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WCLC Highlights 2023

DAIICHI SANKYO CO., LTD.

Sep 11th (US)/ 12th (JP), 2023

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WCLC Highlights 2023

Agenda

1. **WCLC DS presentations - main slides only-**
   - ✓ HERTHENA-Lung01 study snapshot data w/ 6mo FU
   - ✓ TROPION-Lung04 study safety and efficacy data
   - ✓ DESTINY-Lung02 study primary data
   - ✓ DS-7300 Ph1/2 study SCLC subgroup analysis
2. **Q&A**

Speakers

Ken Takeshita
Head of Global R&D

Mark Rutstein
Head of Global
Oncology Clinical Development

Content will be delivered on-demand after the meeting

Patritumab Deruxtecan (HER3-DXd) in *EGFR*-Mutated NSCLC Following EGFR TKI and Platinum-Based Chemotherapy: HERTHENA-Lung01

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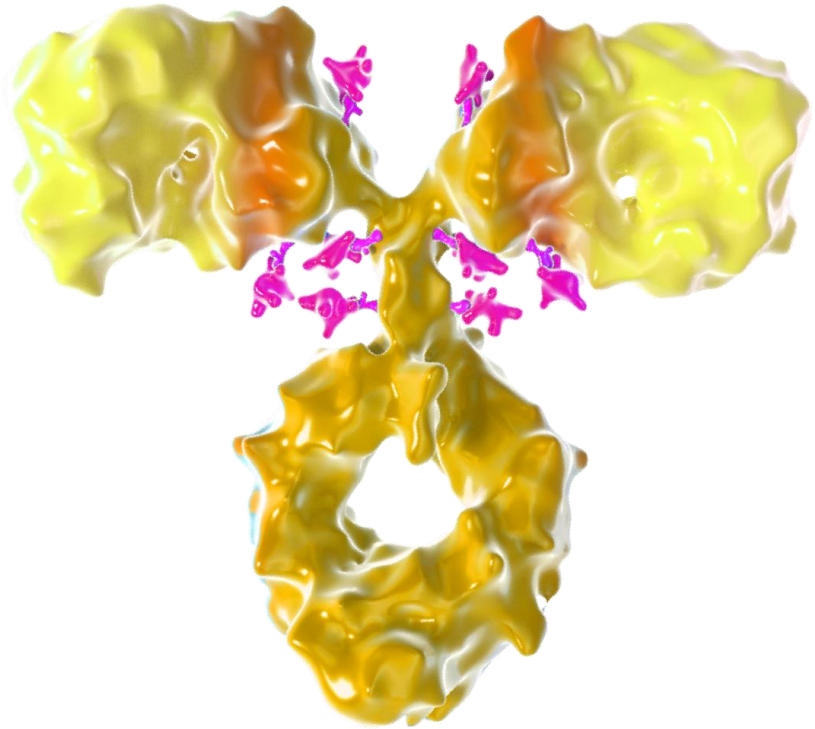
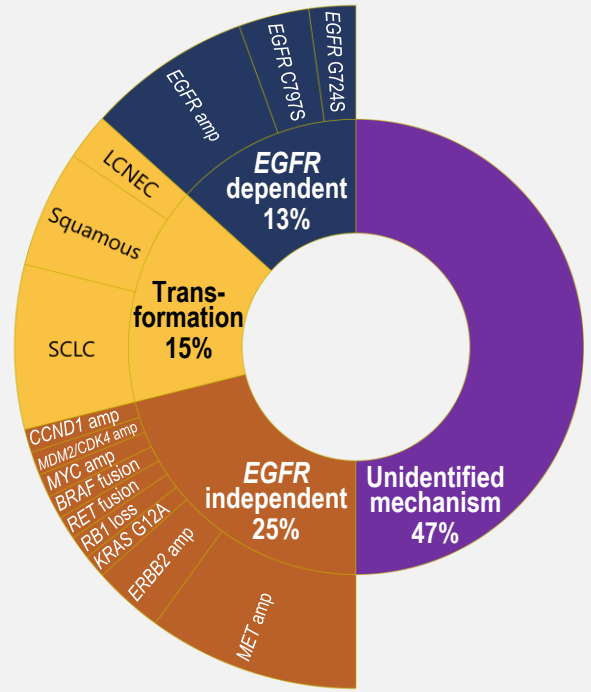


Efficacious and Tolerable New Therapies Are Needed for *EGFR*-Mutated NSCLC After Failure of an EGFR TKI and Platinum-Based Chemotherapy

- *EGFR*-activating mutations occur in 14% to 38% of patients with NSCLC[1,a]
  - Development of resistance to EGFR TKI therapy is typical[2]
  - Platinum-based chemotherapy is commonly administered after failure of EGFR TKI therapy[3]
- Salvage therapies after EGFR TKI therapy and platinum-based chemotherapy provide only a limited and transient clinical benefit[5,6]
  - Real-world PFS after progression with osimertinib and platinum-based chemotherapy: 3.3 (95% CI, 2.8-4.4) months[6]
  - Estimated real-world cORR: 14.1% (95% CI, 3.7%-33.1%)[7]
- CNS metastases are common in this population,[8] and therapies to ensure CNS control are needed

Mechanisms of Resistance to First-Line Osimertinib Are Diverse[4]



HERTHENA-Lung01 evaluated the efficacy and safety of patritumab deruxtecan (HER3-DXd) in patients with *EGFR*-mutated NSCLC after progression with EGFR TKI therapy and platinum-based chemotherapy

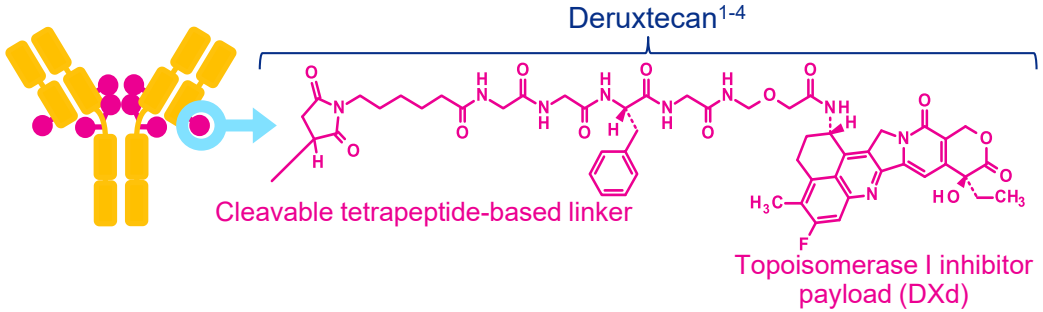
CNS, central nervous system; cORR, confirmed objective response rate; LCNEC, large cell neuroendocrine carcinoma; PFS, progression-free survival; SCLC, small cell lung cancer; TKI, tyrosine kinase inhibitor.
[a] Data for patients with adenocarcinoma.

1. Zhang Y-L, et al. *Oncotarget.* 2016;7(48):78985-78993. 2. Schoenfeld AJ, Yu HA. *J Thorac Oncol*. 2020;15(1):18-21. 3. Han B, et al. *Onco Targets Ther.* 2018;11:2121-2129. 4. Choudhury NJ, et al. *J Thorac Oncol.* 2023;18(4):463-475. 5. Yang C-J, et al. *BMC Pharmacol Toxicol.* 2017;18(1):82. 6. Patel JD, et al. AACR 2023. Poster 6754. 7. Patel JD, et al. IASLC 2023 WCLC. Abstract 2201. 8. Gillespie CS, et al. *J Thorac Oncol*. Epub, June 29, 2023.

Patritumab Deruxtecan (HER3-DXd)

HER3-DXd is an ADC composed of 3 parts[1-4]:

- A fully human anti-HER3 IgG1 mAb (patritumab)
- A topoisomerase I inhibitor payload (DXd)
- A tetrapeptide-based cleavable linker that covalently bonds the other 2 components

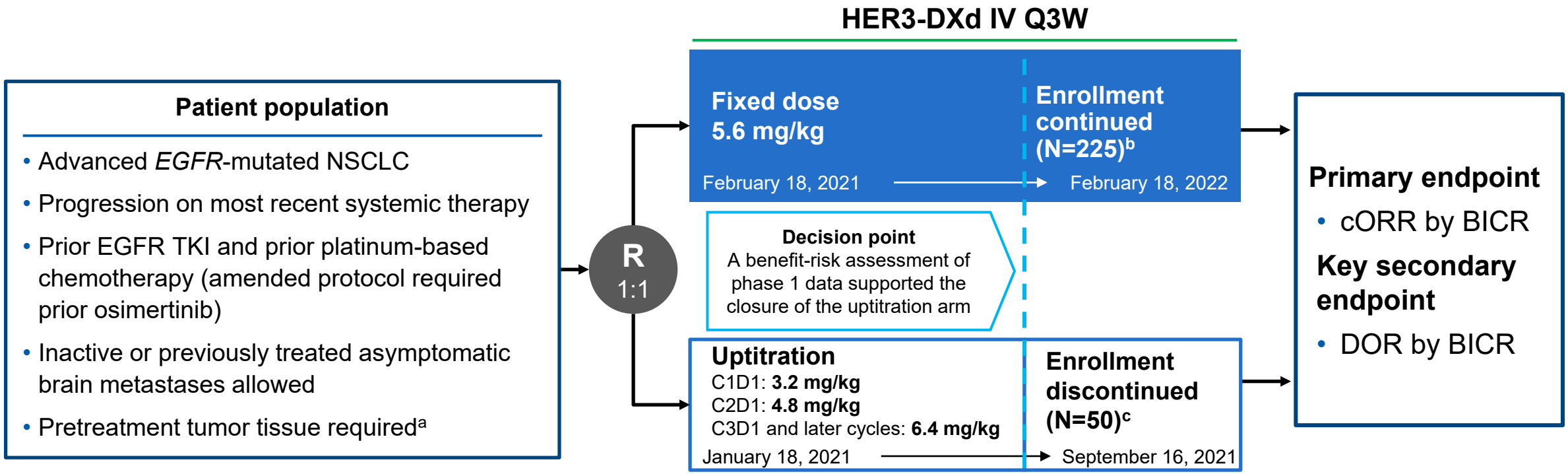


Payload mechanism of action: topoisomerase I inhibitor[1-4,a]
High potency of payload[1-4,a]
High drug to antibody ratio ≈8[1,2,a]
Payload with short systemic half-life[2,3,a,b]
Stable linker-payload[2-4,a]
Tumor-selective cleavable linker[1-5,a]
Bystander antitumor effect[2,6,a]

- A phase 1 study of HER3-DXd for advanced NSCLC demonstrated efficacy in patients with *EGFR*-activating mutations and diverse mechanisms of resistance to EGFR TKIs (including *EGFR*-dependent and -independent mechanisms)[7]
  - The study showed that HER3-DXd 5.6 mg/kg administered intravenously every 3 weeks was associated with a tolerable and manageable safety profile
- Promising data from the phase 1 trial led to initiation of the phase 2 HERTHENA-Lung01 trial of HER3-DXd in patients with *EGFR*-mutated NSCLC who were treated previously with EGFR TKI and platinum-based chemotherapy

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. 7. Jänne PA et al. *Cancer Discov.* 2022;12(1):74-89.

HERTHENA-Lung01 Study Design[1]



Primary data cutoff, 21 Nov 2022[d]
Snapshot data cutoff, 18 May 2023 (additional 6 months follow-up)
Data are presented for the 5.6-mg/kg fixed-dose arm

- Efficacy from snapshot data cutoff—median study follow-up, 18.9 (range, 14.9-27.5) months
- Safety from primary data cutoff—median treatment duration, 5.5 (range, 0.7-18.2) months

BICR, blinded independent central review; C, cycle; cORR, confirmed objective response rate (complete or partial response confirmed ≥4 weeks after initial response [RECIST version 1.1]); D, day; DOR, duration of response; HER, human epidermal growth factor receptor; IV, intravenous; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TKI, tyrosine kinase inhibitor.
[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 months of follow-up or had discontinued from the study earlier.
1. Yu HA, et al. *Future Oncol*. 2023;19:1319-1329.

Patients Were Heavily Pretreated and Had Adverse Prognostic Characteristics

Baseline characteristics		HER3-DXd 5.6 mg/kg (N=225)
Age, median (range), years		64 (37-82)
Female, n (%)		132 (59)
Asian, n (%)		105 (47)
Time since initial NSCLC diagnosis, median (range), months		41.0 (9.1-224.7)
ECOG performance status, n (%)	0/1	73 (32)/149 (66)
	2[a]	3 (1)
Sum of target lesion diameters at baseline (BICR), median (range), mm		68 (11-248)
History of CNS metastasis, n (%)		115 (51)
Brain metastasis at baseline (BICR), n (%)		72 (32)
Liver metastasis at baseline (BICR), n (%)		75 (33)
EGFR-activating mutations, n (%)[b]	Ex19del	142 (63)
	L858R	82 (36)
No. of prior lines of systemic therapy (locally advanced/metastatic)	Median (range)	3 (1-11)[c]
	2 prior lines, n (%)	58 (26)
	>2 prior lines, n (%)	165 (73)
Prior cancer regimens, n (%)	Prior EGFR TKI therapy	225 (100)
	Prior third-generation EGFR TKI	209 (93)
	Prior platinum-based chemotherapy	225 (100)
	Prior immunotherapy	90 (40)

BICR, blinded independent central review; CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; TKI, tyrosine kinase inhibitor.
[a] These patients had ECOG performance status of 0 or 1 at screening. [b] One patient had Ex19del and L858R mutations. [c] 2 patients had 1 prior line of therapy.

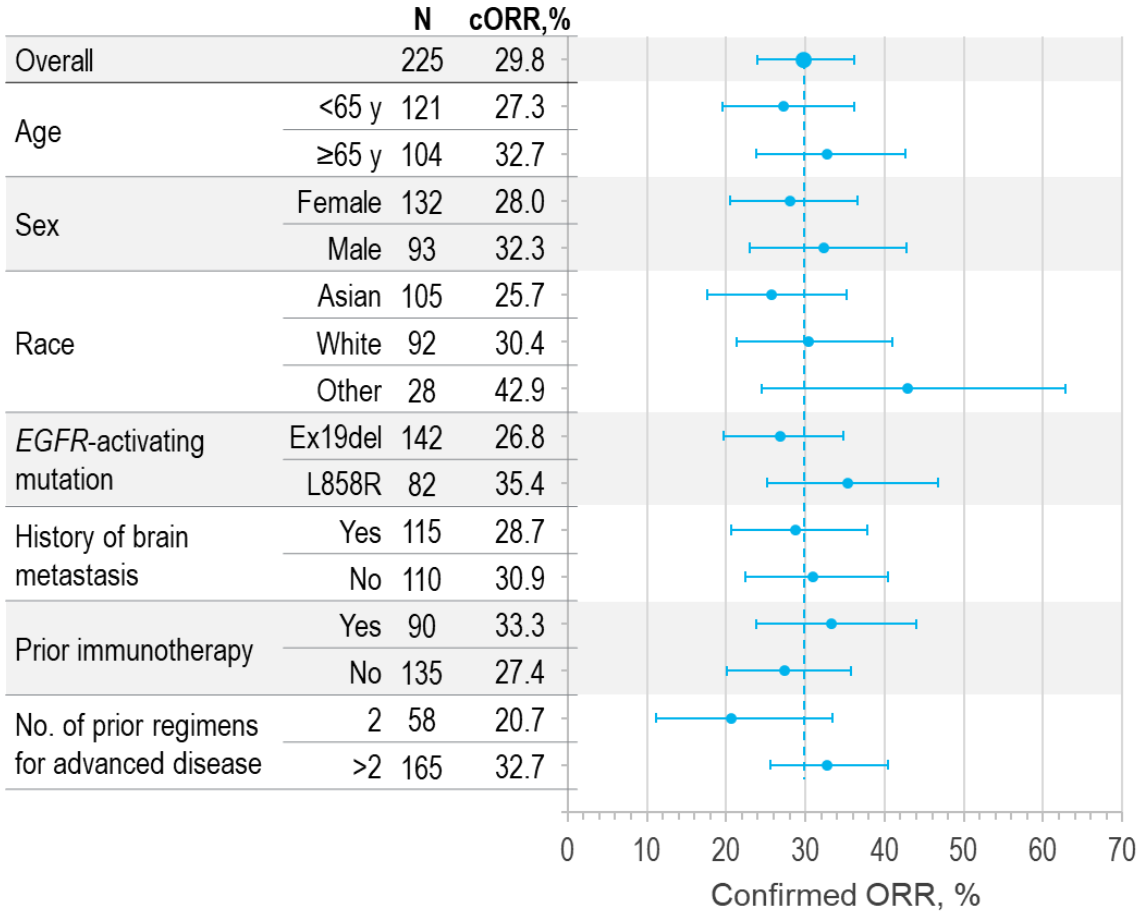
Presented by: **Helena A. Yu, Memorial Sloan Kettering Cancer Center, USA**

Clinically Meaningful Efficacy Was Observed in the Overall Population and Across Subgroups

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)**
Best overall response (BICR), n (%)	CR	1 (0.4)	1 (0.5)
	PR	66 (29.3)	60 (28.7)
	SD[a]	99 (44.0)	91 (43.5)
	PD	43 (19.1)	41 (19.6)
	NE[b]	16 (7.1)	16 (7.7)
DCR (95% CI), %		73.8 (67.5-79.4)	72.7 (66.2-78.6)
DOR, median (95% CI), mo		6.4 (4.9-7.8)	6.4 (5.2-7.8)
PFS, median (95% CI), mo		5.5 (5.1-5.9)	5.5 (5.1-6.4)
OS, median (95% CI), mo		11.9 (11.2-13.1)	11.9 (10.9-13.1)

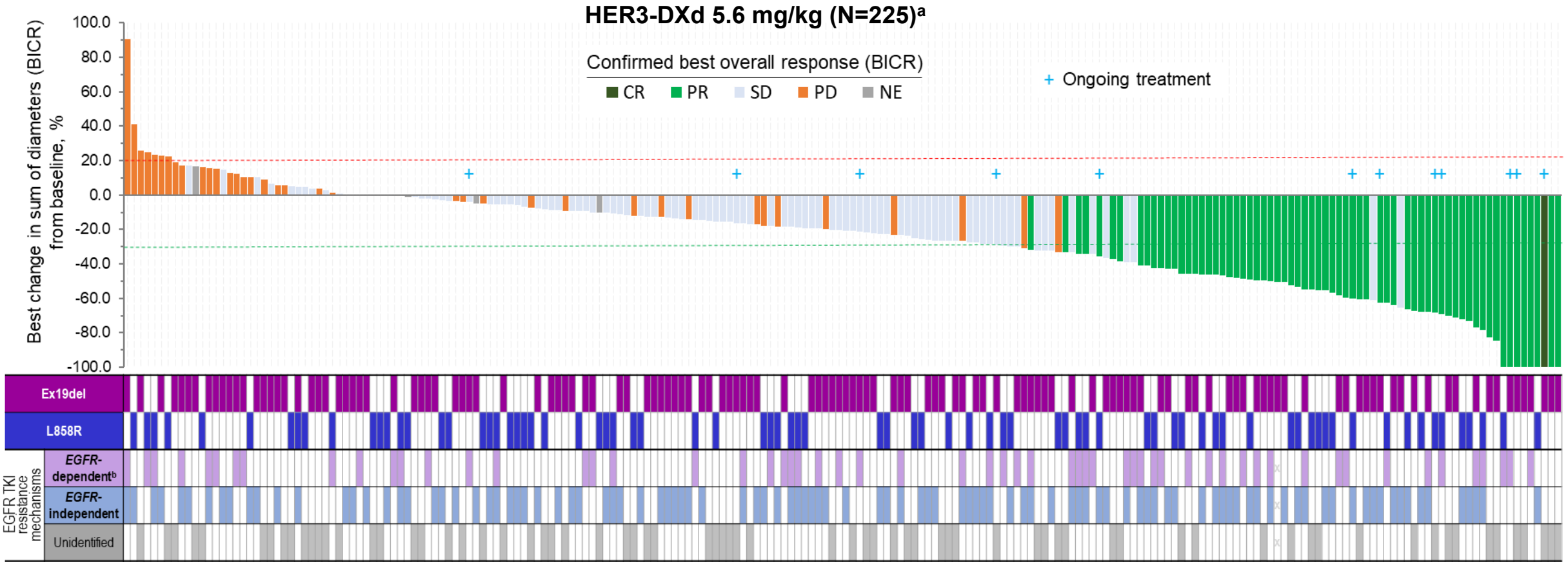
Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

cORR by Patient and Disease Characteristics at Study Entry



3G, third generation; BICR, blinded independent central review; cORR, confirmed objective response rate (CR or PR confirmed ≥4 weeks after initial response [RECIST v1.1]); CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; OS, overall survival; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] Includes non-CR/non-PD. [b] No adequate postbaseline tumor assessment (n=12); SD too early (SD <5 weeks after start of study treatment [n=4]).

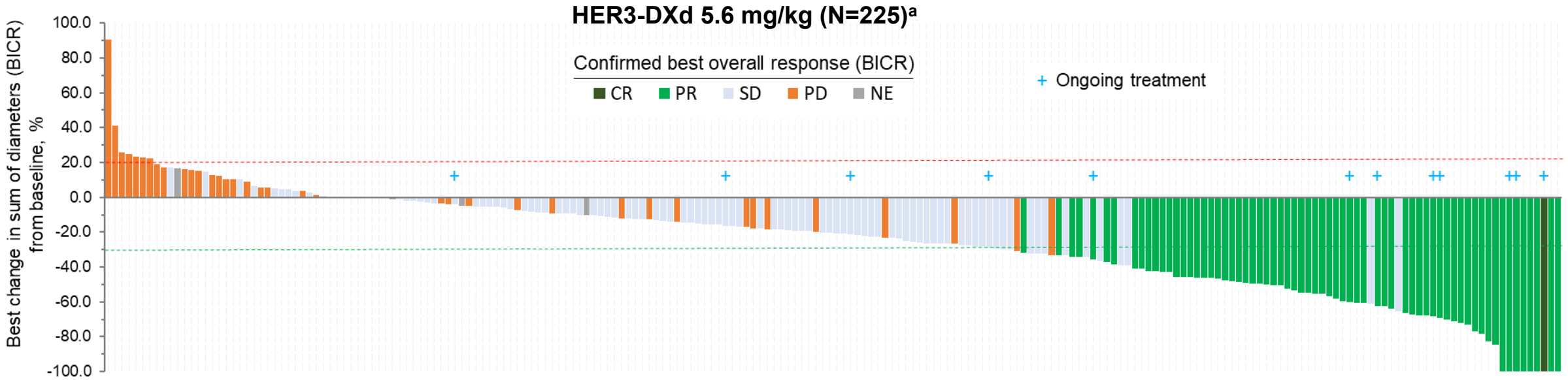
Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance



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

BICR, blinded independent central review; CR, complete response; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] 210 patients had evaluable target lesion measurements at both baseline and post baseline and are included. [b] T790M was not included as an *EGFR*-dependent mechanism of EGFR TKI resistance.

Tumor Reduction Across Diverse Mechanisms of EGFR TKI Resistance



	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)

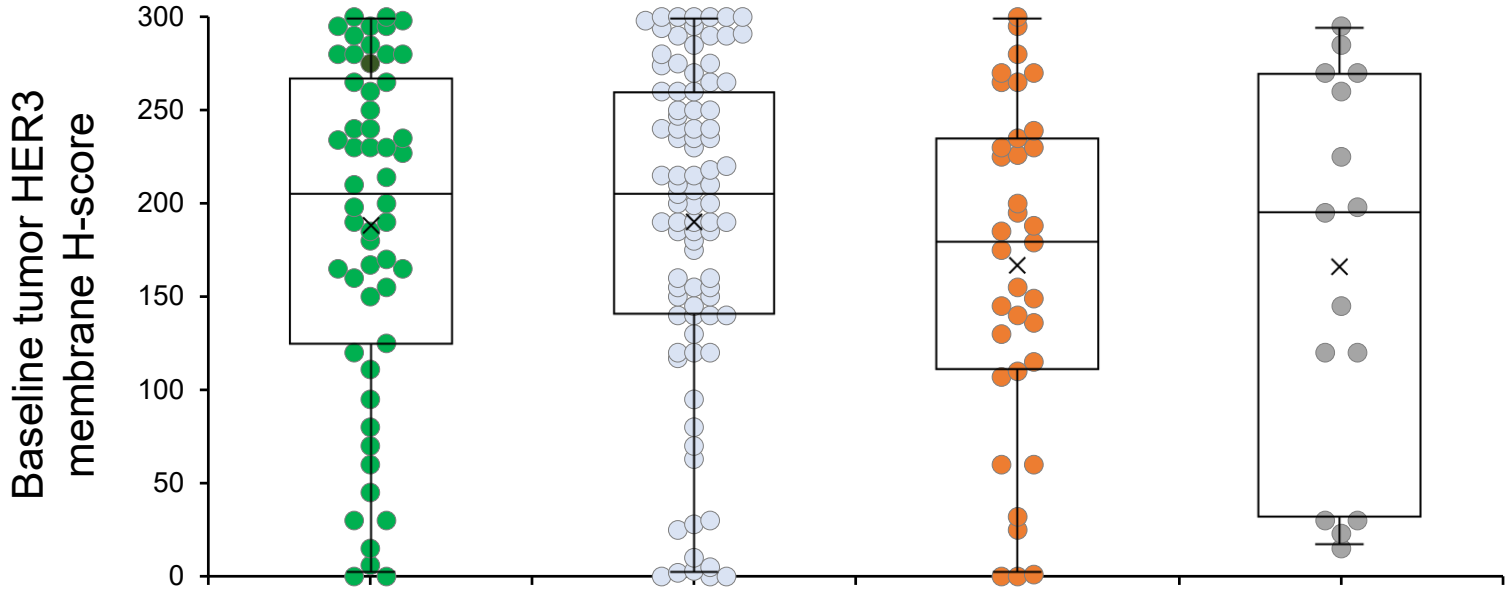
Snapshot data cutoff, 18 May 2023.
Median study follow-up, 18.9 (range, 14.9-27.5) months.

BICR, blinded independent central review; CR, complete response; HER, human epidermal growth factor receptor; IHC, immunohistochemistry; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.
[a] 210 patients had evaluable target lesion measurements at both baseline and post baseline and are included.

Presented by: **Helena A. Yu, Memorial Sloan Kettering Cancer Center, USA**

Efficacy Observed Across a Broad Range of Pretreatment Tumor HER3 Membrane Expression Levels

Association of Baseline Tumor HER3 Membrane H-Score With Confirmed BOR by BICR Following Treatment With HER3-DXd 5.6 mg/kg (N=225)[a]



Confirmed BOR (BICR)	CR/PR	SD	PD	NE
Biomarker-evaluable patients, n/n	54/67	89/99	35/43	15/16
H-score, median	205	205	179	195
(range)	(0-300)	(0-300)	(0-300)	(15-295)

Response data are for the snapshot data cutoff, 18 May 2023.
Medians are indicated by horizontal lines; means are indicated by X.

BICR, blinded independent central review; BOR, best overall response; CR, complete response; HER, human epidermal growth factor receptor; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
[a] 193 patients had tumor tissue evaluable for H-score. Baseline was the sample on or before the first dose date and not earlier than 90 days before the first dose date. Highest HER3 membrane H-score value was used if multiple records were available.

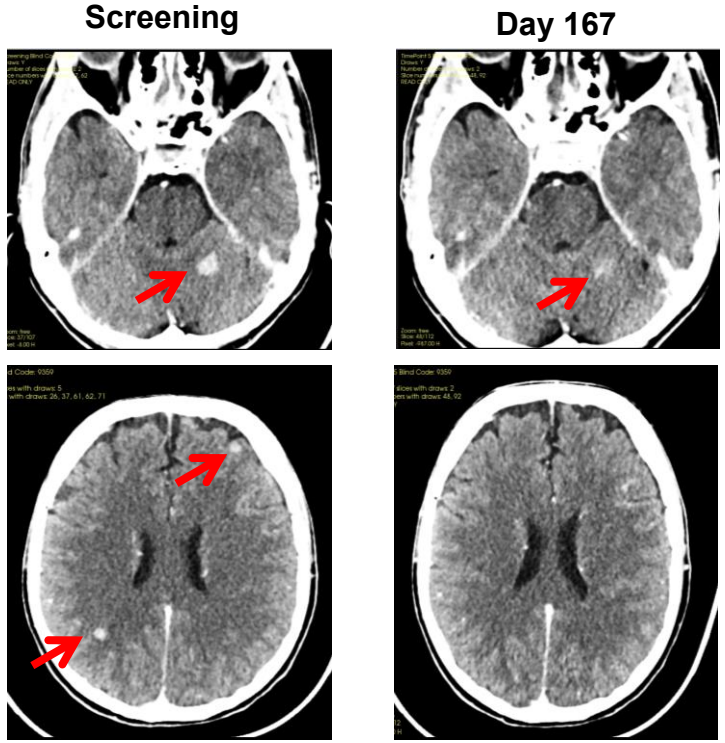
Intracranial Responses (by CNS BICR) Observed With HER3-DXd

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]
Confirmed ORR (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)
DOR, median (95% CI), mo	8.4 (5.8-9.2)

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

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



BICR, blinded independent central review; CNS, central nervous system; CR, complete response; DCR, disease control rate (CR+PR+SD); DOR, duration of response; MRI, magnetic resonance imaging; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[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.

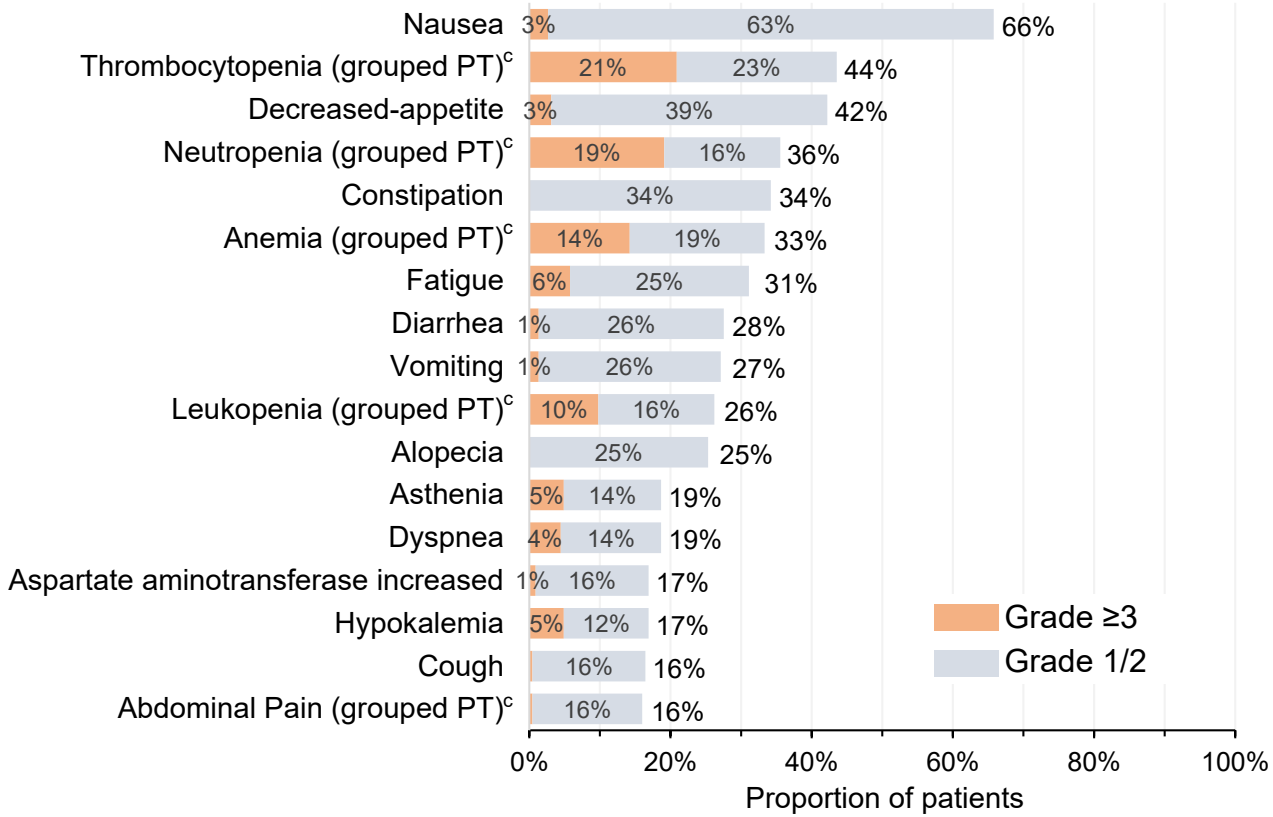
Presented by: Helena A. Yu, Memorial Sloan Kettering Cancer Center, USA

The Safety Profile of HER3-DXd Was Manageable and Tolerable

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)

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

Most Common TEAEs Occurring in ≥15% of Patients (N=225)



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

GI, gastrointestinal; TEAE, treatment-emergent adverse event.
[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.

Presented by: Helena A. Yu, Memorial Sloan Kettering Cancer Center, USA

Conclusions

- HER3-DXd provided clinically meaningful and durable efficacy (cORR, 29.8%) in patients with advanced *EGFR*-mutated NSCLC that progressed following EGFR TKI and platinum-based chemotherapy; efficacy was observed across diverse mechanisms of EGFR TKI resistance and across a broad range of pretreatment tumor HER3 membrane expression
- HER3-DXd showed clinically meaningful intracranial antitumor activity in patients with untreated brain metastases
  - Intracranial cORR, 33.3%
  - Intracranial DCR, 76.7%
- The safety profile of HER3-DXd in this population of heavily pretreated patients was manageable and tolerable and was consistent with previous reports
  - TEAE associated with treatment discontinuation, 7.1%
  - Adjudicated treatment-related ILD, 5.3%
- HER3-DXd has emerged as a promising therapy for patients with *EGFR*-mutated NSCLC after the failure of EGFR TKI and platinum-based chemotherapy, for whom available treatment options provide only limited efficacy

Datopotamab Deruxtecan (Dato-DXd) + Durvalumab ± Carboplatin in Advanced/Metastatic NSCLC: Initial Results from the Phase 1b TROPION-Lung04 Study

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[1]START San Antonio, San Antonio, TX, USA; [2]University Hospitals, Case Comprehensive Cancer Center, Cleveland, OH, USA; [3]The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [4]Kanagawa Cancer Center, Yokohama, Japan; [5]John Theurer Cancer Center, Hackensack, NJ, USA; [6]Shizuoka Cancer Center, Shizuoka, Japan; [7]Virginia Cancer Specialists, Fairfax, VA, USA; [8]Jessa Hospital, Hasselt, Belgium; [9]Limburg Clinical Research Center, Hasselt University, Diepenbeek, Belgium; [10]AstraZeneca, Cambridge, UK; [11]AstraZeneca, Gaithersburg, MD, USA; [12]Washington University School of Medicine in St. Louis, St. Louis, MO, USA

Background

- **Dato-DXd:** An ADC consisting of a humanized anti-TROP2 IgG1 monoclonal antibody covalently linked to a highly potent topoisomerase-I inhibitor payload via a plasma-stable, tumor-selective, tetrapeptide-based cleavable linker[1]
- **Pre-clinical data:** Dato-DXd enhances antitumor response to PD-1/PD-L1 inhibitors[2]
- **Phase 1 data:** Dato-DXd showed encouraging early clinical efficacy and manageable safety in patients with advanced or metastatic NSCLC:[3,4]

TROPION-PanTumor01 study[3,a]

ORR (confirmed): 26%

with Dato-DXd 6 mg/kg monotherapy in heavily pre-treated NSCLC

TROPION-Lung02 study[4,b]

ORR (confirmed and pending): 50% and 57%

with Dato-DXd + pembro and Dato-DXd + pembro + platinum-based chemotherapy, respectively, in 1L NSCLC

- **Phase 3 data:** Dato-DXd 6 mg/kg monotherapy demonstrated a statistically significant improvement in PFS versus docetaxel in previously treated advanced or metastatic NSCLC (TROPION-Lung01 study)[5]

[a] N=50 patients in the Dato-DXd 6 mg/kg cohort with an ORR of 26% (95% CI: 14.6, 40.3). [b] N=34 patients in the doublet cohort with an ORR of 50% (95% CI: 32, 68). N=53 patients in the triplet cohort with an ORR of 57% (95% CI: 42, 70).
1L, first-line; ADC, antibody-drug conjugate; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; Ig, immunoglobulin; NSCLC, non-small-cell lung cancer; ORR, objective response rate; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; pembro, pembrolizumab; PFS: progression-free survival; TROP2, trophoblast cell surface protein 2.

1. Okajima D, et al. Mol Cancer Ther 2021;20:2329–40; 2. Okajima D, et al. Poster 2932. Presented at AACR 2023; 3. Shimizu T, et al. J Clin Oncol 2023;10.1200/JCO.23.00059:ePub; 4. Goto Y, et al. Oral 9004. Presented at ASCO 2023; 5. AstraZeneca Press Release. Datopotamab deruxtecan met dual primary endpoint of progression-free survival in patients with advanced non-small cell lung cancer in TROPION-Lung01 Phase III trial. Available at: https://www.astrazeneca.com/media-centre/press-releases.html (accessed July 2023).

TROPION-Lung04 Study Design

Phase 1b, multicenter, open-label, dose escalation/confirmation and expansion study

TROPION-Lung04 is investigating Dato-DXd in combination with different immunotherapy agents ± carboplatin across 11 cohorts. This interim analysis reports the first data from Cohorts 2 and 4

Key eligibility

- Adults (≥18 years) with previously treated or treatment-naïve advanced or metastatic NSCLC[a]
- No actionable genomic alterations
- ECOG PS 0–1

	1 Part 1: Sequential dose escalation[b]	2 Part 2: Dose expansion
Cohort 1 (Doublet)	Dato-DXd 4 mg/kg + durvalumab 1120 mg, Q3W (n=5)	
Cohort 2 (Doublet)	Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=3)	Dato-DXd 6 mg/kg + durvalumab 1120 mg, Q3W (n=16)
Cohort 3[c] (Triplet)	Dato-DXd 4 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W	
Cohort 4 (Triplet)	Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=6)	Dato-DXd 6 mg/kg + durvalumab 1120 mg + 4 cycles carboplatin AUC 5, Q3W (n=8)

- **Primary endpoint:** Safety and tolerability
- **Key secondary endpoints:** ORR and disease control rate by investigator assessment per RECIST v1.1

Data cut-off: March 6 2023.

[a] Patients in Cohort 1 and one patient in Cohort 2 had received ≥1 platinum-based chemotherapy regimen and anti-PD-1/PD-L1 therapy as per an earlier version of the clinical study protocol. Subsequent patients were treatment-naïve or had ≤1 prior line of systemic chemotherapy without concomitant immune checkpoint inhibitors. [b] Dose escalation was guided by a mTPI-2 design and conducted sequentially from Cohort 1 to 2 (Dato-DXd 4 mg/kg to 6 mg/kg) and Cohort 2 to 4 (doublet to triplet combination). [c] Cohort 3 was skipped as there were sufficient data available from the Dato-DXd development program to conclude that 4 mg/kg Dato-DXd in combination with immunotherapy and carboplatin has an acceptable safety profile.

AUC, area under the curve; ECOG PS, Eastern Cooperative Oncology Group performance status; mTPI-2, modified toxicity probability interval-2; Q3W, once every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Baseline Characteristics and Patient Disposition

Characteristic, n (%)		Cohort 2 (doublet) N=19[a]	Cohort 4 (triplet) N=14[a]
Age, median (range), years		63 (49–75)	67 (55–72)
Male		14 (73.7)	9 (64.3)
Dato-DXd combination line of therapy	1L	14 (73.7)	13 (92.9)
	2L+	5 (26.3)[b]	1 (7.1)[b]
Histology	Squamous	5 (26.3)	4 (28.6)
	Non-squamous	14 (73.7)	10 (71.4)
History of brain metastases		4 (21.1)	3 (21.4)
PD-L1 expression	<1%	6 (31.6)	6 (42.9)
	1–49%	6 (31.6)	3 (21.4)
	≥50%	7 (36.8)	5 (35.7)
Tumor stage at study entry	IIIA, IIIB or IIIC	0	2 (14.3)
	IV, IVA or IVB	19 (100)	12 (85.7)

At the time of data cut-off, for Cohort 2 and Cohort 4, respectively:

- Study treatment was ongoing in 31.6% and 50.0% of patients
- Median (range) study treatment duration was 6.0 months (0.7–12.5) and 6.2 months (1.5–11.0)

Data cut-off: March 6 2023.
Patients were enrolled across sites in Japan and the USA only in Cohorts 2 and 4. [a] Includes patients from Part 1 (dose escalation) and Part 2 (dose expansion). Cohort 1 was not expanded. [b] There were 4/5 (80.0%) 2L+ patients in Cohort 2 and 1/1 (100%) 2L+ patients in Cohort 4 who had received prior radiation therapy.
2L+: second line and later.

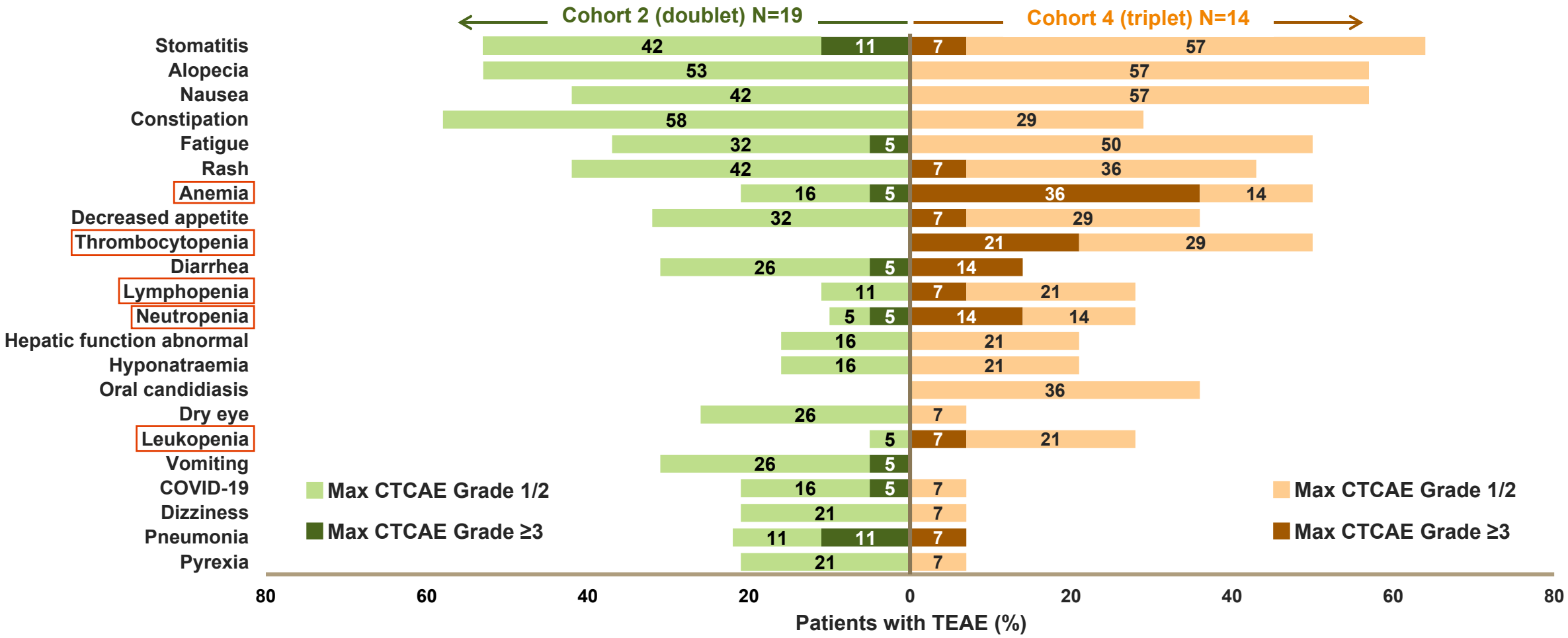
Safety Summary

Events, n (%)		Cohort 2 (doublet) N=19	Cohort 4 (triplet) N=14
TEAEs		**19 (100)**	**14 (100)**
Study treatment-related[a]		19 (100)	14 (100)
Grade ≥3 TEAEs		**8 (42.1)**	**10 (71.4)**
Study treatment-related[a]		6 (31.6)	8 (57.1)
SAEs		**7 (36.8)**	**5 (35.7)**
Study treatment-related[a]		6 (31.6)	5 (35.7)
TEAEs associated with	Death	0	0
	Discontinuation of any drug	4 (21.1)	3 (21.4)
	Discontinuation of Dato-DXd	4 (21.1)	2 (14.3)
ILD adjudicated as drug-related		**3 (15.8)**	**1 (7.1)**
Grade 1		1 (5.3)	0
Grade 2		1 (5.3)	1 (7.1)
Grade ≥3		1 (5.3)[b]	0

- There were **no DLTs** in **Cohort 1** or **Cohort 2** during Part 1 (dose escalation)
- **Two patients** reported DLTs in **Cohort 4** (1 patient had Grade 3 febrile neutropenia and 1 patient had both Grade 3 stomatitis and Grade 3 maculo-papular rash)[c]
- Dose expansion subsequently occurred in Cohort 2 (doublet) and Cohort 4 (triplet)
- There were **no Grade 5 adjudicated ILD events**. There was one Grade 4 adjudicated ILD event in a patient in Cohort 2[b]

Data cut-off: March 6 2023.
TEAEs are defined as AEs with a start date or worsening date on or after the start of study treatment until 97 days after the last dose. [a] Treatment-related TEAEs are related to Dato-DXd, durvalumab or carboplatin. [b] There was one Grade 4 ILD adjudicated as drug-related in a patient who received sotorasib after PD/discontinuation of IP. [C] One patient had Grade 3 stomatitis and Grade 3 maculo-popular rash AEs that reached DLT criteria due to Cycle 2 dosing being delayed by >2 weeks.
AE, adverse event; ILD, interstitial lung disease; IP, investigational product; PD, progression of disease; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

TEAEs in ≥15% of Patients



Data cut-off: March 6 2023.
TEAEs by preferred term/grouped preferred term. TEAEs in ≥15% of patients is based on the total number of safety subjects in Cohort 2 and Cohort 4. Red boxes indicate hematological events.
CTCAE, Common Terminology Criteria for Adverse Events.

Antitumor Activity

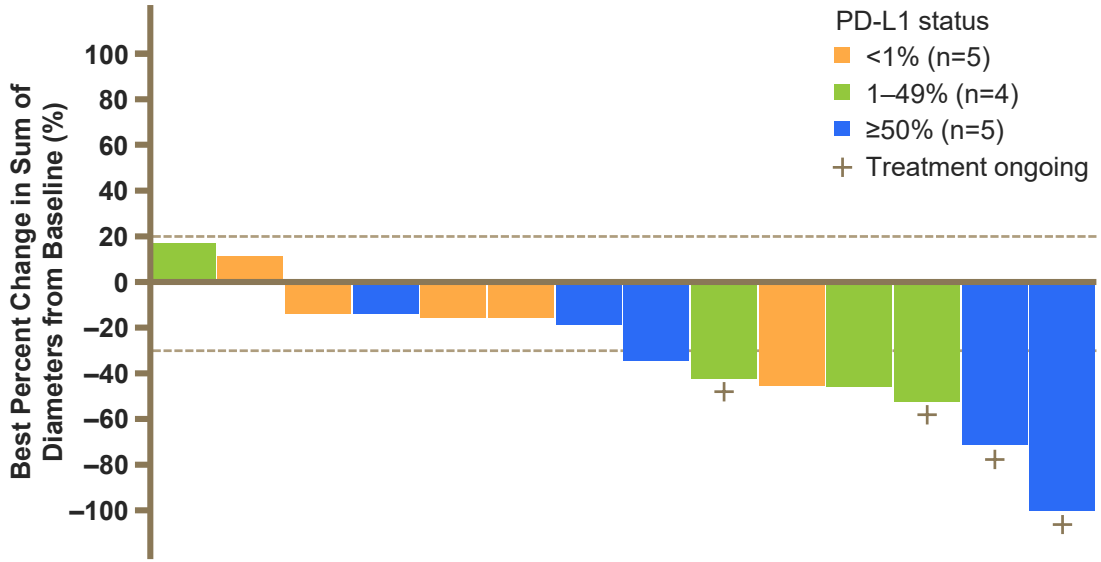
Response in patients in the 1L setting,[a] n (%)		Cohort 2 (doublet) N=14	Cohort 4 (triplet) N=13
Objective response rate (confirmed)		**7 (50.0)**	**10 (76.9)[b]**
[95% CI]		[23.0, 77.0]	[46.2, 95.0]
Best objective response	Complete response	0	0
	Partial response	7 (50.0)	10 (76.9)[b]
	Stable disease	6 (42.9)	2 (15.4)
	Progressive disease	1 (7.1)	1 (7.7)
Disease control rate		**13 (92.9)**	**12 (92.3)**
[95% CI]		[66.1, 99.8]	[64.0, 99.8]

- In the 1L setting, ORRs were **50.0%** for Cohort 2 and **76.9%[b]** for Cohort 4
- In the overall population (1L/2L+), ORRs were **47.4%** for Cohort 2 (N=19) and **71.4%[b]** for Cohort 4 (N=14)
- Responses were numerically higher with the triplet versus doublet combination and were observed across all PD-L1 expression levels

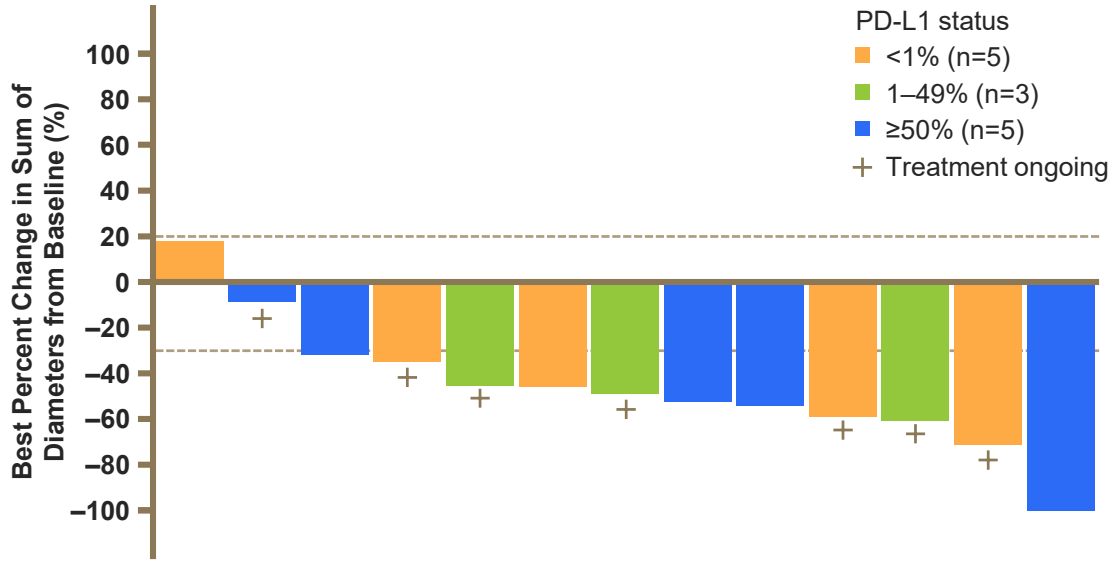
Data cut-off: March 6 2023.
All subjects must have had at least one scan (6 weeks of follow-up) to be included in the ORR interim analysis set. The 2-sided 95% CIs are exact Clopper-Pearson intervals. [a] As assessed by investigator per RECIST v1.1. [b] One of the 10 partial responses in Cohort 4 was confirmed after data cut-off.

Best Change in Sum of Diameters of Target Lesions[a]

Cohort 2 (doublet), 1L setting (N=14)
ORR: 50.0%; DCR: 92.9%



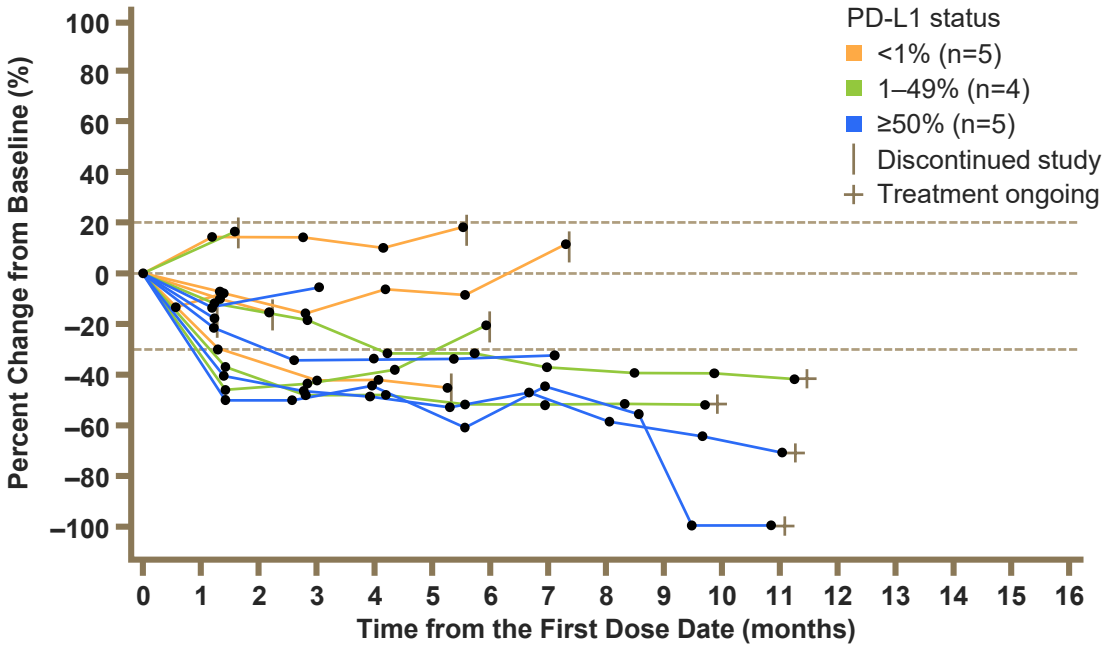
Cohort 4 (triplet), 1L setting (N=13)
ORR: 76.9%;[b] DCR: 92.3%



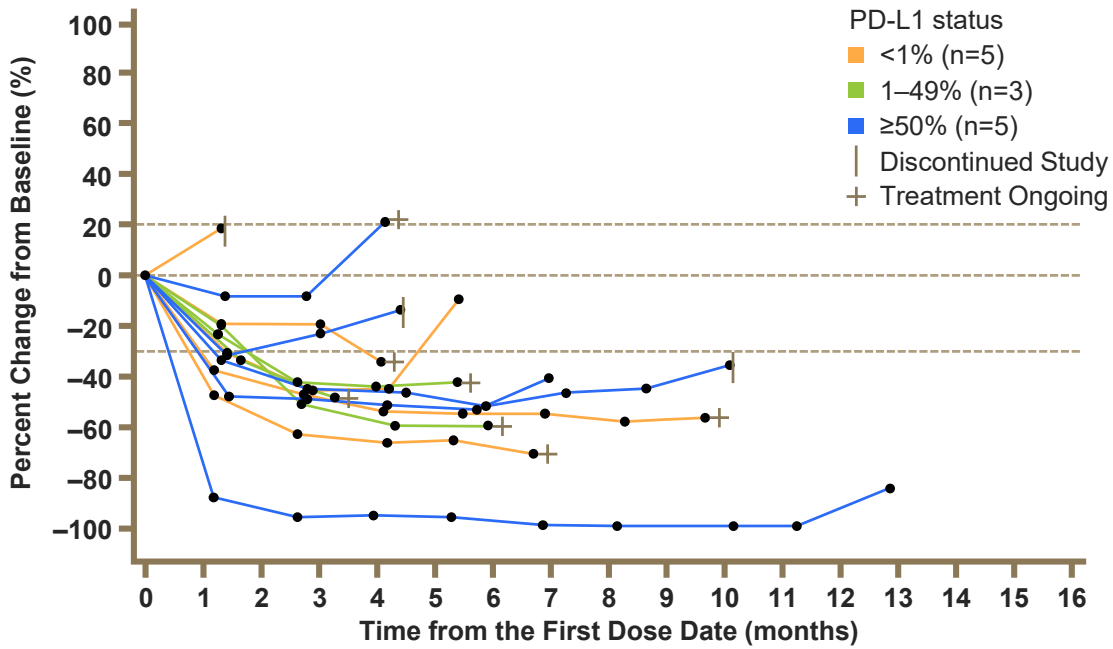
Data cut-off: March 6 2023.
[a] As assessed by investigator per RECIST v1.1. [b] One of the 10 partial responses in Cohort 4 was confirmed after data cut-off.
DCR, disease control rate.

Depth and Durability of Response[a]

Cohort 2 (doublet), 1L setting (N=14)



Cohort 4 (triplet), 1L setting (N=13)



Data cut-off: March 6 2023.
[a] As assessed by investigator per RECIST v1.1.

Conclusions

Safety	No new safety signals were observed in Cohort 2 and Cohort 4 investigating Dato-DXd in combination with durvalumab ± carboplatin, throughout dose escalation and dose expansion
	The most frequent TEAEs of any grade were stomatitis, alopecia and nausea. In general, Grade ≥3 TEAEs were more frequently observed with the triplet versus the doublet combination, which was mainly driven by more hematological events. There were four cases of ILD adjudicated as drug-related; three cases were Grade 1 or 2 and none were Grade 5
Efficacy	Interim efficacy analyses demonstrated promising ORRs with durable responses for both the doublet and triplet combination, both in the 1L setting and the overall population
	Responses were numerically higher with the triplet versus doublet combination and were observed across all PD-L1 expression levels

The Phase 3 AVANZAR (NCT05687266), TROPION-Lung07 (NCT05555732) and TROPION-Lung08 (NCT05215340) trials are evaluating Dato-DXd and immune checkpoint inhibitor combinations as potential 1L treatment options in patients with advanced or metastatic NSCLC[1–3]

1. Aggarwal C, et al. Poster P2.04-02. Presented at WCLC 2023; 2. NCT05555732. Available at: https://clinicaltrials.gov/ct2/show/NCT05555732 (accessed August 2023); 3. NCT05215340. Available at: https://clinicaltrials.gov/ct2/show/NCT05215340 (accessed August 2023).

Trastuzumab Deruxtecan in Patients With *HER2*-Mutant Metastatic Non–Small Cell Lung Cancer: Primary Results of DESTINY-Lung02

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On behalf of the DESTINY-Lung02 investigators

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DESTINY-Lung02

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

Background

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

Statistical considerations

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

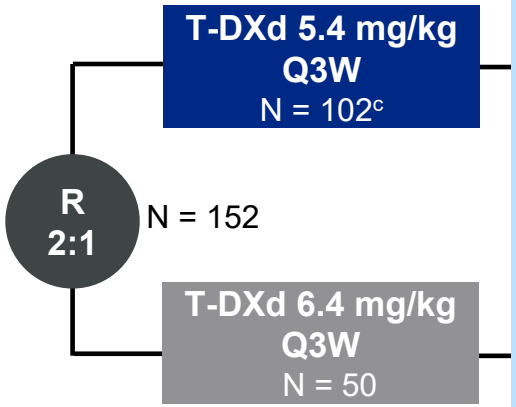
Key Eligibility Criteria[a]

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

Stratification Factor:

- Prior anti–PD-(L)1 treatment

Study Design



Primary Endpoint

- Confirmed ORR by BICR

Secondary Endpoints

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

Patients and investigators were blinded to the dose level

Primary analysis data cutoff: 23 December 2022

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

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

Baseline Characteristics and Efficacy Summary

Baseline Characteristics

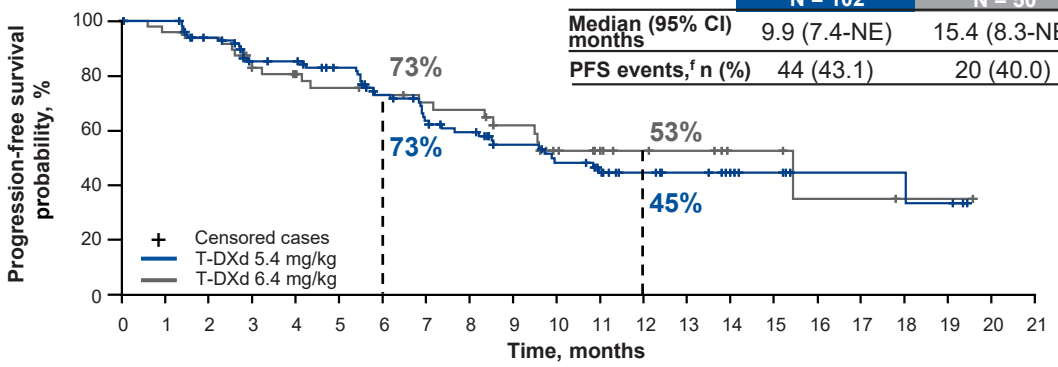
In the T-DXd 5.4 mg/kg and 6.4 mg/kg arms, respectively:

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

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

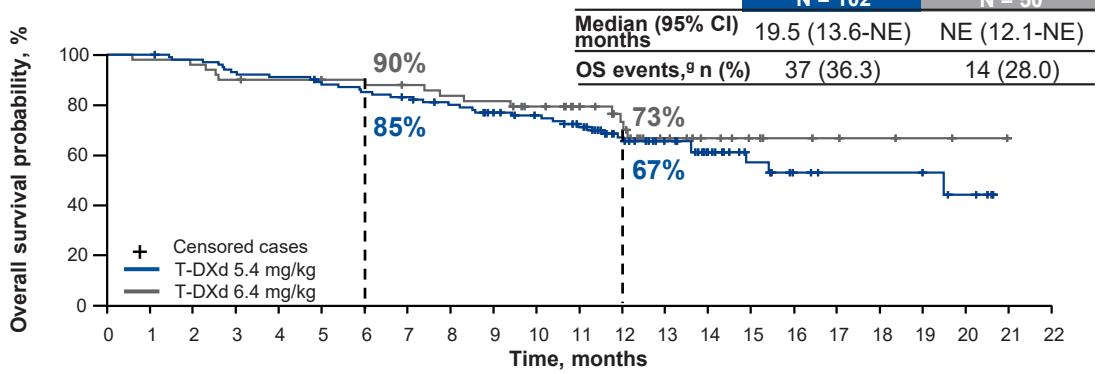
PFS

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



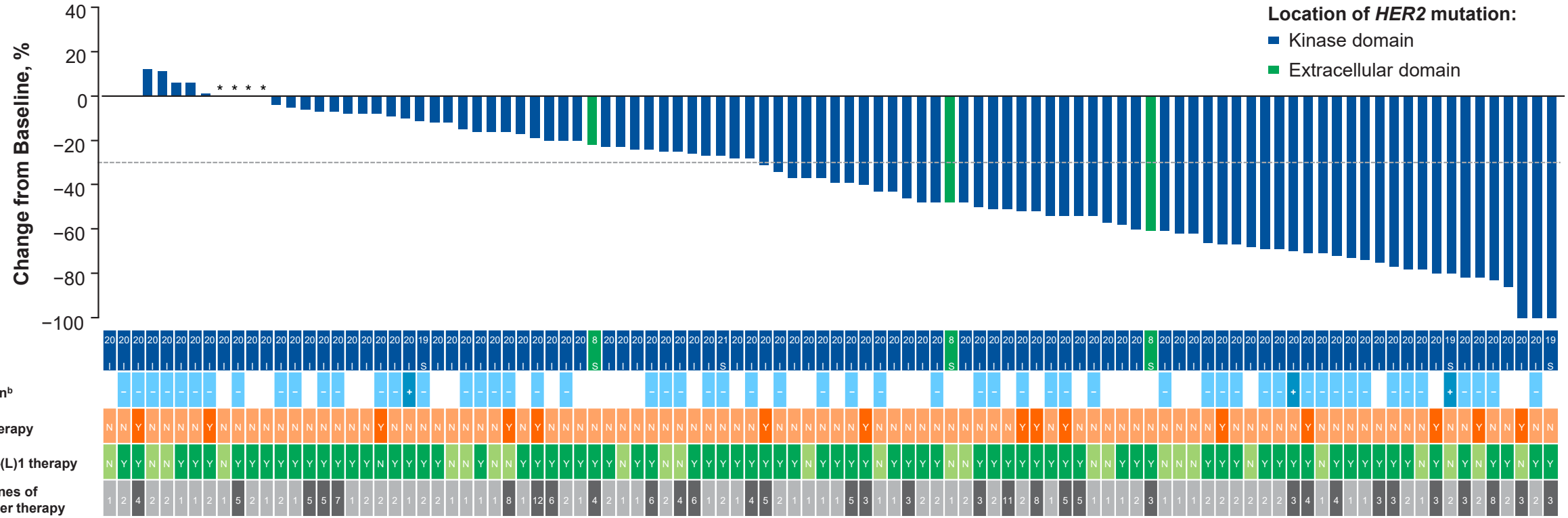
OS

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



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

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

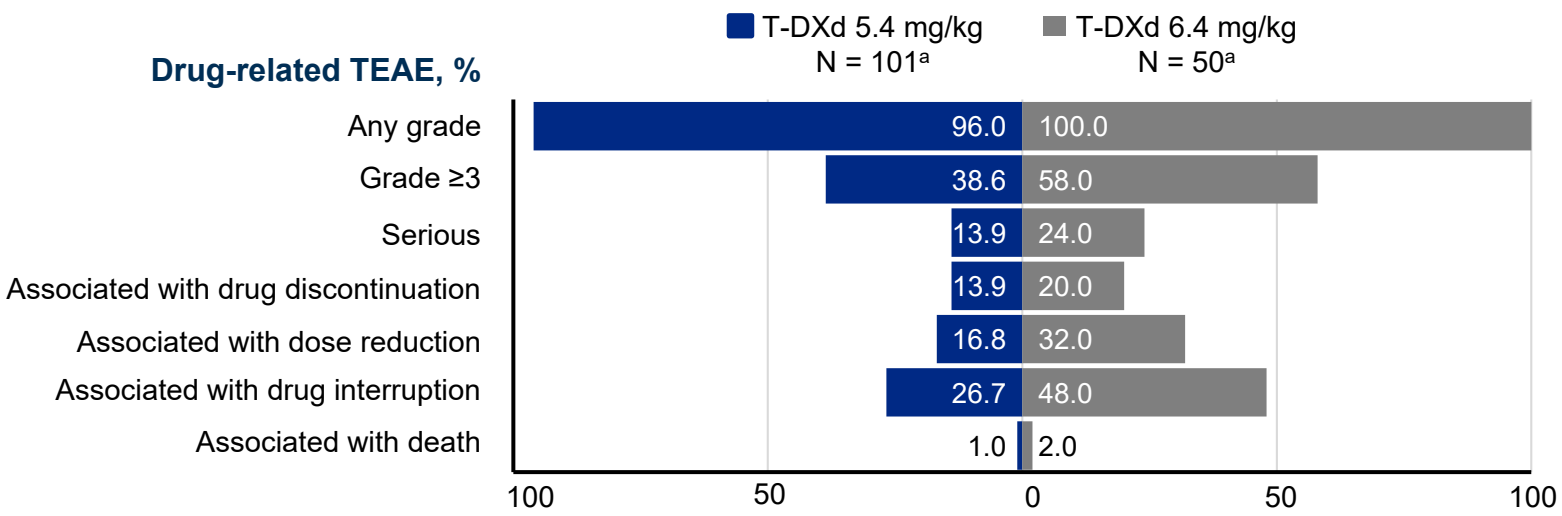


Responses were observed regardless of *HER2* mutation type, *HER2* amplification status, and number or type of prior therapies

BICR, blinded independent central review; I, insertion; HER2, human epidermal growth factor receptor 2; N, no; PD-(L)1, programmed death (ligand)1; S, substitution; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Y, yes. The line at −30% indicates a partial response. *Indicates the patient had 0 best percentage change from baseline in the sum of diameters for all target lesions. Numbers in the *HER2* mutation row indicate in which exon the mutation occurred (8, 19, or 20). *HER2* amplification was only assessed in patients who received T-DXd 5.4 mg/kg. [a]Activating *HER2* mutation documented from an archival or fresh tumor tissue sample by certified local laboratory assessment. [b]*HER2* amplification status was evaluated using an exploratory Oncomine DX Target test copy number algorithm on NSCLC formalin-fixed paraffin-embedded tissue samples. Thermo Fisher Scientific and its affiliates are not endorsing, recommending, or promoting any use or application of Thermo Fisher Scientific products presented by third parties during this seminar. Information and materials presented or provided by third parties are provided as-is and without warranty of any kind, including regarding intellectual property rights and reported results. Parties presenting images, text and material represent they have the rights to do so.

Overall Safety Summary

Overall Safety



Adjudicated Drug-Related ILD

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

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

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

Conclusions

- **T-DXd** demonstrated **deep and durable responses** at **both the 5.4 mg/kg and 6.4 mg/kg dose**
  - The lower limit of the ORR 95% CI of both doses exceeded the benchmark of 26.4%
  - Responses were consistent regardless of *HER2* mutation type, *HER2* amplification status, and prior systemic anticancer therapy

- The **safety profile** was **acceptable and generally manageable at both doses** and **favored the 5.4 mg/kg dose**
  - The observed safety profile was consistent with previous studies and no new safety signals were observed
  - Lower incidence of drug-related grade ≥3 TEAEs, serious TEAEs, and TEAEs associated with study drug discontinuations, dose reductions, and drug interruptions were observed with the 5.4 mg/kg dose
  - Adjudicated drug-related ILD rate was lower in the T-DXd 5.4 mg/kg arm than in the 6.4 mg/kg arm

Primary analysis results of DESTINY-Lung02 support the use of T-DXd 5.4 mg/kg for patients with previously treated *HER2*m NSCLC and reinforce T-DXd as the standard of care in this population

HER2, human epidermal growth factor receptor 2; HER2m, human epidermal growth factor receptor 2-mutant; ILD, interstitial lung disease; NSCLC, non–small cell lung cancer; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TEAEs, treatment-emergent adverse events.

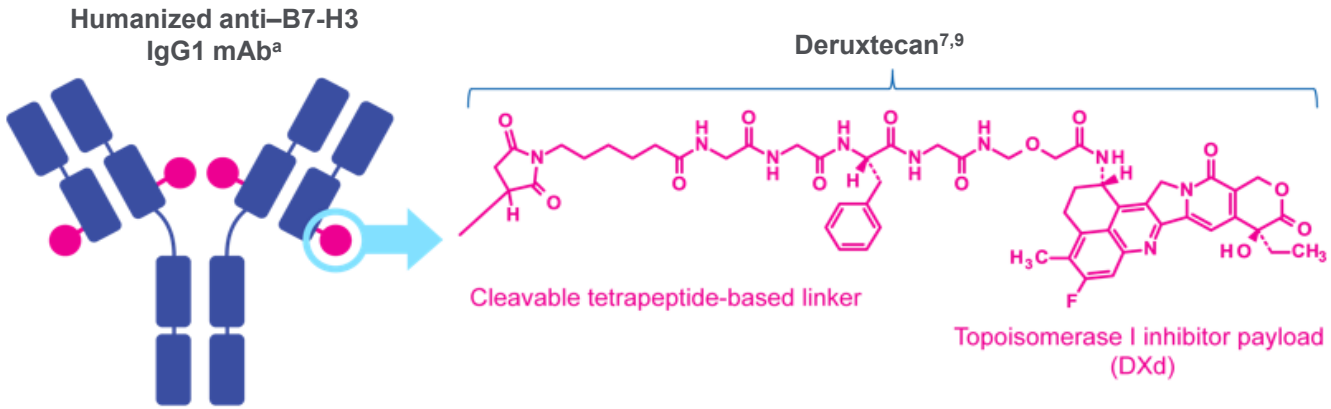
Ifinatamab deruxtecan (I-DXd; DS-7300) in patients with refractory SCLC: a subgroup analysis of a phase 1/2 study

Melissa Johnson,[1] Mark Awad,[2] Takafumi Koyama,[3] Martin Gutierrez,[4] Gerald S Falchook,[5] Sarina A Piha-Paul,[6] Toshihiko Doi,[7] Taroh Satoh,[8] Naoko Okamoto,[9] Jasmeet Singh,[9] Naoto Yoshizuka,[9] Meng Qian,[9] Xiaozhong Qian,[9] Brittany P Tran,[9] Ololade Dosunmu,[1] Rakesh Mucha,[1] Hillarie Windish,[1] Manish R Patel[1,10]

[1]Sarah Cannon Research Institute, Nashville, TN, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]National Cancer Center Hospital, Tokyo, Japan; [4]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [5]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; [6]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]National Cancer Center Hospital East, Chiba, Japan; [8]Osaka University Hospital, Osaka, Japan; [9]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [10]Florida Cancer Specialists and Research Institute, Sarasota, FL, USA

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

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

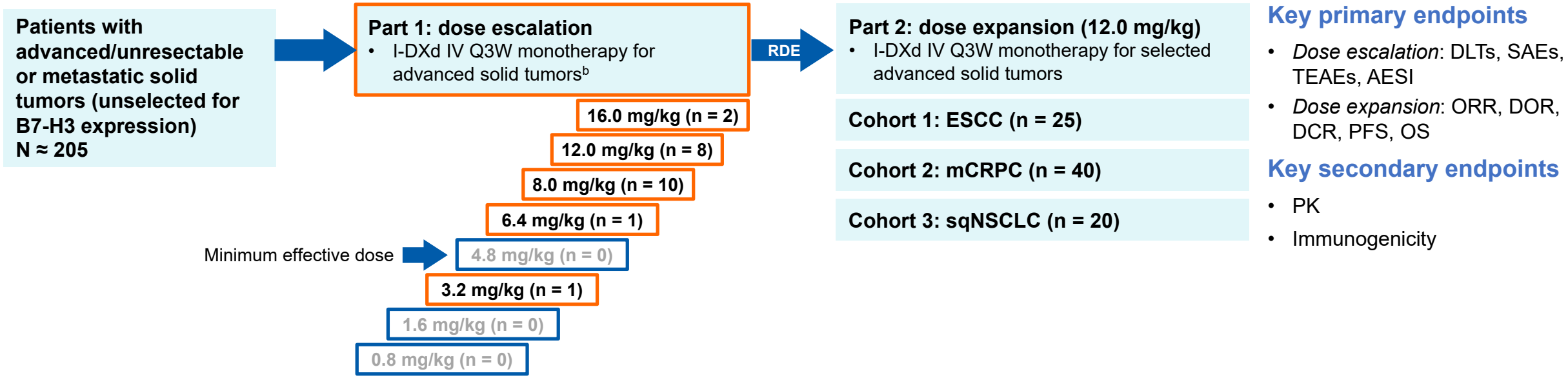


Payload mechanism of action: topoisomerase I inhibitor[7,9,11,b]
High potency of payload[9,11,b]
Optimized drug-to-antibody ratio ≈ 4[6–8,10,b]
Payload with short systemic half-life[9,11,b,c]
Stable linker-payload[9,11,b]
Tumor-selective cleavable linker[9,11,b]
Bystander antitumor effect[7,10,11,b]

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

DS7300-A-J101 Study Design (NCT04145622)

- I-DXd is generally well tolerated with early signs of antitumor activity[1,2]
- **We present a subgroup analysis of patients with SCLC (N = 22[a]) from part 1 treated with I-DXd at all doses studied**
  - Patients dosed at ≥6.4 mg/kg (n = 21) were evaluable for efficacy
  - Baseline tumor biopsies were retrospectively examined for B7-H3 protein level by IHC and used for correlative analysis in biomarker-evaluable patients dosed at ≥6.4 mg/kg (n = 17)



Key primary endpoints

- *Dose escalation*: DLTs, SAEs, TEAEs, AESI
- *Dose expansion*: ORR, DOR, DCR, PFS, OS

Key secondary endpoints

- PK
- Immunogenicity

[a]Number of patients with SCLC in parentheses of each dose cohort. [b]Tumor types included advanced/unresectable or metastatic HNSCC, ESCC, mCRPC, sqNSCLC, SCLC, bladder cancer, sarcoma, endometrial cancer, melanoma, and breast cancer.
AESI, adverse event of special interest; B7-H3, B7 homolog 3; DCR, disease control rate; DLT, dose-limiting toxicity; DOR, duration of response; ESCC, esophageal squamous cell carcinoma; IHC, immunohistochemistry; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RDE, recommended dose for expansion; SAE, serious adverse event;; SCLC, small cell lung cancer; sqNSCLC, squamous non-small cell lung cancer; TEAE, treatment-emergent adverse event. 1. Johnson ML, et al. ESMO. 2021. Abstract 513O. 2. Doi T, et al. ESMO. 2022. Abstract 453O.

Patient Demographics and Baseline Characteristics

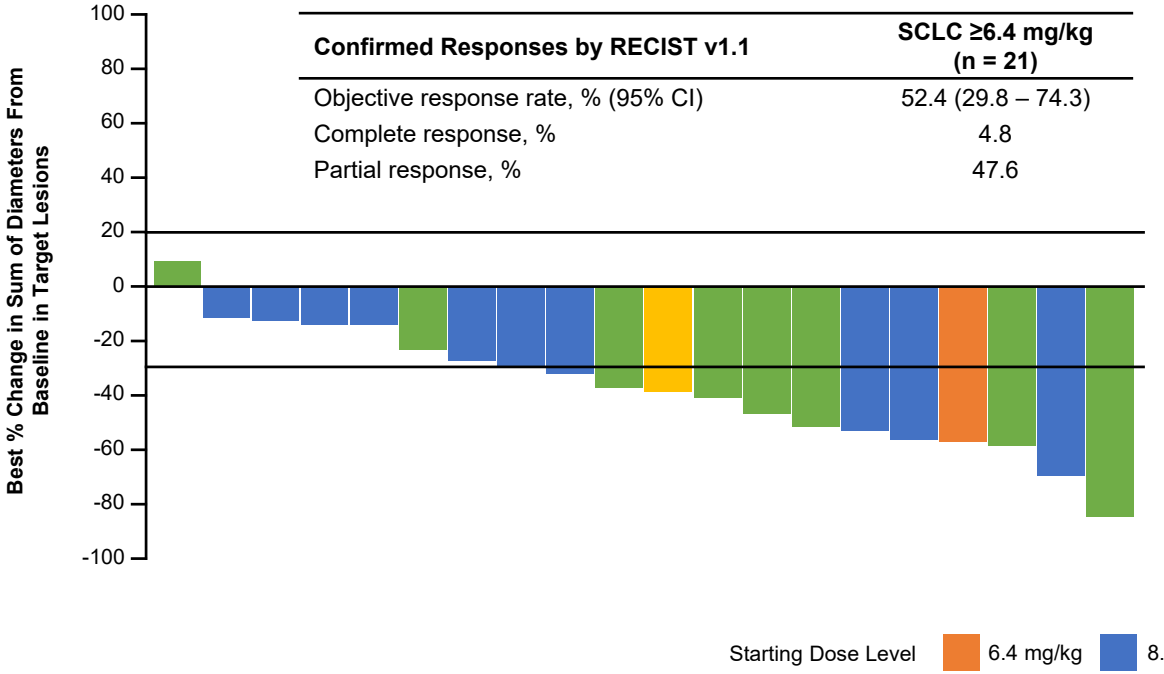
- As of 31 January 2023, 22 patients with SCLC received I-DXd at doses of 3.2 mg/kg to 16.0 mg/kg

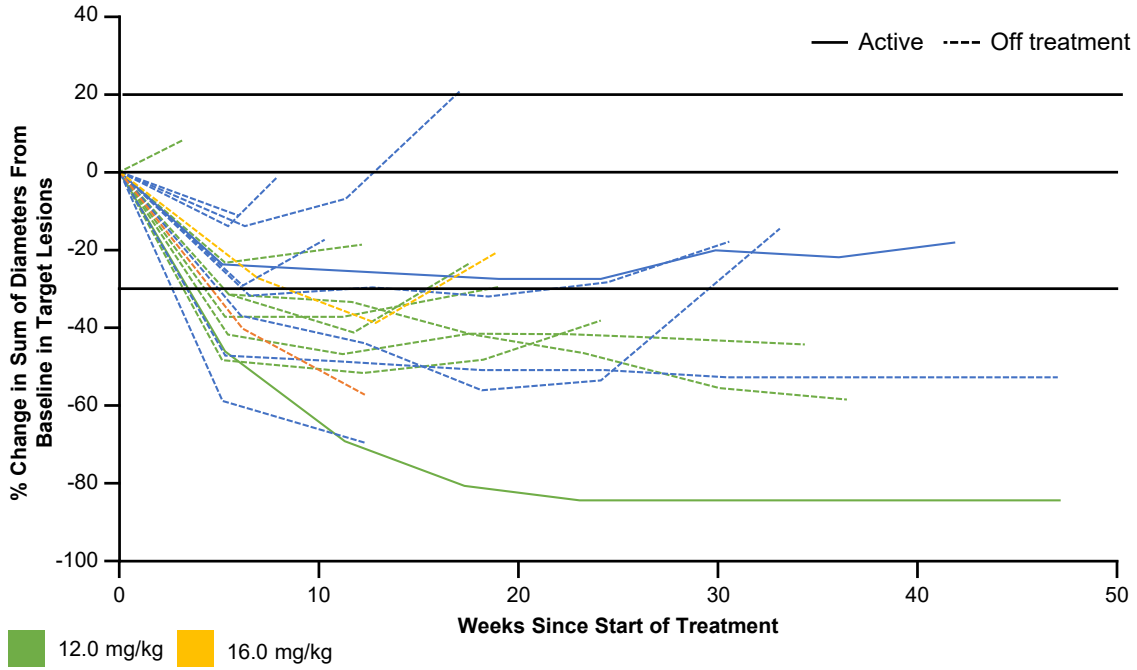
Patient or Disease Characteristic	SCLC (N = 22)
Age, median (range)	61 (40 – 84)
Male, n (%)	14 (63.6)
ECOG PS, n (%)	
0	7 (31.8)
1	15 (68.2)
Brain metastasis at baseline, n (%)	2 (9.1)
Number of prior systemic regimens, median (range)	2 (1 – 7)
Prior anticancer therapy received, n (%)	
Platinum-based chemotherapy	22 (100)
Immuno-oncology	18 (81.8)
Taxane	5 (22.7)
Irinotecan or topotecan	5 (22.7)[a]
Region of enrollment, n (%)	
United States	17 (77.3)
Japan	5 (22.7)

[a]1 patient received both.
ECOG PS, Eastern Cooperative Oncology Group performance status; SCLC, small cell lung cancer.

Antitumor Activity[a]

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



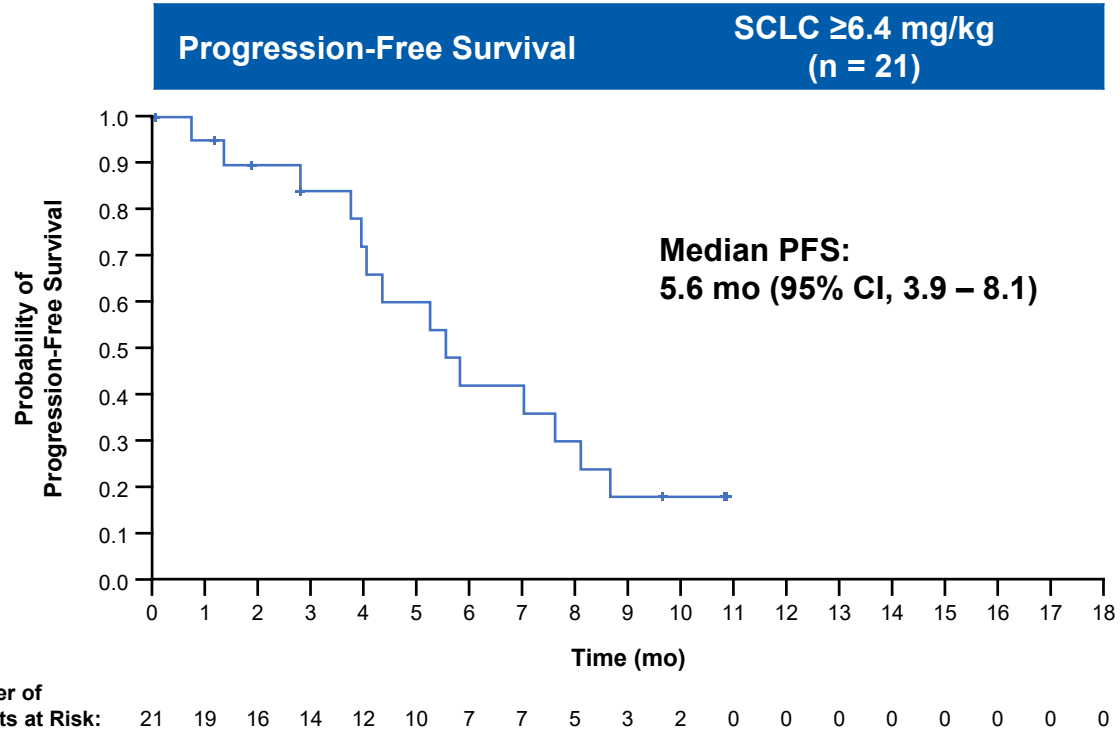


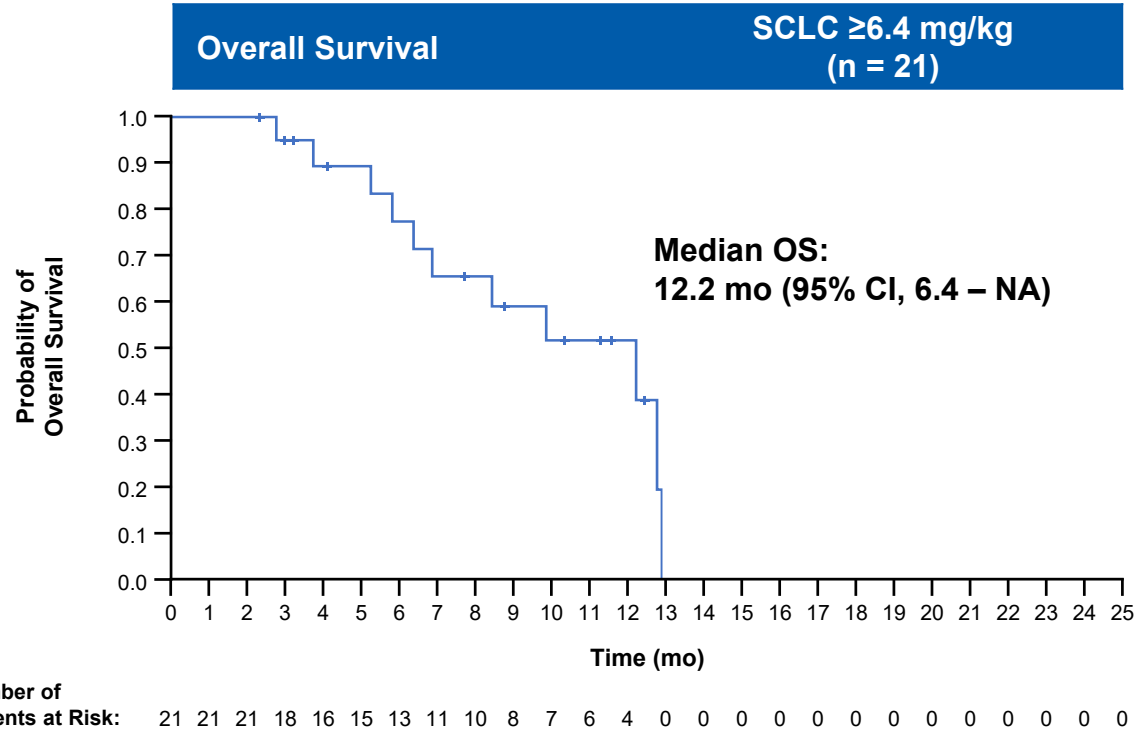
Starting Dose Level: 6.4 mg/kg; 8.0 mg/kg; 12.0 mg/kg; 16.0 mg/kg

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

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

Progression-Free and Overall Survival





Data cutoff: January 31, 2023.
CI, confidence interval; NA, not applicable; mo, months; OS, overall survival; PFS, progression-free survival; SCLC, small cell lung cancer.

Safety Summary

	SCLC (N = 22)
Treatment duration, median (range), months	3.9 (0.03 – 12.5)
Median cycles, number (range)	6.5 (1.0 – 18.0)
Any TEAE, n (%)	22 (100)
TEAE with CTCAE Gr ≥3, n (%)	8 (36.4)
TEAE associated with drug discontinuation, n (%)	5 (22.7)
TEAE associated with dose delay, n (%)	3 (13.6)
TEAE associated with dose reduction, n (%)	3 (13.6)
TEAE associated with death, n (%)	1 (4.5)[a]

- The safety profile is consistent with previous reports in overall population[1,2]
- Five patients discontinued treatment due to TEAEs, including one patient each with ILD (Gr 1, 8.0 mg/kg), pneumonitis (Gr 2, 8.0 mg/kg), cardiac failure (Gr 3, 16.0 mg/kg), embolism (Gr 3, 8.0 mg/kg) and COVID-19 pneumonia[a] (Gr 5, 12.0 mg/kg)

Data cutoff: January 31, 2023.
[a]Grade 5 COVID-19 pneumonia that was determined not to be treatment-related.
COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; Gr, grade; ILD, interstitial lung disease; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event.
1. Johnson ML, et al. ESMO. 2021. Abstract 513O. 2. Doi T, et al. ESMO. 2022. Abstract 453O.

Most Common (≥10%) All-Grade TEAEs Regardless of Causality

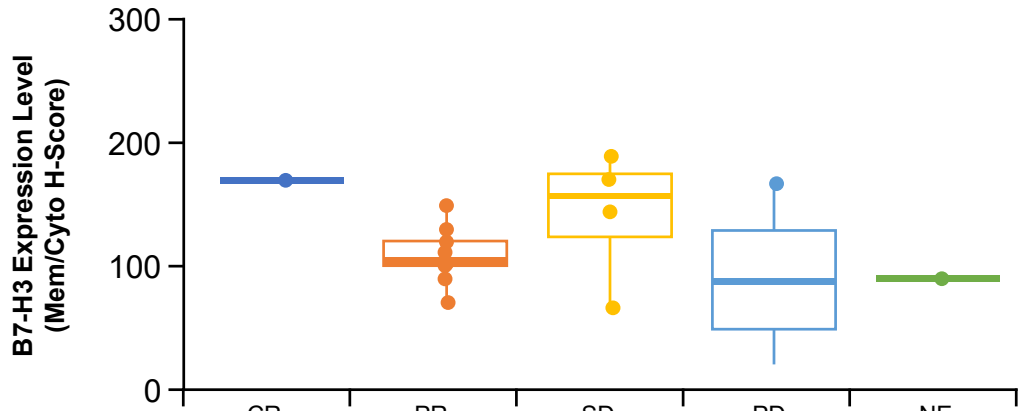
System Organ Class Preferred Term, n (%)	SCLC (N = 22)	
	Any Grade	Grade ≥3
Nausea	13 (59.1)	1 (4.5)
Fatigue	11 (50.0)	0 (0.0)
Anemia	6 (27.3)	1 (4.5)
Vomiting	6 (27.3)	0 (0.0)
Decreased appetite	5 (22.7)	1 (4.5)
Pyrexia	4 (18.2)	0 (0.0)
Constipation	4 (18.2)	1 (4.5)
IRR	3 (13.6)	0 (0.0)
Diarrhea	3 (13.6)	0 (0.0)
Dehydration	3 (13.6)	0 (0.0)
Dyspnea	3 (13.6)	0 (0.0)
Platelet count decreased	3 (13.6)	0 (0.0)
Arthralgia	3 (13.6)	0 (0.0)
Hyponatremia	3 (13.6)	0 (0.0)

- A total of three patients (13.6%) experienced an ILD or pneumonitis event (two Gr 1, one Gr 2)
  - All events were adjudicated by the ILD adjudication committee, of which one was adjudicated as drug-related ILD (Gr 2, 8.0 mg/kg) and discontinued treatment per protocol[a]
- Prophylactic premedication for nausea, vomiting, and IRR were not permitted for primary prophylaxis during cycle 1 of dose escalation

Data cutoff: January 31, 2023.
[a]Outcome was reported as “not recovered” for two events (Gr 1, Gr 2) and “recovered” for one event (Gr 1).
Gr, grade; ILD, interstitial lung disease; IRR, infusion-related reaction; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event.

B7-H3 Correlative Results for SCLC Cohort[a]

B7-H3 Level by BOR Status for Evaluable Patients



	CR	PR	SD	PD	NE
	n = 1	n = 9	n = 4	n = 2	n = 1
Median H-Score	170	105	157.5	89	90
H-Score Range	170	70 – 150	66 – 190	10 – 168	90

Efficacy Parameters by Median B7-H3 Level (n = 17)

B7-H3 mem/cyto H-Score at Baseline, Median (Range)	115 (10 – 190)

	B7-H3 Parameters	
	< median (n = 8)	**≥ median (n = 9)**
H-Score Range	10 – 105	115 – 190
Objective Response Rate	62.5%	55.6%
Median PFS, mo (95% CI)	5.8 (0.7 – NA)	5.3 (1.4 – NA)
Median OS, mo (95% CI)	12.2 (5.8 – NA)	6.9 (2.8 – NA)

- No trend of correlation of B7-H3 combined membrane/cytosol H-score with BOR, PFS, or OS was observed
- The correlative relationship between B7-H3 level and clinical efficacy will be further evaluated in future I-DXd studies

Data cutoff: January 31, 2023.
[a]SCLC tumor cell biopsy samples were retrospectively examined for B7-H3 protein level by IHC in biomarker-evaluable patients dosed at ≥6.4 mg/kg (n = 17). H-score of the combined membrane/cytosol staining was used for the correlative analysis to reflect the unique staining pattern of B7-H3 in SCLC tumor cells.
B7-H3, B7-homolog 3; BOR, best overall response; CI, confidence interval; CR, complete response; cyto, cytosol; IHC, immunohistochemistry; mem, membrane; NA, not applicable; NE, non-evaluable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response, SCLC, small cell lung cancer; SD, stable disease.

Conclusions

- I-DXd, a novel B7-H3–directed DXd-ADC, continues to demonstrate robust and durable efficacy in patients with heavily pretreated SCLC
  - Including 52% ORR, 5.9 months mDOR, 5.6 months mPFS, and 12.2 months mOS
- I-DXd was generally well tolerated; no new safety signals were observed, and the safety profile was consistent with previous reports[1,2]
  - Nausea was the most common TEAE, and antiemetic prophylaxis is now required for all I-DXd studies
- No apparent trend of correlation was observed between B7-H3 level and clinical efficacy parameters in the SCLC cohort
- These data support further clinical development of I-DXd, including a phase 2 study of patients with extensive stage SCLC following 1 – 3 prior lines of therapy (IDeate-1; NCT05280470)
  - TiP Poster #1561 at this meeting describes the design of this study

ADC, antibody–drug conjugate; B7-H3, B7 homolog 3; DXd, deruxtecan; mDOR, median duration of response; mOS, median overall survival; mPFS, median progression-free survival; ORR, objective response rate; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event; TiP, trial in progress.

1. Johnson ML, et al. ESMO. 2021. Abstract 513O. 2. Doi T, et al. ESMO. 2022. Abstract 453O.

WCLC Highlights 2023

Agenda

1. **WCLC DS presentations - main slides only-**
   - ✓ HERTHENA-Lung01 study snapshot data w/ 6mo FU
   - ✓ TROPION-Lung04 study safety and efficacy data
   - ✓ DESTINY-Lung02 study primary data
   - ✓ DS-7300 Ph1/2 study SCLC subgroup analysis
2. **Q&A**

Speakers

Ken Takeshita
Head of Global R&D

Mark Rutstein
Head of Global
Oncology Clinical Development

Content will be delivered on-demand after the meeting

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