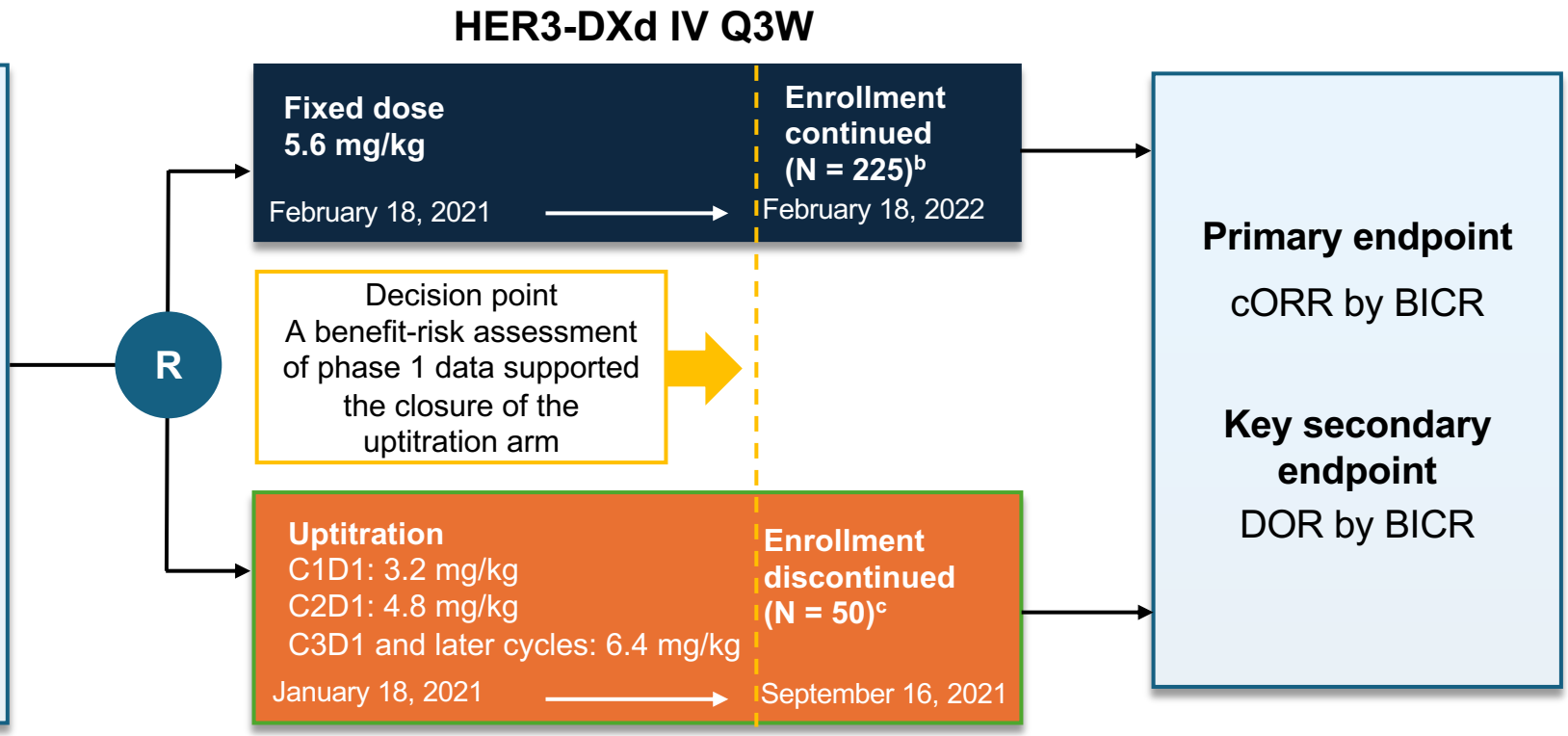


- HER3 is expressed in 83% of NSCLC tumors[7]
- HER3 alterations are not known to be a mechanism of resistance to EGFR TKI in *EGFR*mut NSCLC

1. Hashimoto Y et al. *Clin Cancer Res*. 2019;25:7151-7161. 2. Nakada T et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185. 3. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-5108. 4. Koganemaru S et al. *Mol Cancer Ther*. 2019;18:2043-2050. 5. Haratani K et al. *J Clin Invest*. 2020;130:374-388. 6. Ogitani Y et al. *Cancer Sci*. 2016;107:1039-1046. 7. Scharpenseel H et al. *Sci Rep.* 2019;9:7406.

HERTHENA-Lung01: Study Design[1,2]

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



- Primary data cutoff: November 21, 2022[d]
- Snapshot data cutoff: May 18, 2023 (additional 6 mo follow-up)
  - Efficacy from snapshot data cutoff: median study follow-up, 18.9 (range, 14.9-27.5) mo
  - Safety from primary data cutoff: median treatment duration, 5.5 mo (range, 0.7-18.2) mo

[a] Inclusion not based on detection of HER3 expression. [b] 226 patients were enrolled; 225 received ≥1 dose. [c] 51 patients were enrolled; 50 received ≥1 dose. [d] Data cutoff for the primary analysis occurred when all enrolled patients had either ≥9 mo of follow-up or had discontinued from the study earlier.

1. Yu HA et al. WCLC 2023. Abstract OA05.03. 2. Yu HA et al. *Future Oncol*. 2023;19;1319-1329.

HERTHENA-Lung01: Clinically Meaningful Efficacy Observed in the Overall Population and Across Subgroups[1]

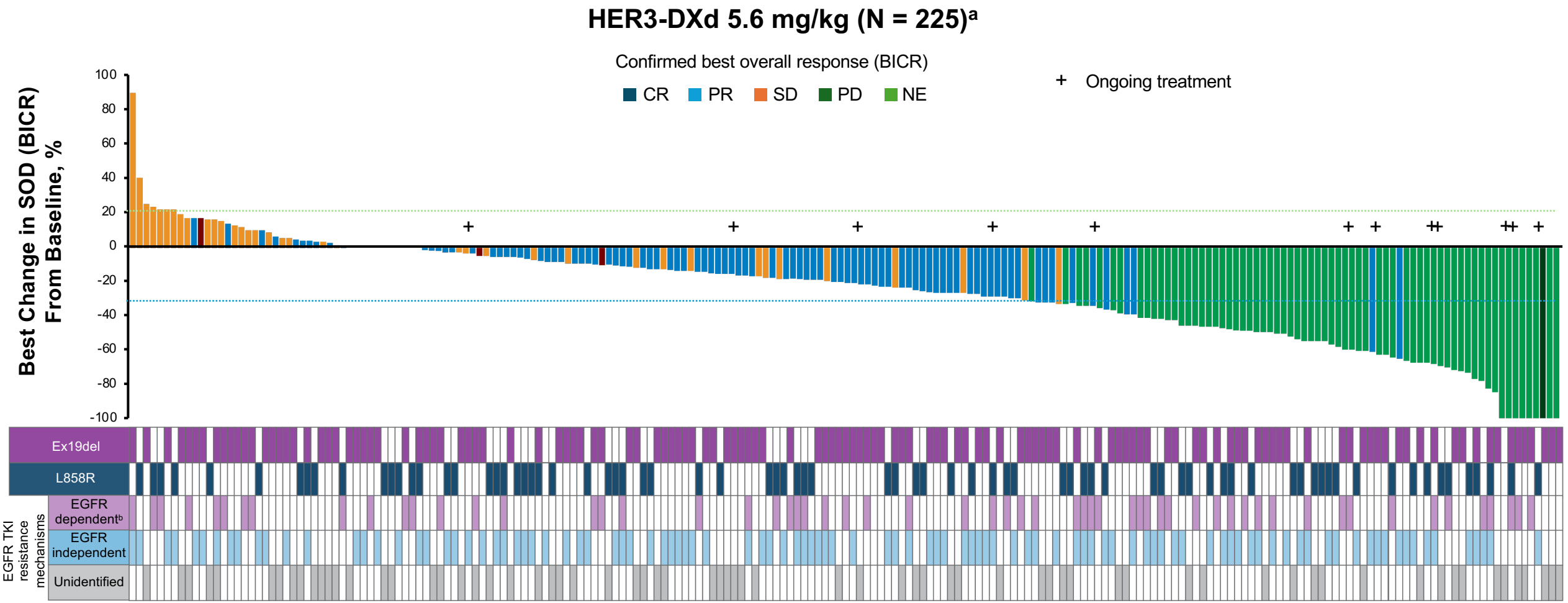
Confirmed Responses and Survival	Prior EGFR TKI (Any) and PBC (N = 225)	Subset With Prior 3G EGFR TKI and PBC (n = 209)
cORR, % (95% CI)	**29.8 (23.9-36.2)**	**29.2 (23.1-35.9)**
CR, n (%)	1 (0.4)	1 (0.5)
PR, n (%)	66 (29.3)	60 (28.7)
SD, n (%)[a]	99 (44.0)	91 (43.5)
PD, n (%)	43 (19.1)	41 (19.6)
NE, n (%)[b]	16 (7.1)	16 (7.7)
DCR, % (95% CI)	73.8 (67.5-79.4)	72.7 (66.2-78.6)
Median DOR, mo (95% CI)	6.4 (4.9-7.8)	6.4 (5.2-7.8)
Median PFS, mo (95% CI)	5.5 (5.1-5.9)	5.5 (5.1-6.4)
Median OS, mo (95% CI)	11.9 (11.2-13.1)	11.9 (10.9-13.1)

Snapshot data cutoff, May 18, 2023. Median study follow-up, 18.9 (range, 14.9-27.5) mo.

[a] Includes non-CR/non-PD. [b] No adequate postbaseline tumor assessment (n = 12); SD too early (SD <5 wk after start of study treatment [n = 4]).

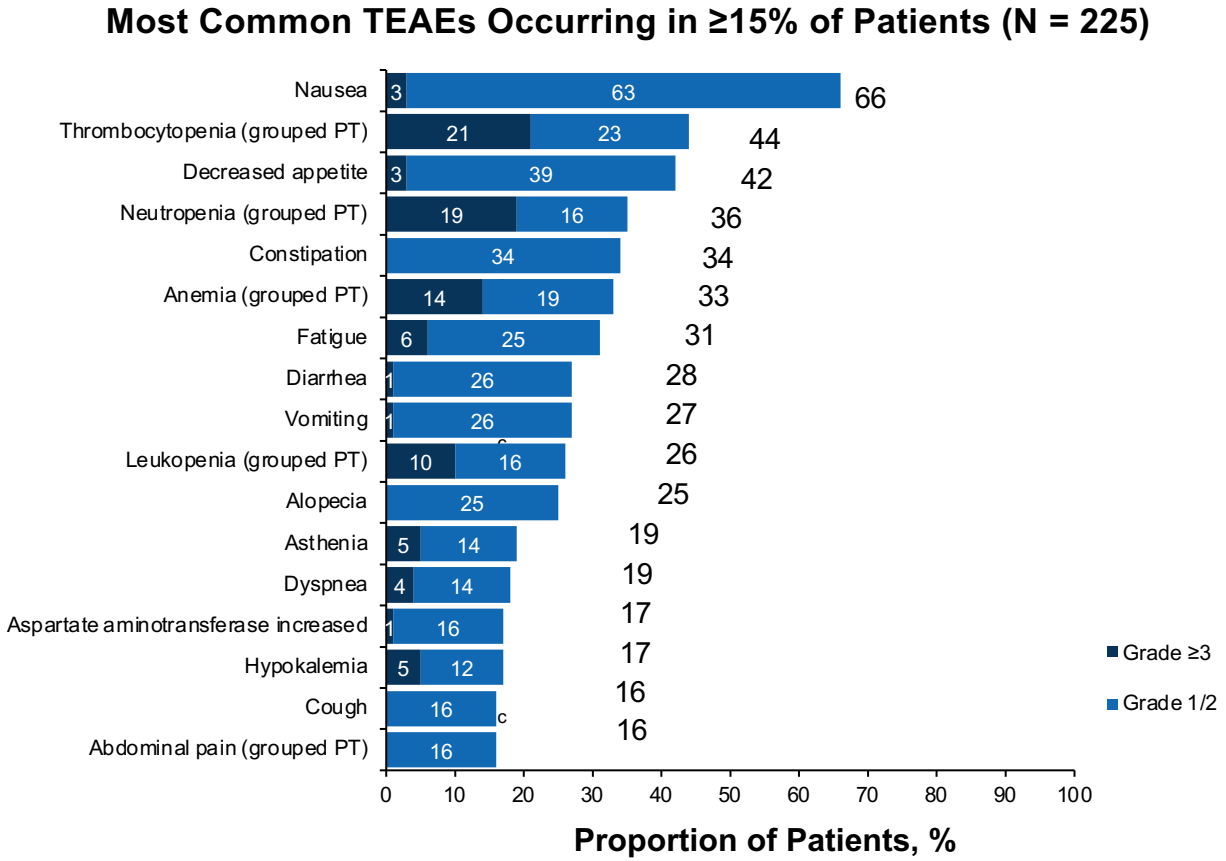
1. Yu HA et al. WCLC 2023. Abstract OA05.03.

HERTHENA-Lung01: Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance[1,2]



HERTHENA-Lung01: The Safety Profile of HER3-DXd Was Manageable and Tolerable[1]

Safety Summary	HER3-DXd 5.6 mg/kg (N = 225)
Any TEAE, n (%)	224 (99.6)
Associated with treatment discontinuation[a]	16 (7.1)
Associated with treatment dose reduction	48 (21.3)
Associated with treatment dose interruption	91 (40.4)
Grade ≥3 TEAE, n (%)	146 (64.9)
Treatment-related TEAE, n (%)	215 (95.6)
Associated with death[b]	4 (1.8)
Grade ≥3	102 (45.3)
Serious TEAE	34 (15.1)
Adjudicated interstitial lung disease, n (%) (All were adjudicated as treatment-related)	12 (5.3)
Grade 1	1 (0.4)
Grade 2	8 (3.6)
Grade 3	2 (0.9)
Grade 4	0
Grade 5	1 (0.4)



Any hematologic toxicities typically occurred early in treatment, were transient, and were not associated with clinical sequelae

Primary data cutoff, Nov 21 2022. Median treatment duration: 5.5 (range, 0.7-18.2) mo.

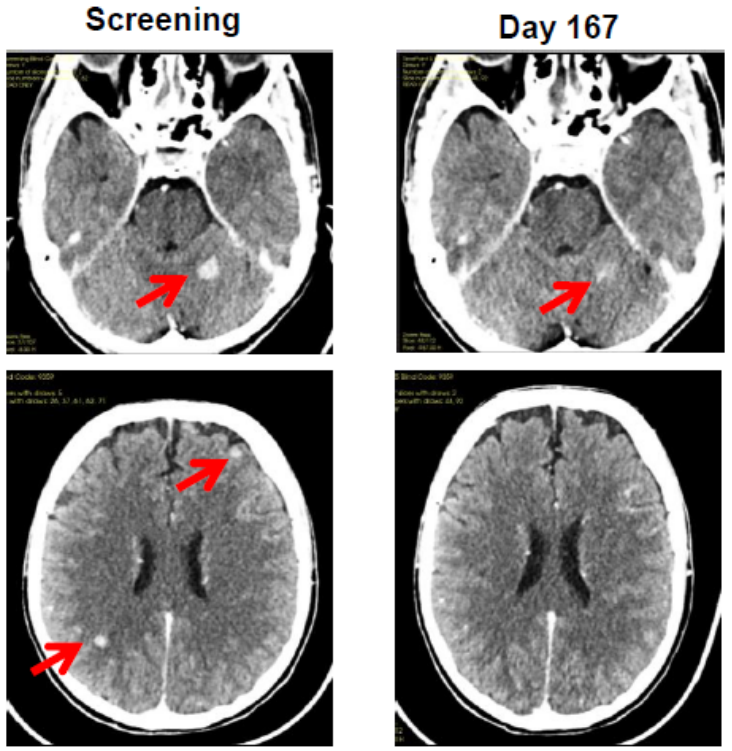
[a] TEAEs leading to discontinuation included pneumonitis (n = 4), blood bilirubin increased (n = 2), dyspnea (n = 2), and cholestatic jaundice, anemia, fatigue, portal hypertension, duodenal perforation, urosepsis, asthenia, and white blood count decreased (n = 1 each). [b] TEAEs associated with death that were considered related to study drug included pneumonitis, respiratory failure, GI perforation, and pneumonia (no neutropenia) in 1 patient each. [c] Grouped terms.

HERTHENA-Lung01: Intracranial Responses (by CNS BICR) Observed With HER3-DXd[1]

Intracranial Efficacy of HER3-DXd in Patients With Brain Metastases at Baseline

Intracranial Response by CNS BICR per CNS RECIST	Patients With Brain Metastasis at Baseline and No Prior Radiotherapy (n = 30)[a]
cORR, % (95% CI)	33.3 (17.3-52.8)
CR, n (%)	9 (30.0)[b]
PR, n (%)	1 (3.3)
SD, n (%)[c]	13 (43.3)
PD, n (%)	4 (13.3)
NE, n (%)	3 (10.0)
DCR, % (95% CI)	76.7 (57.7-90.1)
Median DOR, mo (95% CI)	8.4 (5.8-9.2)

Partial CNS Response in a Patient With a Measurable CNS BICR Target Lesion



Snapshot data cutoff, May 18, 2023. Median study follow-up, 18.9 (range, 14.9-27.5) mo.

[a] 7 patients had measurable target lesions: 23 patients had only nontarget lesions. [b] 8 patients had only nontarget lesions. [c] Includes non-CR/non-PD.

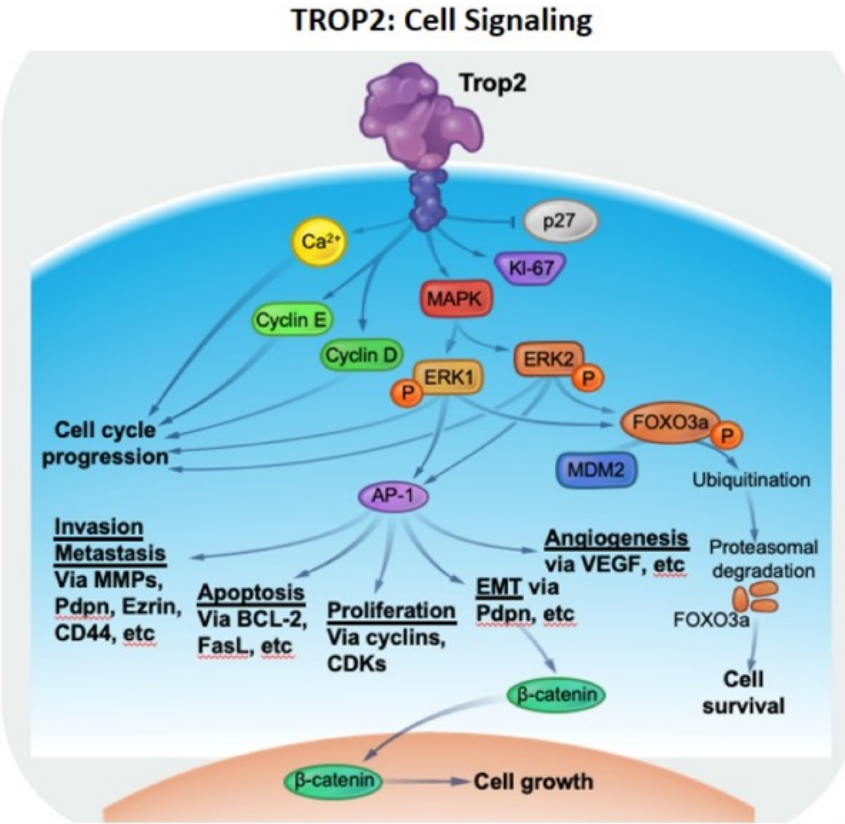
1. Yu HA et al. WCLC 2023. Abstract OA05.03.


Trop2 ADCs

TROP-2 as a target

TROP-2 is a transmembrane glycoprotein overexpressed in solid tumors including TNBC and NSCLC

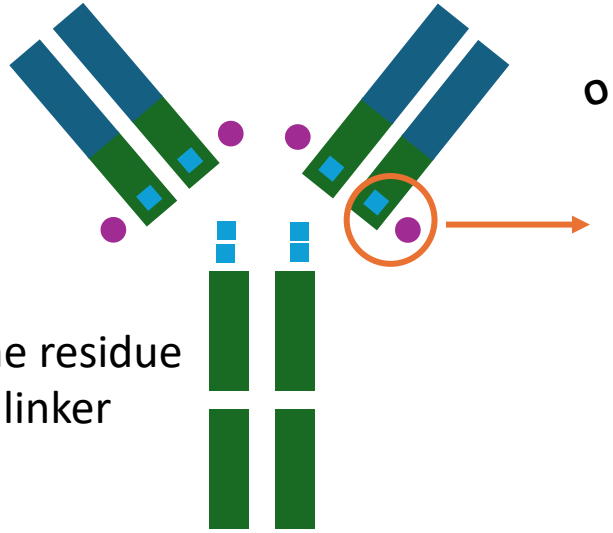
TROP-2 is an epithelial adhesion molecule and regulates stem cell marker–associated cell regeneration



Jiang. Oncol Lett. 2013;6:375. Shvartsur. Genes Cancer. 2015;6:84.

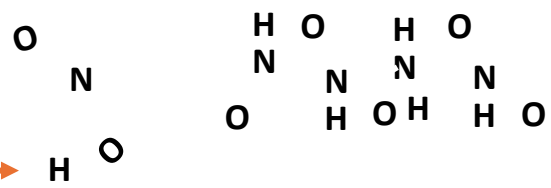
Datopotamab Deruxtecan: TROP-2–Targeted ADC

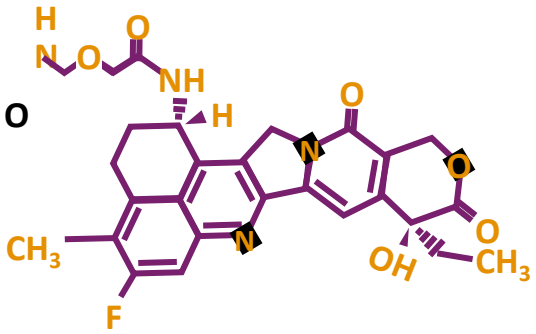
Datopotamab
Humanized
anti–TROP-2 mAb



Cysteine residue
Drug + linker

Tetrapeptide-Based Cleavable Linker





Topoisomerase I Inhibitor Payload (DXd)
Exatecan derivative

Conjugation Chemistry
Drug + linker conjugated to cysteine residues of mAb

- High-potency, membrane-permeable payload with short systemic half-life
- Optimized DAR: ~4:1
- Stable linker–payload
- Tumor-selectable cleavable linker
- Bystander killing effect

Okajima. Mol Cancer Ther. 2021;20:2329. Shastry. Breast. 2022;66:169.
Bardia. SABCS 2022. Abstr P6-10-03. Yasuda. AACR 2023. Abstr 4893.

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MADRID 2023 ESMO congress

Datopotamab deruxtecan (Dato-DXd) vs docetaxel in previously treated advanced/metastatic (adv/met) non-small cell lung cancer (NSCLC): Results of the randomized phase 3 study TROPION-Lung01

Myung-Ju Ahn,[1,a] Aaron Lisberg,[2,a,b] Luis Paz-Ares,[3] Robin Cornelissen,[4] Nicolas Girard,[5] Elvire Pons-Tostivint,[6] David Vicente Baz,[7] Shunichi Sugawara,[8] Manuel Angel Cobo,[9] Maurice Pérol,[10] Céline Mascaux,[11] Elena Poddubskaya,[12] Satoru Kitazono,[13] Hidetoshi Hayashi,[14] Jacob Sands,[15] Richard Hall,[16] Yong Zhang,[17] Hong Zebger-Gong,[18] Deise Uema,[17] Isamu Okamoto[19]

[a]Equal contribution as first author. [b]Indicates presenting author.

[1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea; [2]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [3]Hospital Universitario 12 de Octubre, CNIO-H12O Lung Cancer Unit, Universidad Complutense & CiberOnc, Madrid, Spain; [4]Erasmus MC Cancer Institute, Rotterdam, The Netherlands; [5]Institut Curie, Paris, France; [6]Centre Hospitalier Universitaire de Nantes, Nantes, France; [7]Hospital Universitario Virgen Macarena, Seville, Spain; [8]Sendai Kousei Hospital, Sendai, Japan; [9]FEA Oncología Médica, Medical Oncology Intercenter Unit, Regional and Virgen de la Victoria University Hospitals, IBIMA, Málaga, Spain; [10]Centre Léon Bérard, Lyon, France; [11]Hôpitaux Universitaires de Strasbourg (CHRU), Strasbourg, France; [12]Vitamed LLC, Moscow, Russia; [13]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [14]Kindai University, Osaka, Japan; [15]Dana-Farber Cancer Institute, Boston, MA, USA; [16]University of Virginia Health System, Charlottesville, VA, USA; [17]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [18]Daiichi Sankyo Europe GmbH, Munich, Germany; [19]Kyushu University Hospital, Fukuoka, Japan

TROPION-Lung01: Dato-DXd vs Docetaxel in Previously Treated Advanced NSCLS With or Without AGAs

- Global, randomized, open-label phase III trial

Stratified by histology (squamous vs nonsquamous), actionable genomic alteration (present vs absent), geography (US/Japan/Western Europe vs rest of world), anti–PD-1/PD-L1 mAb in most recent prior therapy

Patients with previously treated* stage IIIB, IIIC, or IV NSCLC; no prior docetaxel; ECOG PS 0-1 (N = 604)

Dato-DXd
6 mg/kg Q3W
(n = 299)

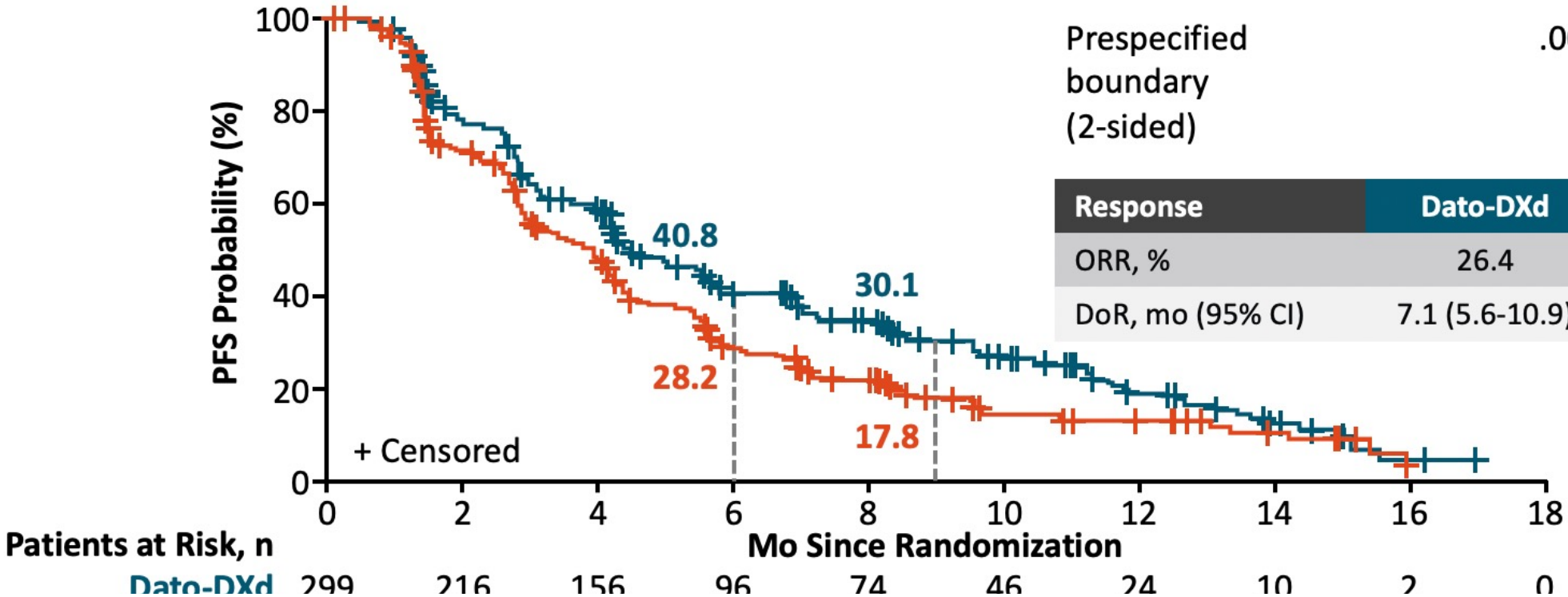
Docetaxel
75 mg/m^2 Q3W
(n = 305)

*Patients without actionable genomic mutations: 1-2 lines, including platinum-based CT and anti–PD-1/PD-L1 mAb; patients with actionable genomic alterations (*EGFR*, *ALK*, *BRAF*, *NTRK*, *MET* exon 14 skipping, *RET*, or *ROS1*): 1-2 prior approved targeted therapies and/or platinum-based CT, with ≤1 anti–PD-1/PD-L1 mAb.

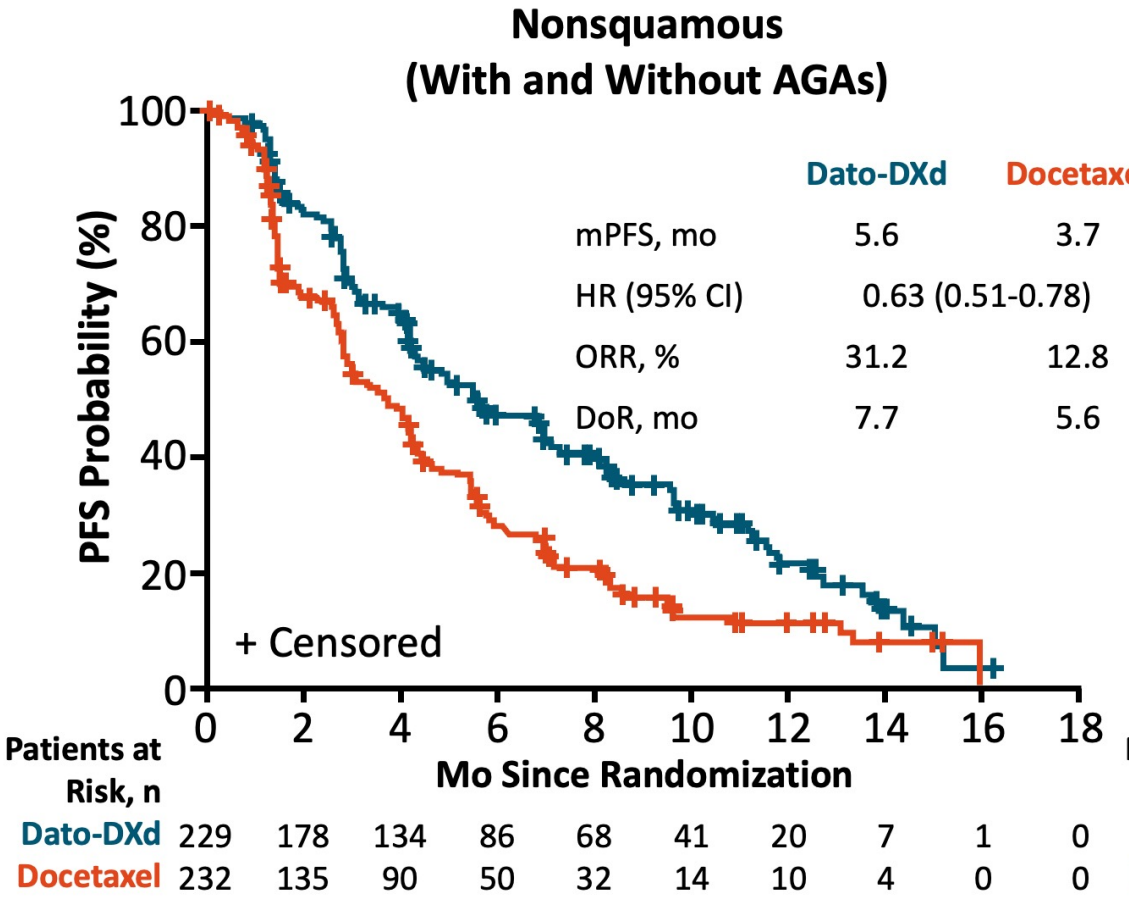
TROPION-Lung01: ITT Population

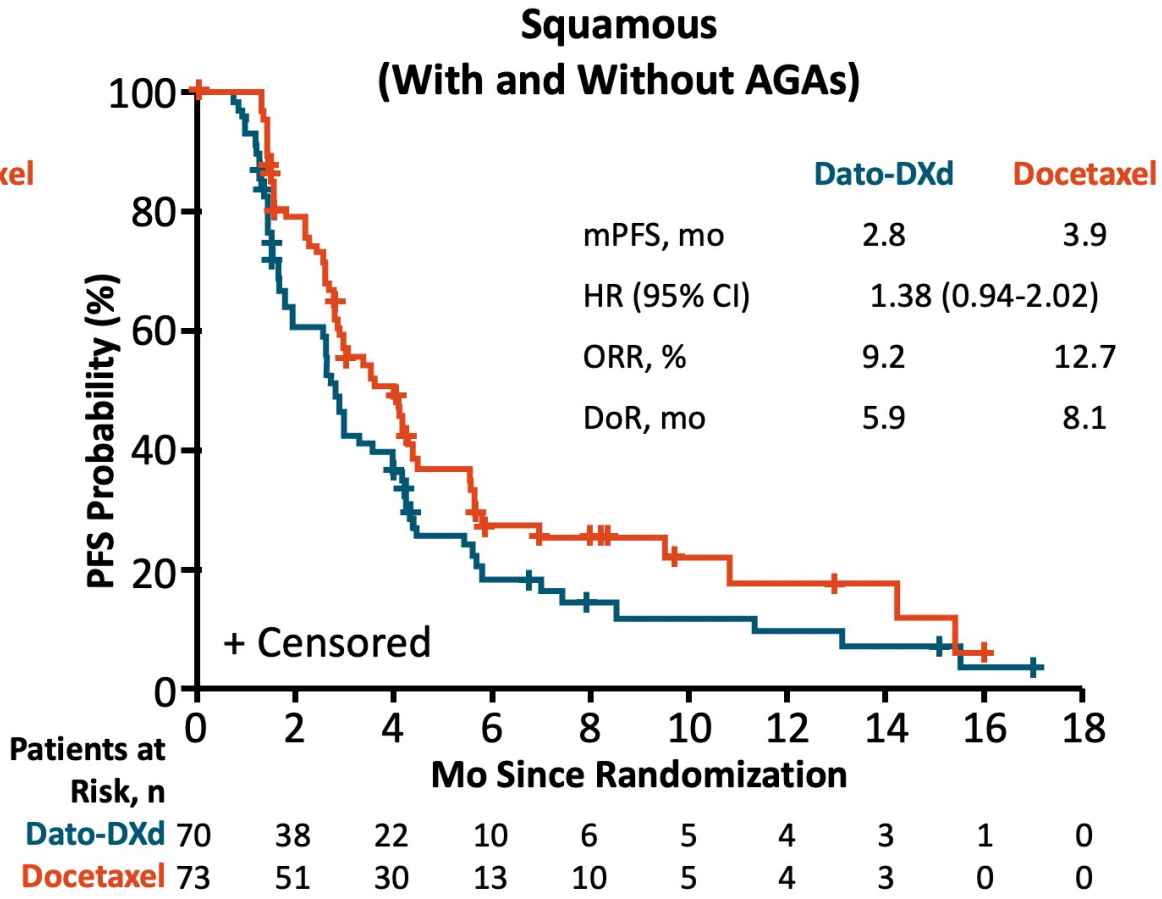
	Dato-DXd	Docetaxel
mPFS, mo	4.4	3.7
HR (95% CI)	0.75 (0.62-0.91; *P* = .004)	
Prespecified boundary (2-sided)	.008	

Response	Dato-DXd	Docetaxel
ORR, %	26.4	12.8
DoR, mo (95% CI)	7.1 (5.6-10.9)	5.6 (5.4-8.1)



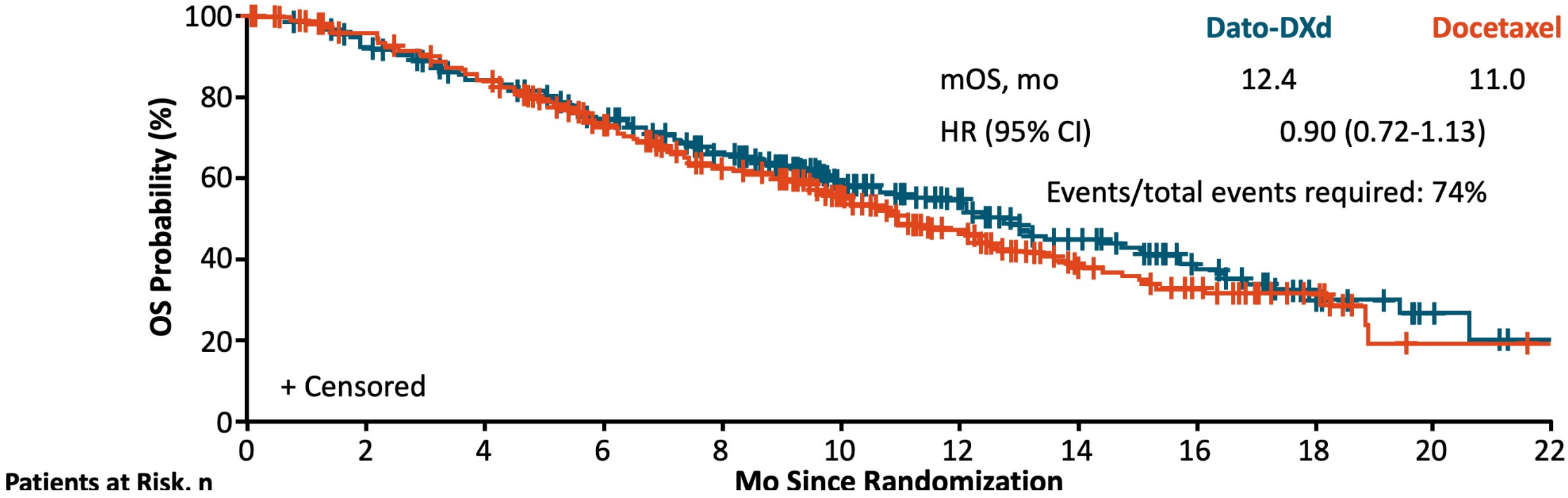
TROPION-Lung01: Efficacy by Histology





TROPION- Lung01: OS in ITT Population

Lisberg. ESMO 2023. Abstr LBA12.



TROPION-Lung01: Overall Safety Summary[1]

TRAEs, n (%)	Dato-DXd (n = 297)	Docetaxel (n = 290)
All grades	257 (87)	252 (87)
Grade ≥3	73 (25)	120 (41)
Associated with dose reduction	58 (20)	85 (29)
Associated with dose delay	49 (17)	31 (11)
Associated with discontinuation	23 (8)	34 (12)
Associated with death[a]	3 (1)	2 (1)
Serious TRAEs	30 (10)	36 (12)
Grade ≥3	25 (8)	33 (11)

- Median treatment durations for Dato-DXd and docetaxel were 4.2 and 2.8 mo, respectively
- Fewer grade ≥3 TRAEs were observed with Dato-DXd compared with docetaxel
- Fewer TRAEs leading to dose reductions or discontinuations were seen with Dato-DXd compared with docetaxel

[a] Investigator assessed. Dato0DXd: two cases of ILD/pneumonitis and one case of sepsis; docetaxel: one case of ILD/pneumonitis and one case of septic shock.
The safety analysis set included all randomized patients who received ≥1 dose of the study drug.
1. Ahn M et al. ESMO 2023. Abstract LBA12.

TROPION-Lung01: TRAEs Occurring in ≥10% of Patients[1]

System Organ Class Preferred term, n (%)	Dato-DXd n = 297		Docetaxel n = 290	
	Any Grade	**Grade ≥3**	**Any Grade**	**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 (16)	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)
General				
Asthenia	55 (19)	8 (3)	55 (19)	5 (2)
Fatigue	34 (11)	2 (1)	40 (14)	6 (2)
Metabolism and nutrition				
Decreased appetite	68 (23)	1 (0.3)	45 (16)	1 (0.3)
Skin and subcutaneous				
Alopecia	95 (32)	0	101 (35)	1 (0.3)[b]
Rash	36 (12)	0	18 (6)	0
Pruritus	30 (10)	0	12 (4)	0

- Stomatitis and nausea were the most frequent TRAEs seen with Dato-DXd and were predominantly grade 1 or 2
- Hematologic toxicities, including neutropenia and febrile neutropenia,[c] were more common with docetaxel
- No new safety signals were observed with Dato-DXd

[a] This category includes the preferred terms “neutropenia” and “neutrophil count decreased.” [b] Includes an event incorrectly reported as grade 3.
[c] 7% vs 0.3% for docetaxel and Dato-DXd, respectively.
1. Ahn M et al. ESMO 2023. Abstract LBA12.

TROPION-Lung01: AEs of Special Interest[1]

AESI	Dato-DXd (n = 297)	Docetaxel (n = 290)
Stomatitis/oral mucositis, n (%)[a]		
All grades	160 (54)	59 (20)
Grade ≥3	19 (6)	4 (1)
Ocular events, n (%)[b]		
All grades	57 (19)	27 (9)
Grade ≥3	5 (2)[c]	0 (0)
Adjudicated drug-related ILD, n (%)[d]		
All grades	25 (8)	12 (4)
Grades ≥3	10 (3)	4 (1)
Grade 5	7 (2)	1 (0.3)

- Stomatitis/oral mucositis associated with Dato-DXd resulted in a low rate of discontinuation (0.7%)
- Dry eye was the most common ocular event with Dato-DXd (6.1%, primarily grade ≤2), followed by increased lacrimation (5.4%)
- Seven adjudicated drug-related grade 5 ILD events
  - Primary cause of death in 4 out of 7 patients was attributed to disease progression by investigator
  - Nonsquamous: 4 out of 232 patients (1.7%) and squamous: 3 of 65 patients (4.6%)[e]
- IRRs were observed in 8% of patients in each arm, all were grade ≤2 with the exception of one grade 3 event with Dato-DXd

[a] Events included the selected PTs oral mucositis/stomatitis, oropharyngeal pain, mouth ulceration, odynophagia, dysphagia, oral pain, glossitis, pharyngeal inflammation, aphthous ulcer, and oral mucosa erosion. [b] Ocular events included selected PTs from the corneal disorder SMQ and selected relevant PTs from the eye disorder SOC. [c] Included four cases of keratitis and one case of ulcerative keratitis. [d] ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or docetaxel (includes cases of potential ILD/pneumonitis based on MedDRA v26.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure).
[e] Among treated patients, histology information per the case report form.

TROPION-Lung02: Dato-DXd + Pembrolizumab ± Platinum CT in Advanced NSCLC Without AGAs

- Multicenter, open-label phase Ib study

Patients with advanced or metastatic NSCLC without actionable genomic alterations*; ≤2 prior lines of therapy (dose-escalation cohort) or ≤1 line of platinum-based CT (dose-expansion cohorts 1 and 2) or treatment naive (dose-expansion cohorts 2 [enrolled after June 30, 2022] and 3-6)

**EGFR, ALK, ROS1, NTRK, BRAF, RET,* or *MET.*

Cohort 1 (n = 20)	**Dato-DXd** 4 mg/kg IV Q3W **Pembrolizumab** 200 mg IV Q3W
Cohort 2 (n = 44)	**Dato-DXd** 6 mg/kg IV Q3W **Pembrolizumab** 200 mg IV Q3W
Cohort 3 (n = 20)	**Dato-DXd** 4 mg/kg IV Q3W **Pembrolizumab** 200 mg IV Q3W **Carboplatin** AUC 5
Cohort 4 (n = 30)	**Dato-DXd** 6 mg/kg IV Q3W **Pembrolizumab** 200 mg IV Q3W **Carboplatin** AUC 5
Cohort 5 (n = 12)	**Dato-DXd** 4 mg/kg IV Q3W **Pembrolizumab** 200 mg IV Q3W **Cisplatin** 75 mg/m^2
Cohort 6 (n = 10)	**Dato-DXd** 6 mg/kg IV Q3W **Pembrolizumab** 200 mg IV Q3W **Cisplatin** 75 mg/m^2

Safety of doublet regimens established prior to evaluation of triplets and of Dato-DXd 4 mg/kg prior to 6 mg/kg

- **Primary objectives:** safety and tolerability
- **Secondary objectives:** efficacy, pharmacokinetics, antidrug antibodies

Goto. ASCO 2023. Abstr 9004.

Data cutoff: April 7, 2023.

TROPION-Lung02: Antitumor Activity

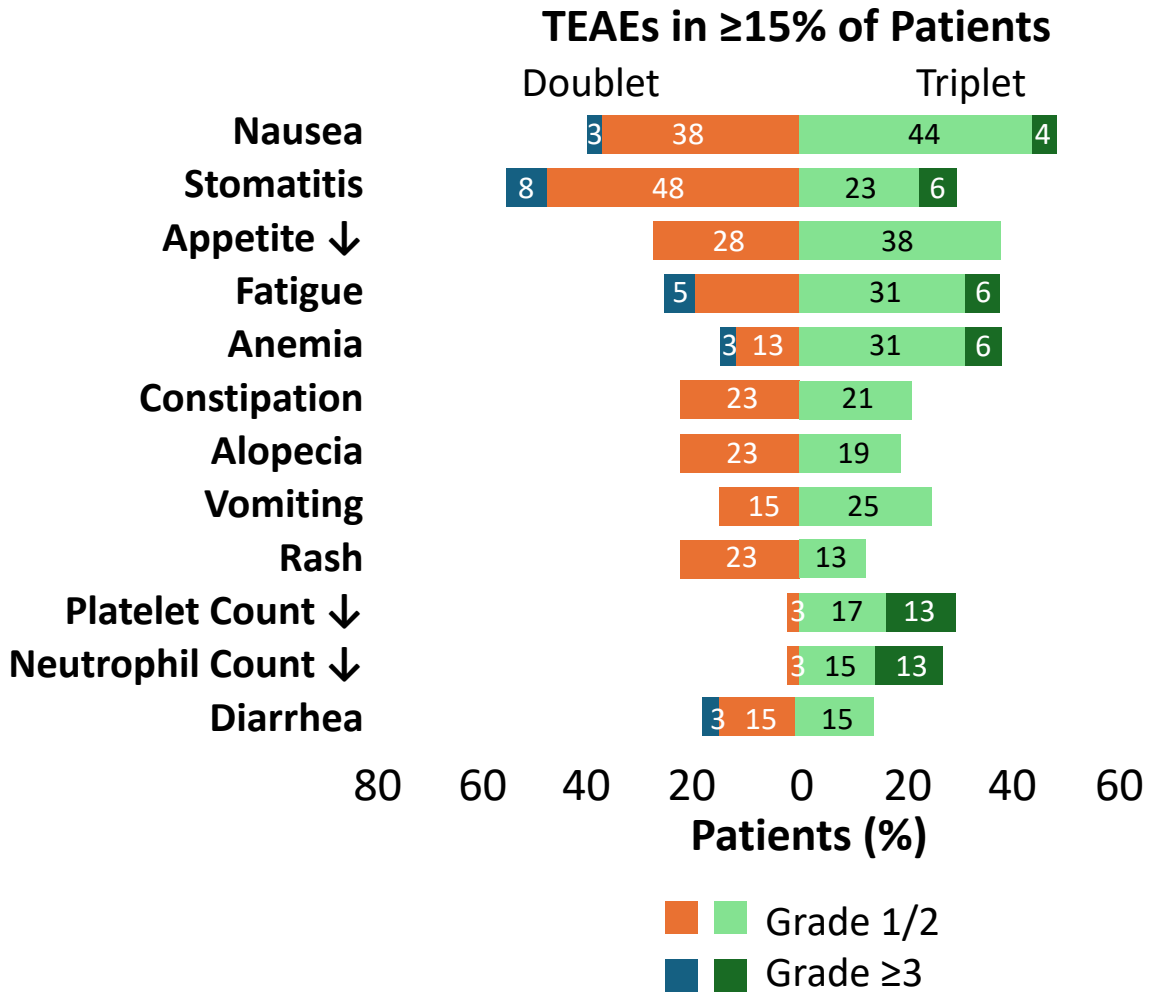
Investigator-Assessed Response	All Patients		First Line	
	Doublet (n = 61)	Triplet (n = 71)	Doublet (n = 34)	Triplet (n = 53)
Confirmed + pending ORR, n (%) [95% CI]	23 (38) [26-51]	35 (49) [37-61]	17 (50) [32-68]	30 (57) [42-70]
Confirmed + pending BOR, n (%) ▪ Confirmed CR ▪ Pending CR ▪ Confirmed PR ▪ Pending PR	 0 0 21 (34) 2 (3)	 1 (1) 0 34 (48) 0	 0 0 15 (44) 2 (6)	 1 (2) 0 29 (55) 0
SD, n (%)	30 (49)	27 (38)	16 (47)	18 (34)
DCR, n (%)	51 (84)	62 (87)	31 (91)	48 (91)
Median DoR, mo (95% CI)	NE (8.8-NE)	NE (5.8-NE)	NE (5.5-NE)	NE (5.7-NE)
Preliminary median PFS, mo (95% CI)	8.3 (6.8-11.8)	7.8 (5.6-11.1)	--	--

Goto. ASCO 2023. Abstr 9004.

TROPION-Lung02: Safety

Safety Outcome, n (%)	Doublet (n = 40)	Triplet (n = 48)
TEAE ▪ Treatment related	37 (93) 33 (83)	47 (98) 46 (96)
Grade ≥3 TEAE ▪ Treatment related	16 (40) 14 (35)	29 (60) 26 (54)
Serious TEAE ▪ Treatment related	9 (23) 4 (10)	13 (27) 7 (15)
TEAE associated with ▪ D/c due to any drug ▪ D/c due to Dato-DXd ▪ Death*	 9 (22) 6 (15) 2 (5)	 9 (19) 5 (10) 1 (2)
ILD adjudicated as drug related ▪ Grade 1/2 ▪ Grade 3	 2 (5) 1 (3)	 0 1 (2)

*Deemed unrelated to study treatment.



Levy. WCLC 2022. Abstr MA13.07.

TROPION-Lung04: Dato-DXd + Durvalumab ± Carboplatin in Advanced NSCLC Without AGAs

Patients (≥18 yr of age) with advanced or metastatic NSCLC without AGAs; dose escalation cohort 1 (and 1 patient in dose escalation cohort 2) had received ≥1 plt-based CT + anti–PD-1/PD-L1 tx; subsequent patients were treatment-naive or had received ≤1 prior lines of systemic CT without concomitant ICIs; ECOG PS 0/1

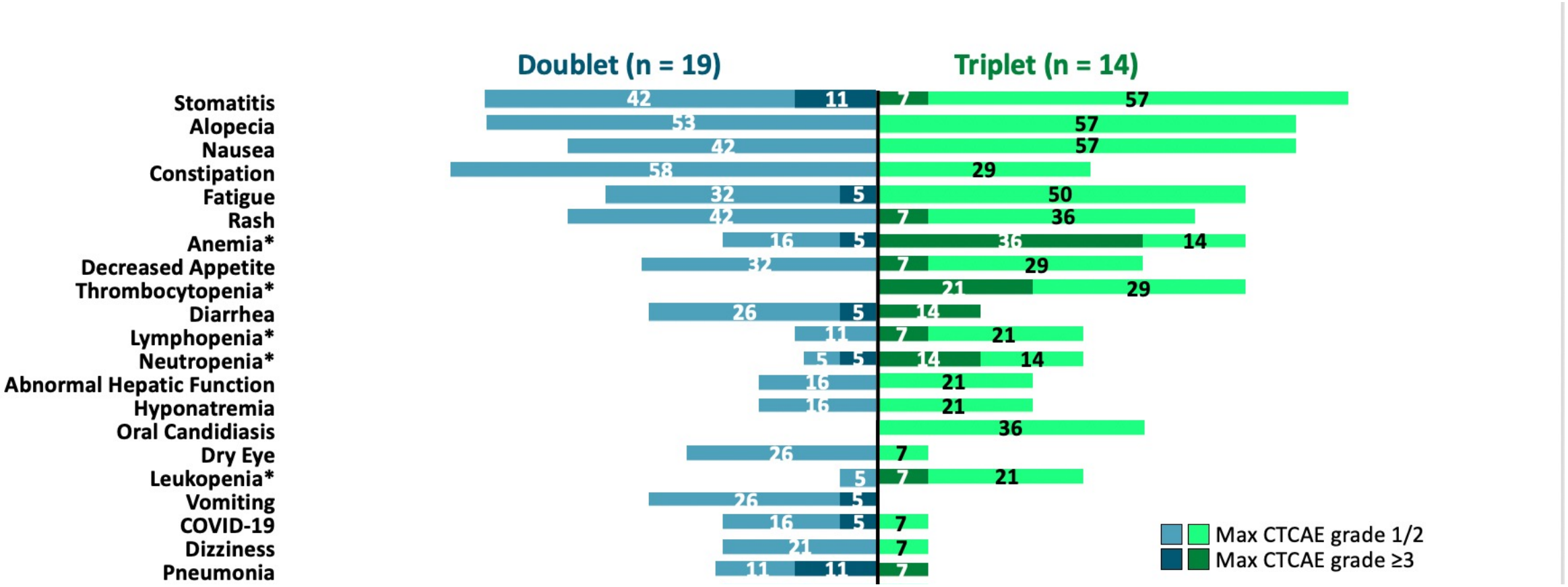
	Sequential Dose Escalation*	Dose Expansion
Cohort 1 (Doublet)	**Dato-DXd** 4 mg/kg IV + **Durvalumab** 1120 mg IV Q3W (n = 5)	**Doublet**
Cohort 2 (Doublet)	**Dato-DXd** 6 mg/kg IV + **Durvalumab** 1120 mg IV Q3W (n = 3)	**Dato-DXd** 6 mg/kg IV + **Durvalumab** 1120 mg IV Q3W (n = 16)
Cohort 3† (Triplet)	**Dato-DXd** 4 mg/kg IV + **Durvalumab** 1120 mg IV Q3W + **Carboplatin** AUC5 (4 cycles)	**Triplet**
Cohort 4 (Triplet)	**Dato-DXd** 6 mg/kg IV + **Durvalumab** 1120 mg IV Q3W + **Carboplatin** AUC5 (4 cycles) (n = 6)	**Dato-DXd** 6 mg/kg IV + **Durvalumab** 1120 mg IV Q3W + **Carboplatin** AUC5 (4 cycles) (n = 8)

- **Primary endpoint:** safety and tolerability
- **Key secondary endpoints:** ORR and DCR (by investigator per RECIST v1.1)

*Sequential dose escalation from cohort 1 to 2 and cohort 2 to 4 was guided by an mTPI-2 design.
†Cohort 3 skipped due to sufficient data on acceptable safety profile.

Papadopoulos. WCLC 2023. Abstr OA05.06.

TROPION-Lung04: TEAEs in ≥15% of Patients



Select Ongoing Trials of Datopotamab Deruxtecan in Advanced or Metastatic NSCLC

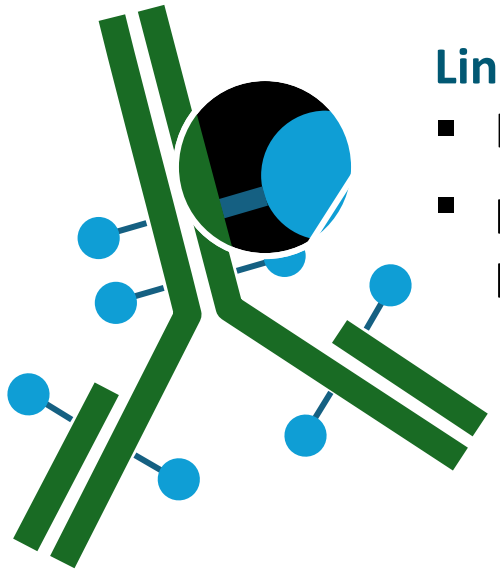
Trial	Phase	Setting	Therapy	Primary EP(s)
TROPION-Lung07 (NCT05555732)	III	1L adv/metastatic NSCLC without AGAs; PD-L1 <50%	Dato-DXd + pembrolizumab + platinum CT vs Dato-DXd + pembrolizumab vs pembrolizumab + platinum/pemetrexed CT	PFS by BICR, OS
TROPION-Lung08 (NCT05215340)	III	1L adv/metastatic NSCLC without AGAs; PD-L1 ≥50%	Dato-DXd + pembrolizumab vs pembrolizumab	PFS by BICR, OS

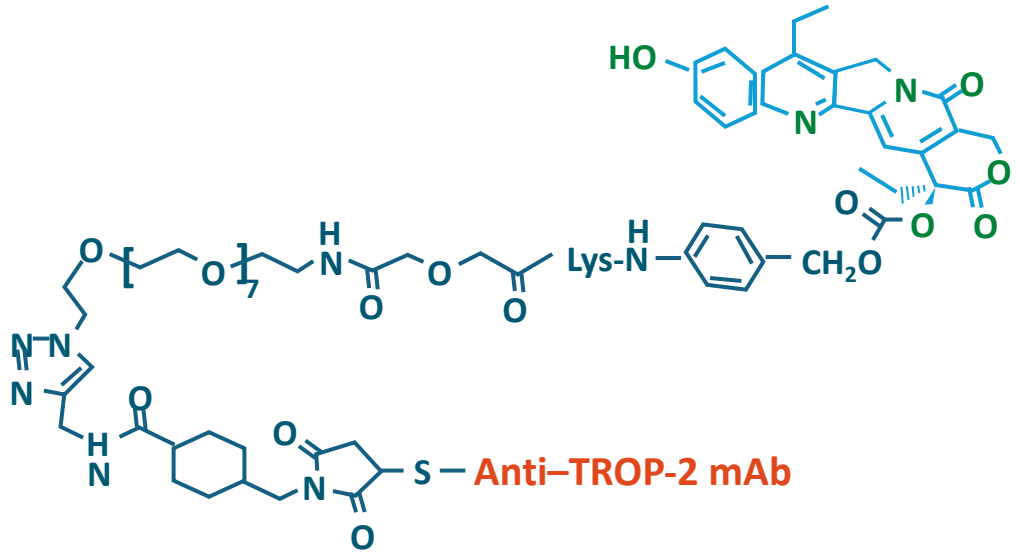
Sacituzumab Govitecan

Goldenberg. Oncotarget. 2015;6:22496. Goldenberg. MAbs. 2019;11:987. Sacituzumab govitecan PI.

Humanized RS7 Antibody

- Targets TROP-2
- Type: hRS7 IgG1κ





Linker for SN-38

- High DAR (7.6:1)
- pH-sensitive linker for rapid release of payload at or inside tumor

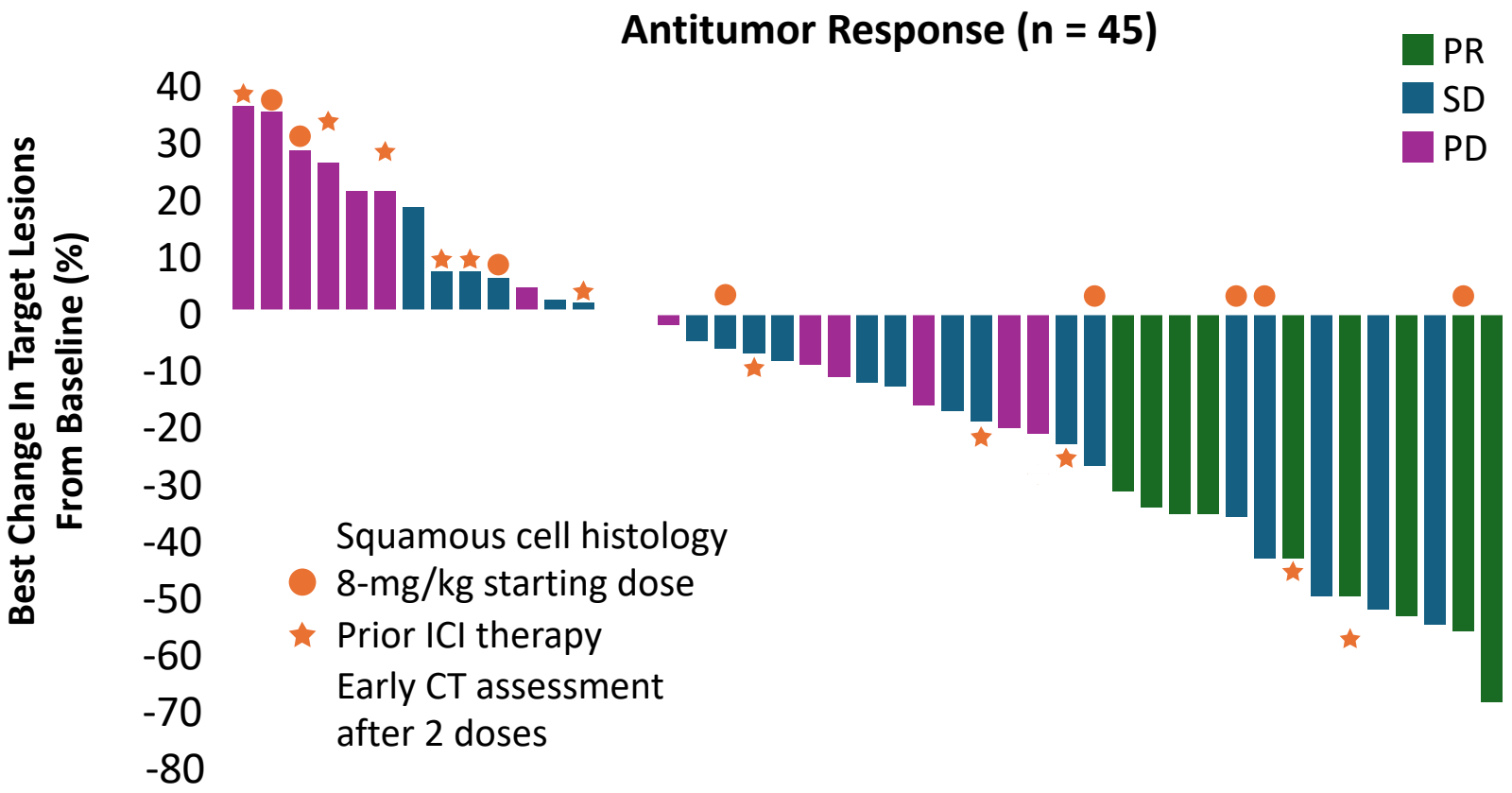
SN-38 Payload

- Delivers 136-fold more to tumors than parent compound irinotecan
- Unique chemistry improves solubility, selectively delivers SN-38 to tumor

FDA approved in locally advanced/metastatic settings for:

- **TNBC** (full approval: April 7, 2021; accelerated approval, April 22, 2020)
- **HR+/HER2- breast cancer** (full approval: February 3, 2023)
- **Urothelial cancer** (accelerated approval: April 13, 2021)

IMMU-132-01 NSCLC Cohort: Efficacy of Sacituzumab Govitecan



Efficacy Outcome	N = 54
ORR, % (95% CI)	16.7 (7.9-29.3)
▪ PR, n (%)*	9 (16.7)
SD, n (%)	22 (40.7)
Median DoR, mo (95% CI)	6.0 (2.5-21.0)
Median PFS, mo (95% CI)	4.4 (2.5-5.4)
Median OS, mo (95% CI)	7.3 (5.6-14.6)

Heist. JCO. 2017;35:2790. Bardia. Ann Oncol. 2021;32:746.

IMMU 132-01 NSCLC Cohort: All-Cause AEs in NSCLC

Adverse Event, n (%)	N = 54	
	All Grades	Grade 3/4
Nausea	43 (80)	4 (7)
Diarrhea	33 (61)	4 (7)
Fatigue	25 (46)	3 (6)
Alopecia	21 (39)	--
Neutropenia	20 (37)	15 (28)
Vomiting	19 (35)	2 (4)
Anemia	17 (31)	2 (4)
Constipation	17 (31)	0

Adverse Event, n (%)	N = 54	
	All Grades	Grade 3/4
Anorexia	13 (28)	1 (2)
Hypophosphatemia	12 (22)	1 (2)
Dehydration	10 (19)	2 (4)
Weight decrease	10 (19)	0
Leukopenia	10 (19)	5 (9)
Hypomagnesemia	9 (17)	0
Dyspnea	8 (15)	2 (4)
Pneumonia	7 (13)	5 (9)

- Febrile neutropenia: n = 2 (4%)
- Discontinued due to TRAEs: n = 2 (4%)
- 25% dose reduction: 49% (mostly due to neutropenia)

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Sacituzumab Govitecan + Pembrolizumab in 1L Metastatic Non-Small Cell Lung Cancer: Preliminary Results of the EVOKE-02 Study

Byoung Chul Cho,[1] Manuel Cobo Dols,[2] Roxana Reyes Cabanillas,[3] David Vicente,[4] Jose Fuentes Pradera,[5] Salvatore Grisanti,[6] Afshin Eli Gabayan,[7] Ki Hyeong Lee,[8] Eun Kyung Cho,[9] Sabeen Mekan,[10] Farnoush Safavi,[10] Nelumka Fernando,[10] Michael J. Chisamore,[11] Martin Reck[12]

[1]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea; [2]Regional and Virgen de la Victoria University Hospitals, IBIMA, Malaga, Spain; [3]Hospital Clinic de Barcelona, Barcelona, Spain; [4]Hospital Universitario Virgen Macarena, Seville, Spain; [5]Hospital Universitario Virgen de Valme, Seville, Spain; [6]Azienda Ospedaliera Spedali Civili di Brescia, Brescia, Italy; [7]Beverly Hills Cancer Center, Beverly Hills, CA, USA; [8]Chungbuk National University Hospital, Chungbuk, Republic of Korea; [9]Gachon University Gil Medical Center, Incheon, Republic of Korea; [10]Gilead Sciences, Inc., Foster City, CA, USA; [11]Merck & Co., Inc., Rahway, NJ, USA; [12]Airway Research Center North, German Center for Lung Research (DZL), LungenClinic, Grosshansdorf, Germany

EVOKE-02: An Open-Label, Multicohort Phase 2 Study

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Key eligibility criteria
- Stage IV NSCLC
- Measurable disease per RECIST v1.1
- No known actionable genomic alterations
- ECOG PS 0-1
- No prior systemic treatment for metastatic NSCLC

N ≈ 176-224

Cohort A
PD-L1 TPS ≥ 50%
Nsq or Sq
n ≈ 30

Cohort B
PD-L1 TPS < 50%
Nsq or Sq
n ≈ 60

21-day cycles:
SG 10 mg/kg IV on D1 and D8
(until PD or unacceptable toxicity) +
Pembro 200 mg IV on D1
(up to 35 cycles)

Carboplatin Safety Run-in[a]
Any PD-L1 TPS
Nsq or Sq
n ≈ 6-18

Cohort C
Any PD-L1 TPS
Nsq only
n ≈ 40

Cohort D
Any PD-L1 TPS
Sq only
n ≈ 40

21-day cycles:
SG RP2D IV on D1 and D8
(until PD or unacceptable toxicity) +
Pembro 200 mg IV on D1
(up to 35 cycles) +
Carboplatin[b] IV on D1
(up to 4 cycles)

End points

Primary
- ORR[c]
- DLTs in safety run-in

Secondary
- DCR, DOR, and PFS[c]
- OS
- Safety

- At data cutoff (16 June 2023), median (range) follow-up for Cohorts A and B was 5.0 (1.7-12.0) and 5.8 (1.0-12.2) months, respectively
- The preliminary efficacy data reported in this presentation are results by investigator assessment

[a]Dose de-escalation safety run-in period to determine the RP2D of SG for Cohorts C and D. [b]Carboplatin dosed as area under the concentration versus time curve 5. [c]Per RECIST v1.1.
ECOG PS, Eastern Cooperative Oncology Group performance status; D, day; DLT, dose-limiting toxicity; DCR, disease control rate; DOR, duration of response; IV, intravenous; NSCLC, non-small cell lung cancer; Nsq, nonsquamous; ORR, objective response rate; OS, overall survival; PD-L1, programmed death ligand 1; PD, progressive disease; Pembro, pembrolizumab; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RP2D, recommended phase 2 dose; SG, sacituzumab govitecan; Sq, squamous; TPS, tumor proportion score.

Patient Baseline Characteristics, Exposure, and Disposition

[redacted]

Characteristic	Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro n = 30	Cohort B (PD-L1 TPS < 50%) SG + Pembro n = 33
Median age (range), years	67 (47-77)	68 (47-80)
Male, %	80	79
Race, %		
Asian	20	15
Black	7	3
White	73	82
ECOG PS 1, %	80	76
Histology, %		
Nonsquamous	60	61
Squamous	40	39
Stage IV disease at diagnosis,[a] %	80	85
PD-L1 TPS,[b] %		
≥ 50%	100	0
1-49%	0	48
< 1%	0	52

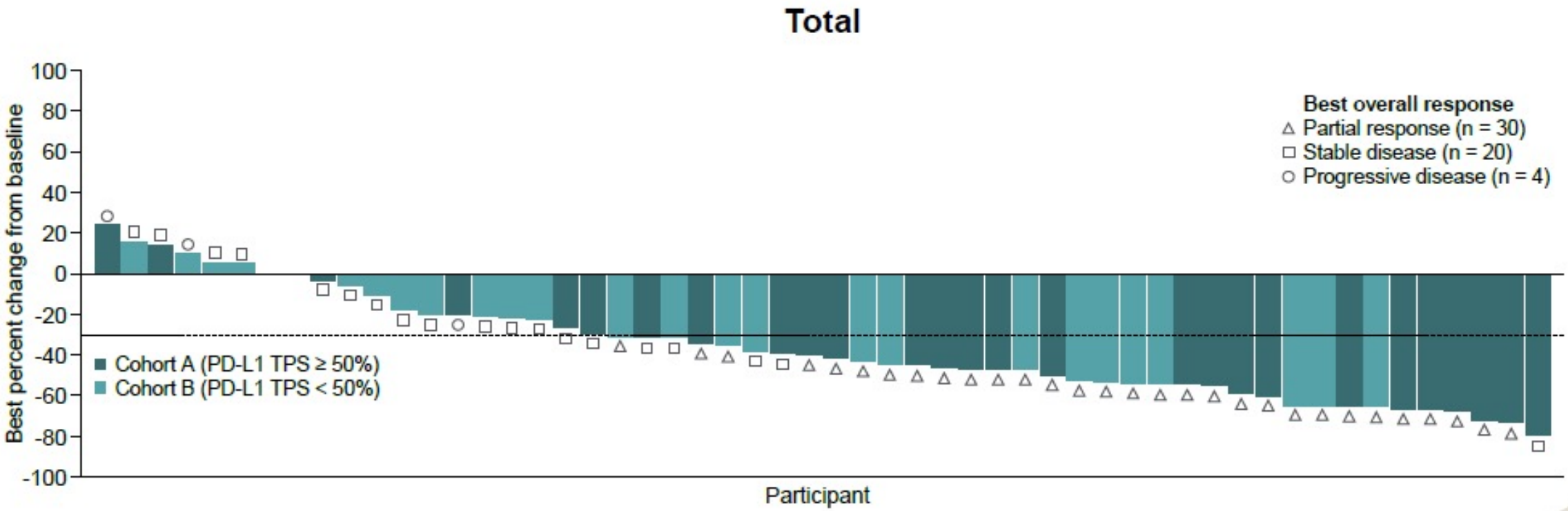
Patient exposure and disposition	Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro n = 30	Cohort B (PD-L1 TPS < 50%) SG + Pembro n = 33
Median duration of treatment (range), months		
SG	4.1 (0-11.2+)	4.1 (0-11.9+)
Pembro	3.6 (0-11.2+)	3.8 (0-11.7+)
Median number of cycles received (range), cycles		
SG	6 (1-17+)	6 (1-17+)
Pembro	6 (1-17+)	6 (1-17+)
Continuing treatment with SG, %	63	39
Continuing treatment with Pembro, %	63	42
Discontinued all study treatment, %	37	58

- Across both cohorts, the most common reason for discontinuation of sacituzumab govitecan was progressive disease

[a]Disease stage at diagnosis: Stage I-III (Cohort A, n = 5; Cohort B, n = 5). [b]The PD-L1 IHC 22C3 pharmDx assay was required for PD-L1 testing. Local and central tumor tissue testing were allowed.
ECOG PS, Eastern Cooperative Oncology Group performance status; PD-L1, programmed death ligand 1; Pembro, pembrolizumab; SG, sacituzumab govitecan; TPS, tumor proportion score.

Waterfall Plot for Change in Target Lesions

Back to Congress Datasets



Only patients enrolled ≥ 13 weeks prior to the data cutoff date (16 June 2023) were included in the efficacy analysis. PD-L1, programmed death ligand 1; TPS, tumor proportion score.

Depth and Duration of Response

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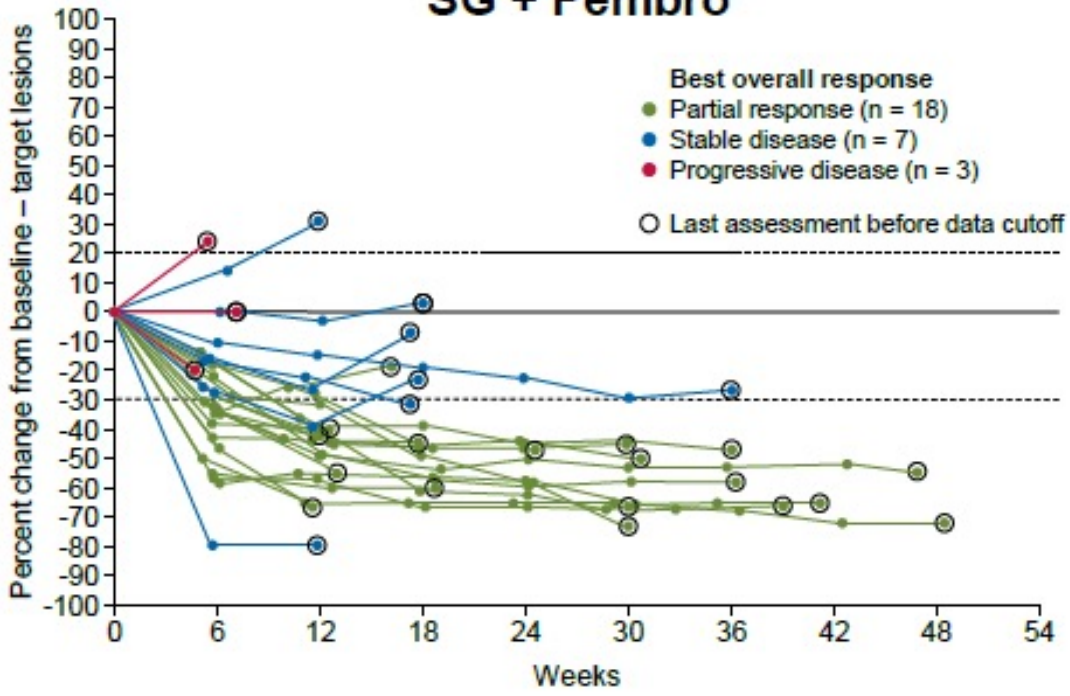
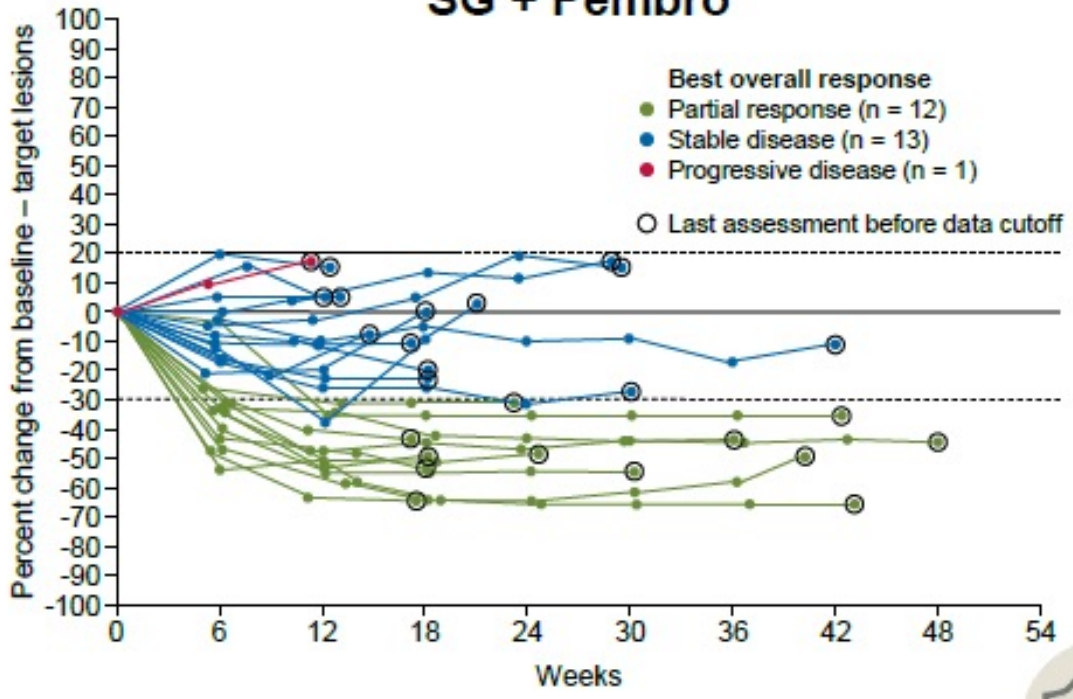
Cohort A (PD-L1 TPS ≥ 50%) SG + Pembro

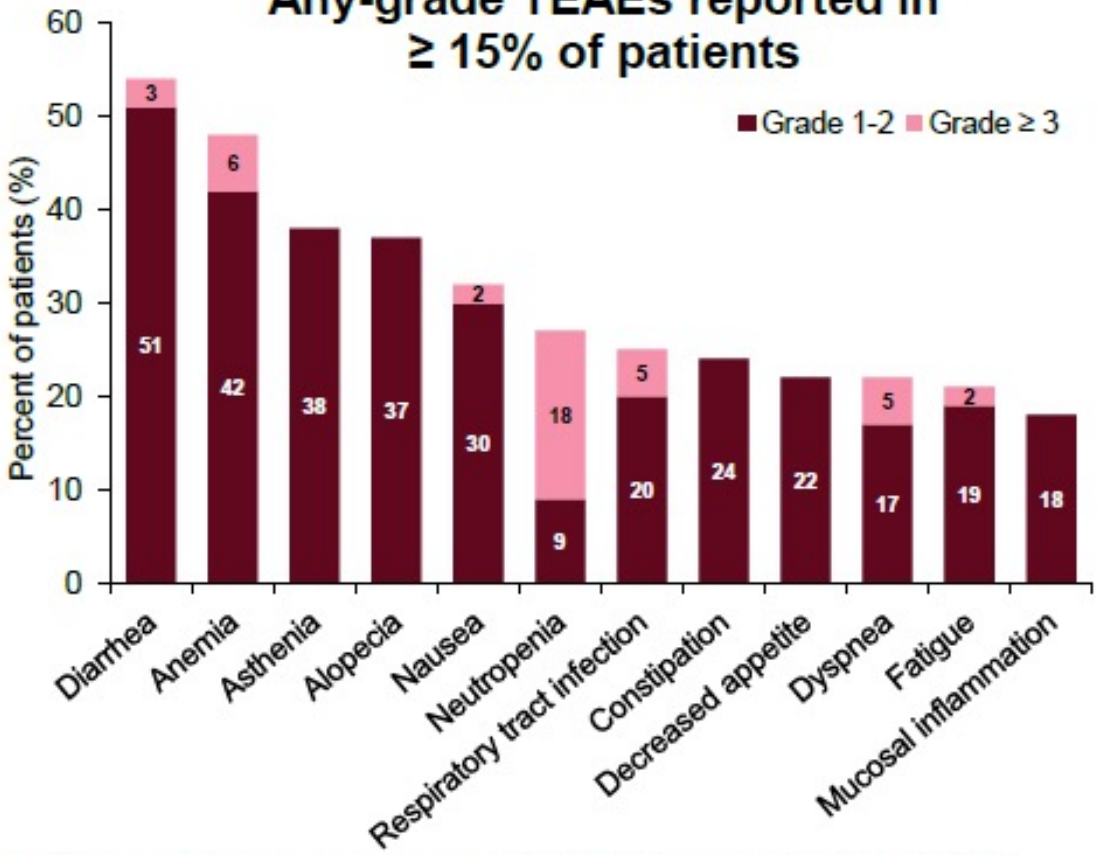


Cohort B (PD-L1 TPS < 50%) SG + Pembro

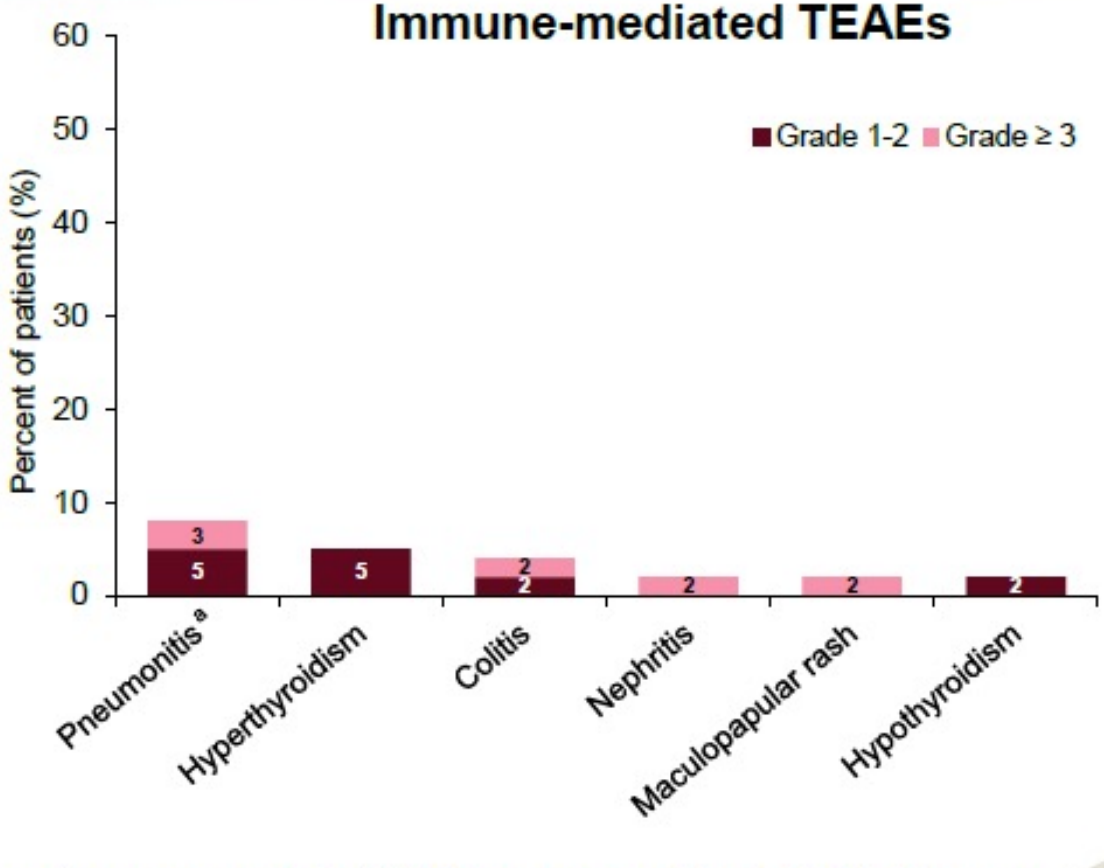


Only patients enrolled ≥ 13 weeks prior to the data cutoff date (16 June 2023) were included in the efficacy analysis. PD-L1, programmed death ligand 1; Pembro, pembrolizumab; SG, sacituzumab govitecan; TPS, tumor proportion score.

Any-grade TEAEs reported in ≥ 15% of patients



Immune-mediated TEAEs



- The most common any-grade TEAEs were diarrhea (54%), anemia (48%), and asthenia (38%)
- Immune-mediated TEAEs were consistent with the known safety profile of Pembro

All patients who received ≥ 1 dose of study treatment were included in the safety analysis. [a]Grade 3 pneumonitis was the highest grade observed to date (n = 2). Pembro, pembrolizumab; TEAE, treatment-emergent adverse event.

Select Ongoing Trials of Sacituzumab Govitecan in Advanced or Metastatic NSCLC

Trial	Phase	Setting	Therapy	Primary EP(s)
EVOKE-01 (NCT05089734)	III	Advanced/metastatic NSCLC previously treated with platinum CT and PD-1/PD-L1 inhibitor; if AGA present, must also have received appropriate TKI	Sacituzumab govitecan vs docetaxel	OS
EVOKE-03 (NCT05609968)	III	1L advanced/metastatic NSCLC without AGAs; PD-L1 ≥50%	Sacituzumab govitecan + pembrolizumab vs pembrolizumab	PFS, OS

9114

SKB264 (MK-2870, TROP2-ADC) for the treatment of patients with advanced NSCLC: Efficacy and safety data from a phase 2 study

Back to Congress Datasets

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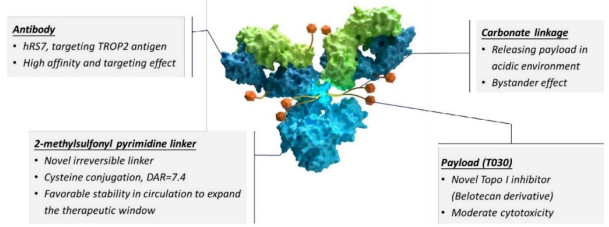
Background

- TROP2 (trophoblast cell surface antigen 2) is overexpressed in approximately 70% of non-small cell lung cancer (NSCLC) and associated with poor prognosis.[1-2] For EGFR mutant NSCLC, TROP2 has been reported to be correlated with gefitinib resistance[3]
- SKB264 is a novel anti-TROP2 ADC developed with sulfonyl pyrimidine-CL2A-carbonate linker to conjugate the payload, a belotecan-derivative topoisomerase I inhibitor, to achieve an average Drug-to-antibody Ratio (DAR) of 7.4. The design was to achieve a more effective balance between stability in circulation and release of the ADC payload in tumor cells
- SKB264 has demonstrated a manageable safety profile with promising antitumor activity in mTNBC[4]
- Here we report the clinical efficacy and safety results of SKB264 for the treatment of patients with NSCLC from a phase 2 expansion cohort (NCT04152499)

Figure 1. Structure of SKB264



Methods

- KL264-01 (MK2870-001) is a phase 1/2 study in patients with advanced solid tumors including NSCLC which had been heavily treated. Both patients with EGFR wild-type and EGFR mutant NSCLC were enrolled in the phase 2 expansion cohort
- All NSCLC patients received SKB264 at 5 mg/kg IV Q2W. Tumor assessments per RECIST 1.1 were performed every 8 weeks by investigators

Results

Patient Population

- As of February 9th, 2023, 43 patients (21 and 22 with EGFR wild-type and EGFR mutant, respectively) were enrolled
- Median follow-up was 11.5 months (mo; 95% CI, 10.4-12.2)

Presented at the American Society of Clinical Oncology (ASCO) 2023 Annual Meeting; June 2-6, 2023, Chicago, IL, USA.

Results

Table 1. Patient demographics and baseline characteristics

	All NSCLC (N=43)	EGFR mutant (N=22)	EGFR wild-type (N=21)
Age, median (range), years	58.0 (44.0-74.0)	56.0 (44.0-74.0)	63.0 (49.0-74.0)
Sex, male, n (%)	27 (62.8)	9 (40.9)	18 (85.7)
ECOG, n (%)			
0	5 (11.6)	3 (13.6)	2 (9.5)
1	38 (88.4)	19 (86.4)	19 (90.5)
Histology, n (%)			
Nonsquamous	29 (67.4)	20 (90.9)	9 (42.9)
Squamous	14 (32.6)	2 (9.1)	12 (57.1)
Location of metastasis, n (%)			
Lung	12 (27.9)	4 (18.2)	8 (38.1)
Liver	10 (23.3)	4 (18.2)	6 (28.6)
Bone	7 (16.3)	6 (27.3)	1 (4.8)
Pleura	13 (30.2)	8 (36.4)	5 (23.8)
Brain	5 (11.6)	2 (9.1)	3 (14.3)
Lymph nodes	23 (53.5)	11 (50)	12 (57.1)
Other	11 (25.6)	6 (27.3)	5 (23.8)
Number of previous treatment regimens for metastatic disease, n (%)			
≥2	33 (76.7)	17 (77.3)	16 (76.2)
Prior chemotherapy, n (%)	32 (74.4)	11 (50.0)	21 (100.0)
Prior immunotherapy, n (%)	21 (48.8)	0	21 (100.0)
Prior third-generation EGFR-TKI, n (%)	13 (30.2)	13 (59.1)	0

Efficacy

- 39 patients are response-evaluable (≥1 post-baseline scan). The overall ORR for NSCLC was 43.6% (17/39). Median DoR was 9.3 mo (range, 1.3+ to 11.2+) and 6-mo DoR rate was 77.4%. Median PFS was 6.2 mo. Median OS was not reached and 12-mo OS rate was 70.6%
- For patients with TKI resistant EGFR mutant NSCLC (50% of whom also failed at least one line of chemotherapy), the ORR was 60.0% (12/20), and DCR was 100%
- For patients with EGFR wild-type NSCLC who received anti-PD-1/L1 inhibitors and at least one line of chemotherapy (76.2% of whom received ≥2 lines of prior therapy), the ORR was 26.3% (5/19), and DCR was 89.5%

Table 2. Tumor Response assessed by investigator

	All NSCLC (N=43)	EGFR mutant (N=22)	EGFR wild-type (N=21)
ORR, %	43.6%	60.0%	26.3%
Confirmed ORR (cORR), %	38.5%	55.0%	21.1%
DCR, %	94.9%	100%	89.5%
DoR, median (95% CI), mo	9.3 (3.7, NE)	9.3 (2.0,NE)	9.6 (3.5, NE)
PFS, median (95% CI), mo	6.2 (5.3, 11.3)	11.1 (5.7, 13.1)	5.3 (3.5, 6.2)
9-mo PFS rate (95% CI), %	46.7 (30.2, 61.6)	66.7 (40.4, 83.4)	27.7 (10.3, 48.5)
OS, median (95% CI), mo	NR (NE, NE)	NR (NE, NE)	NR (10.7, NE)
12-mo OS rate (95% CI), %	70.6 (53.9, 82.1)	80.7 (56.3, 92.3)	60.6 (36.1, 78.2)

DCR, disease control rate; DoR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; PFS, progression-free survival; OS, overall survival.
*Based on response evaluable patients who have had at least on post-baseline scan (N=39).

Results

Figure 2. Best change from baseline in sum of target lesions

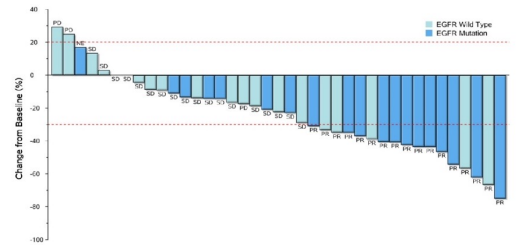


Figure 3. Time to response and duration of treatment for response

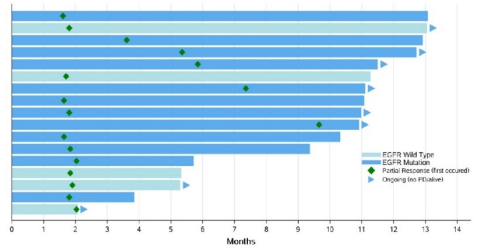


Figure 4. Change from baseline in sum of target lesions over time

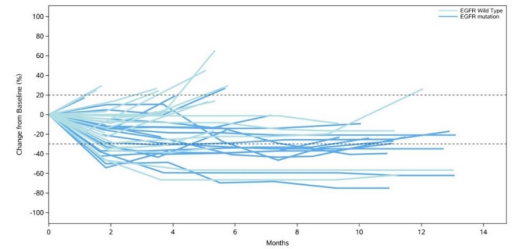
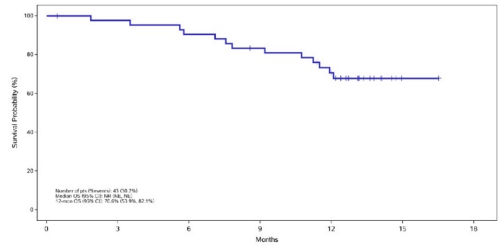


Figure 5. Kaplan-Meier plot of overall survival



Results

Safety

- TRAEs were mainly hematologic. No neuropathy, ocular toxicity, or drug-related ILD/pneumonitis was reported
- Most of the hematology toxicity occurred within the first 2 months of treatment and recovered after treatment with G-CSF or erythropoietin without blood transfusions
- Among patients with dose delay, approximately 80% of patients with maximum length of delays was for less than 2 weeks. Recurrent dose delay was not commonly occurred

Table 3. Overview of treatment-related adverse events (TRAEs)

	NSCLC (N=43) n (%)	
	All Grade	≥Grade 3
TRAEs	41 (95.3)	29 (67.4)
TRAEs associated with dose delay	21 (48.8)	17 (39.5)
TRAEs associated with dose reduction	10 (23.3)	9 (20.9)
TRAEs associated with discontinuation	0	0
Treatment-related SAEs	9(20.9)	9 (20.9)
TRAEs associated with death	0	0
TRAEs by preferred term in ≥20% of patients		
Anemia	31 (72.1)	13 (30.2)
White blood cell count decreased	24 (55.8)	10 (23.3)
Alopecia	23 (53.5)	0
Neutrophil count decreased	23 (53.5)	14 (32.6)
Stomatitis	21 (48.8)	4 (9.3)
Rash	17 (39.5)	3 (7.0)
Nausea	16 (37.2)	0
Decreased appetite	15 (34.9)	0
Vomiting	14 (32.6)	2 (4.7)
Platelet count decreased	10 (23.3)	1 (2.3)
Hypoalbuminemia	9 (20.9)	0

Conclusions

- SKB264 demonstrated manageable safety profile and encouraging antitumor activity in patients with advanced or metastatic NSCLC. Higher response was observed for EGFR mutant NSCLC
- Response was durable, with median DoR of 9.3 mo. Median OS was not reached, and 12-mo OS rate was 70.6%
- A phase 3 study of SKB264 for the treatment of patients with locally advanced or metastatic EGFR mutant NSCLC who have failed EGFR-TKI therapy is ongoing in China and global phase 3 studies in NSCLC are planned.

Acknowledgements

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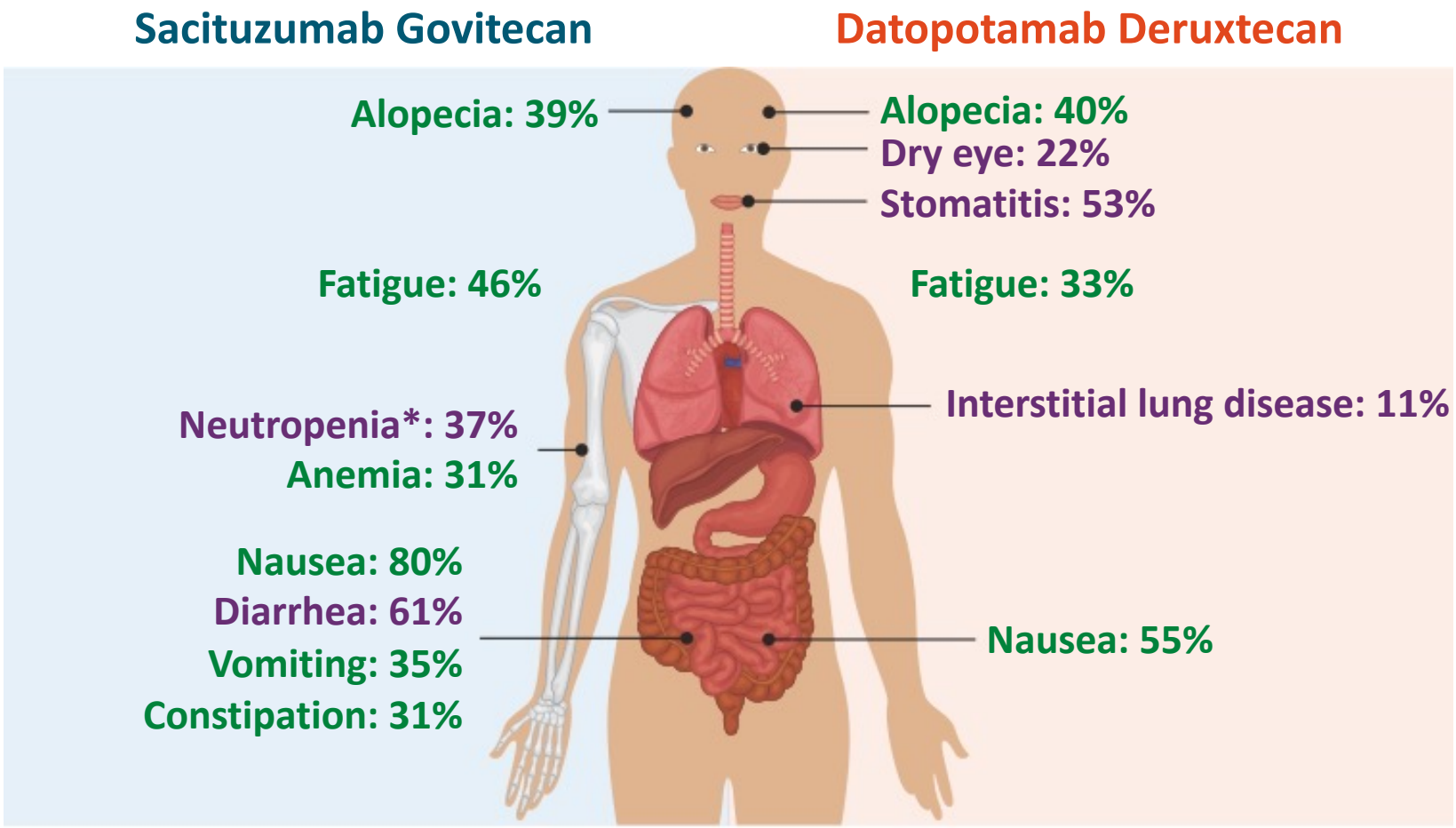
https://bit.ly/42QWNH1

Common and Notable Toxicities Associated With TROP-2–Directed ADCs



*Most common severe AE.

Heist. JCO. 2017;35:2790. Shimizu. JCO. 2023;41:4678.

TROPION-PanTumor01 Substudy: Prophylactic Mouthwash for Mucositis/Stomatitis

Substudy of phase I dose expansion

Adults with R/R advanced/metastatic cancer enrolling on ongoing and new cohorts of dose expansion (planned N = 76)

Stratified by tumor type

1:1

Prophylactic Steroid Mouthwash (n = 38)

Prophylactic Nonsteroid Mouthwash (n = 38)

After 8 wk, evaluate for incidence and severity of mucositis/stomatitis

Mouthwash can be extended for additional 8 wk at investigator discretion

NCT03401385.

Conclusions

A new category of drugs! But they are all different!

Multiple different toxicities (ILD, mucositis, etc)

It is still a ? If they will arrive to the first line

CEACAM5 closed the research area


Thank you - Grazie