Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

ESMO Highlights 2023

DAIICHI SANKYO CO., LTD.

Oct 24th (Japan), 2023

Forward-Looking Statements

Management strategies and plans, financial forecasts, future projections and policies, and R&D information that Daiichi Sankyo discloses in this material are all classified as Daiichi Sankyo's future prospects. These forward looking statements were determined by Daiichi Sankyo based on information obtained as of today with certain assumptions, premises and future forecasts, and thus, there are various inherent risks as well as uncertainties involved. As such, please note that actual results of Daiichi Sankyo may diverge materially from Daiichi Sankyo's outlook or the content of this material. Furthermore, there is no assurance that any forward-looking statements in this material will be realized. Regardless of the actual results or facts, Daiichi Sankyo is not obliged and does not have in its policy the duty to update the content of this material from the date of this material onward.

Some of the compounds under discussion are investigational agents and are not approved by the FDA or any other regulatory agency worldwide as a treatment for indications under investigation. Efficacy and safety have not been established in areas under investigation. There are no guarantee that these compounds will become commercially available in indications under investigation.

Daiichi Sankyo takes reasonable care to ensure the accuracy of the content of this material, but shall not be obliged to guarantee the absolute accuracy, appropriateness, completeness and feasibility, etc. of the information described in this material. Furthermore, any information regarding companies, organizations or any other matters outside the Daiichi Sankyo Group that is described within this material has been compiled or cited using publicly available information or other information, and Daiichi Sankyo has not performed in-house inspection of the accuracy, appropriateness, completeness and feasibility, etc. of such information, and does not guarantee the accuracy thereof.

The information described in this material may be changed hereafter without notice. Accordingly, this material or the information described herein should be used at your own judgment, together with any other information you may otherwise obtain.

This material does not constitute a solicitation of application to acquire or an offer to sell any security in the United States, Japan or elsewhere.

This material disclosed here is for reference purposes only. Final investment decisions should be made at your own discretion.

Daiichi Sankyo assumes no responsibility for any damages resulting from the use of this material or its content, including without limitation damages related to the use of erroneous information.

ESMO Highlights 2023

Agenda

1 ESMO presentations

- ✓ TROPION-Lung01 study TLR
- ✓ TROPION-Lung05 Ph2 study results
- ✓ TROPION-Breast01 study TLR
- ✓ BEGONIA study longer follow-up data
- ✓ DESTINY-PanTumor02 primary analysis data
- ✓ DS-6000 Ph1 study OVC subgroup analysis data
- ✓ DS-7300 Ph1/2 study updated data (extract)

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

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]

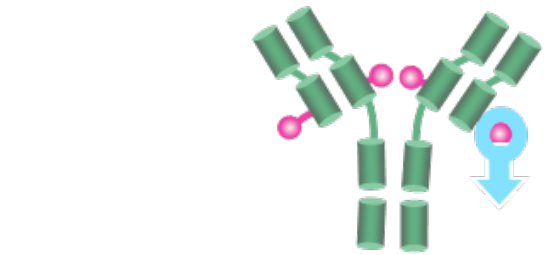
[a]Equal contribution as first author. [b]Indicates presenting author.

[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

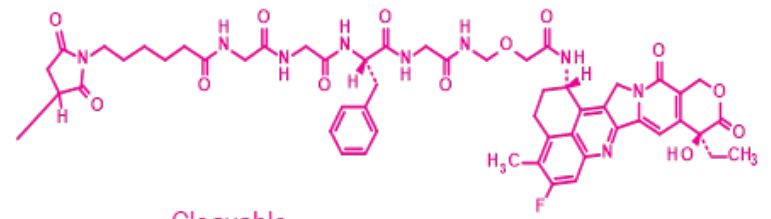
Background

- Standard-of-care, **second-line chemotherapy** for metastatic NSCLC is associated with a **modest benefit and substantial toxicity**
- **Dato-DXd** is a **TROP2-directed ADC** that selectively delivers a potent topoisomerase I inhibitor payload directly into tumor cells[1]
- **Promising antitumor activity** was seen with Dato-DXd in patients with adv/met NSCLC in the phase 1 TROPION-PanTumor01 trial (26% ORR)[1]

Dato-DXd: Humanized anti-TROP2 IgG1 mAb[2-5]



Deruxtecan



Cleavable tetrapeptide-based linker

Topo-I inhibitor payload (DXd)

Image is for illustrative purposes only; actual drug positions may vary.

ADC, antibody-drug conjugate; adv/met, advanced/metastatic; Dato-DXd, datopotamab deruxtecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; TROP2, trophoblast cell-surface antigen 2.

1. Shimizu T, et al. *J Clin Oncol*. 2023;41:4678-4687. 2. Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329-2340. 3. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173-185. 4. Ogitani Y, et al. Clin Cancer Res. 2016;22:5097-5108. 5. Ogitani Y, et al. *Cancer Sci*. 2016;107:1039-1046.

TROPION-Lung01 Study Design

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

Key Eligibility Criteria

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

Without actionable genomic alterations[a]

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

With actionable genomic alterations

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

R 1:1

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

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

Dual Primary Endpoints

- PFS by BICR
- OS

Secondary Endpoints

- ORR by BICR
- DOR by BICR
- Safety

Stratified by: histology,[b] actionable genomic alteration,[c] anti–PD-(L)1 mAb included in most recent prior therapy, geography[d]

Enrollment period: 19 February 2021 to 7 November 2022.
BICR, blinded independent central review; CT, chemotherapy; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PD-(L)1, programmed cell death 1 (ligand 1); PFS, progression-free survival; Q3W, every 3 weeks; R, randomized.
[a]Patients with *KRAS* mutations in the absence of known actionable genomic alterations are eligible; must meet prior therapy requirements for patients without actionable genomic alterations. [b]Squamous vs non-squamous. [c]Presence vs absence. [d]United States/Japan/Western Europe vs rest of world.

Demographics and Baseline Characteristics

Characteristic		Dato-DXd N=299	Docetaxel N=305
Age, median (range), years		63 (26-84)	64 (24-88)
Male, n (%)		183 (61)	210 (69)
Race, n (%)	Asian	119 (40)	120 (39)
	White	123 (41)	126 (41)
	Black or African American	6 (2)	4 (1)
	Other[a]	51 (17)	55 (18)
ECOG PS, n (%)	0	89 (30)	94 (31)
	1	210 (70)	211 (69)
Histology, n (%)	Non-squamous	234 (78)	234 (77)
	Squamous	65 (22)	71 (23)

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

ECOG PS, Eastern Cooperative Oncology Group performance status; PD-(L)1, programmed cell death 1 (ligand 1).
[a]Race data missing for 8 patients in each arm. [b]Patients who are no longer symptomatic and who require no treatment with corticosteroids and anticonvulsants and have recovered from acute toxic effects of radiation are eligible.
[c]In the Dato-DXd arm, 2 patients did not receive prior treatment with a platinum-containing therapy and 1 patient with actionable genomic alterations did not receive previous targeted therapy, deviating from the protocol.
Data cutoff: 29 March 2023.

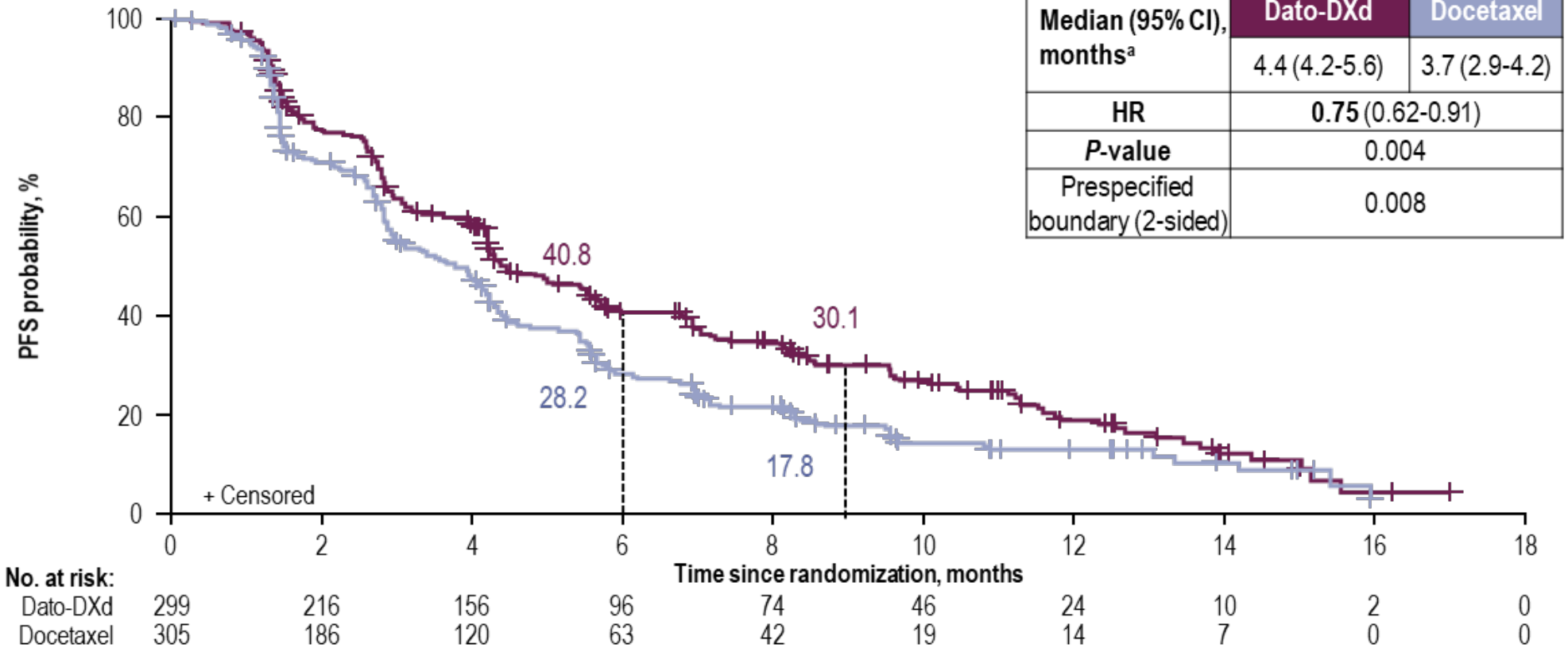
Patient Disposition

Disposition, n (%)	Dato-DXd N=297	Docetaxel N=290
Treatment status		
Ongoing on study treatment	52 (18)	17 (6)
Discontinued from study treatment	245 (83)	273 (94)
Treatment duration		
0-3 months	118 (40)	168 (58)
>3 to ≤6 months	73 (25)	66 (23)
>6 to ≤9 months	47 (16)	34 (12)
>9 months	59 (20)	22 (8)
Primary reason for treatment discontinuation		
Adverse event	39 (13)	46 (16)
Progressive disease	173 (58)	180 (62)
Clinical progression	9 (3)	11 (4)
Withdrawal/physician decision	12 (4)	23 (8)
Death	10 (3)	10 (3)
Other	2 (1)	3 (1)

Median study follow-up: Dato-DXd – **13.1** months; docetaxel – **13.0** months

Progression-Free Survival: ITT

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

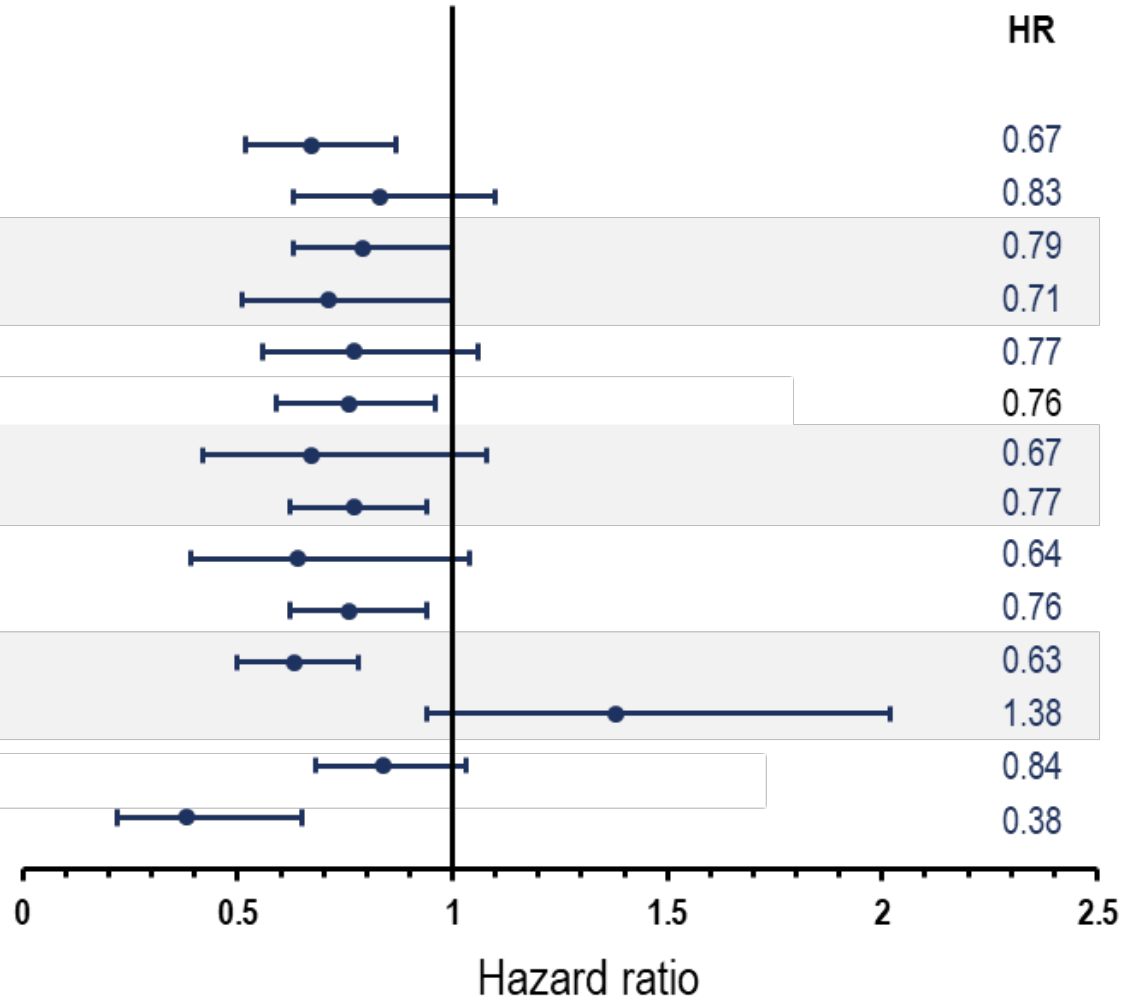


	Dato-DXd	Docetaxel
ORR (95% CI), %[b]	**26.4** (21.5-31.8)	**12.8** (9.3-17.1)
DOR (95% CI), mo	**7.1** (5.6-10.9)	**5.6** (5.4-8.1)

CR, complete response; DOR, duration of response; HR, hazard ratio; ITT, intention to treat; ORR, objective response rate; PFS, progression-free survival; PR, partial response.
[a]Median PFS follow-up was 10.9 (95% CI, 9.8-12.5) and 9.6 (95% CI, 8.2-11.9) months for Dato-DXd and docetaxel, respectively. [b]Included 4 CRs and 75 PRs for Dato-DXd and 39 PRs for docetaxel.

PFS in Key Subgroups

		Events/n		HR
		Dato-DXd	Docetaxel	
Age at randomization	<65 years	118/162	115/155	0.67
	≥65 years	95/137	103/150	0.83
Sex	Male	136/183	158/210	0.79
	Female	77/116	60/95	0.71
Race	Asian	76/119	82/120	0.77
	Non-Asian	131/172	129/177	0.76
Smoking status	Never	36/61	33/52	0.67
	Former/current	177/238	184/251	0.77
Brain metastasis at baseline	With	33/50	31/47	0.64
	Without	180/249	187/258	0.76
Histology	Non-squamous	156/229	168/232	0.63
	Squamous	57/70	50/73	1.38
Actionable genomic alterations[a]	Absent	189/252	184/255	0.84
	Present	24/47	34/50	0.38

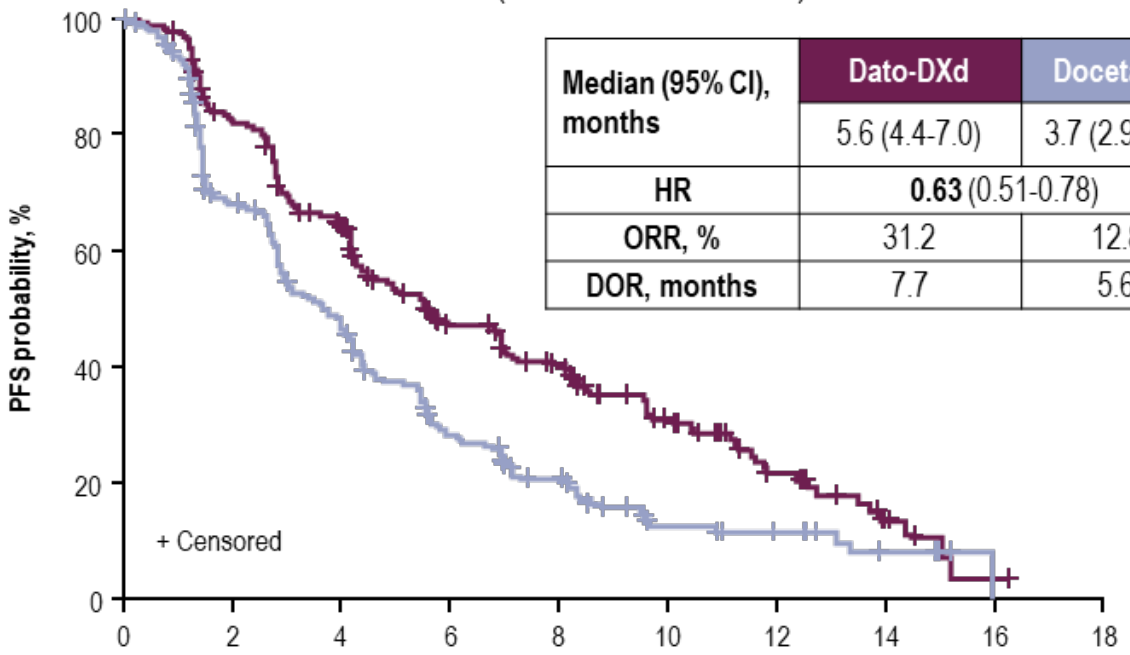


[a]Regardless of histology.

PFS by Histology

Non-squamous
(with and without AGAs)

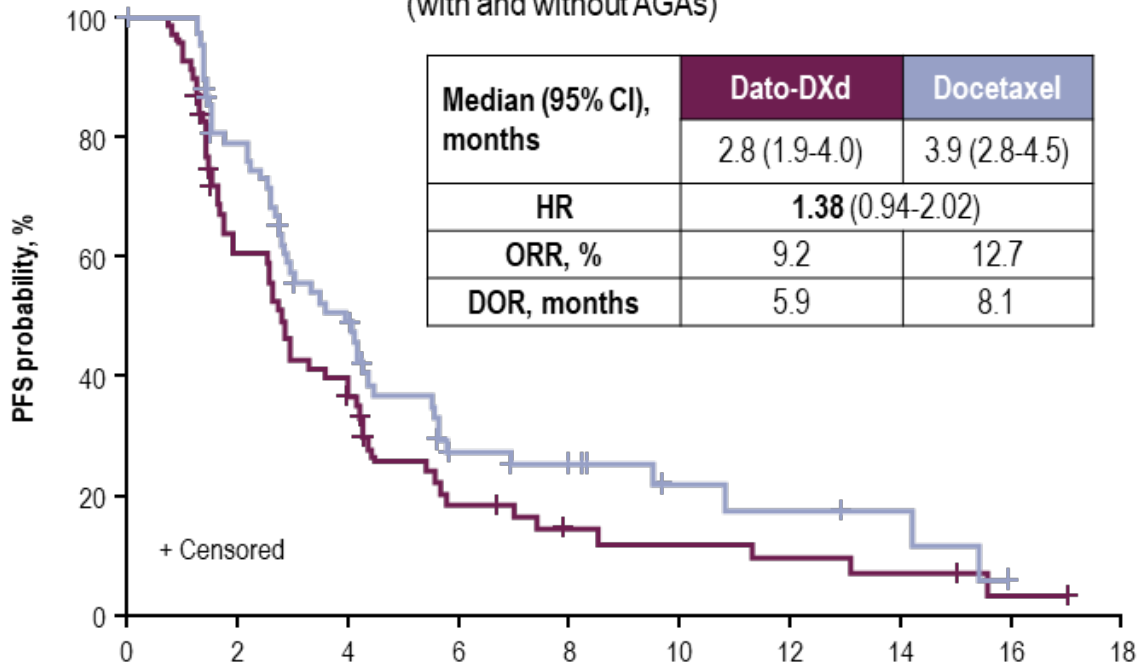
Median (95% CI), months	Dato-DXd	Docetaxel
	5.6 (4.4-7.0)	3.7 (2.9-4.2)
HR	**0.63** (0.51-0.78)	
ORR, %	31.2	12.8
DOR, months	7.7	5.6



No. at risk										
Dato-DXd	229	178	134	86	68	41	20	7	1	0
Docetaxel	232	135	90	50	32	14	10	4	0	0

Squamous
(with and without AGAs)

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

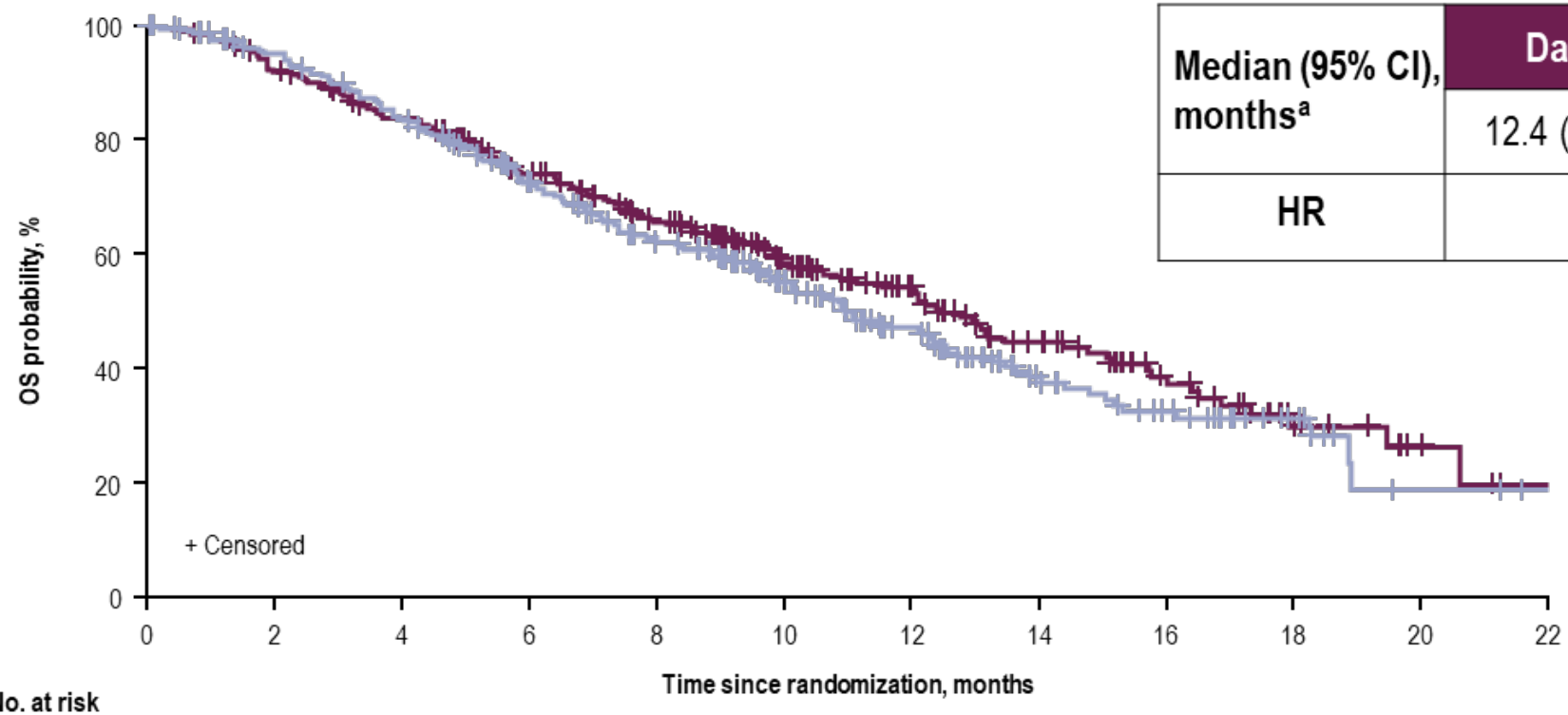


No. at risk										
Dato-DXd	70	38	22	10	6	5	4	3	1	0
Docetaxel	73	51	30	13	10	5	4	3	0	0

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

AGA, actionable genomic alteration; DOR, duration of response; HR, hazard ratio; ORR, objective response ratel PFS, progression-free survival.
Squamous subset included 3 patients with AGAs

Interim Overall Survival: ITT



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

No. at risk												
Dato-DXd	299	273	243	201	166	121	85	56	33	14	6	1
Docetaxel	305	273	239	193	156	115	76	42	29	13	4	1

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

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

Trial is continuing to final OS analysis

HR, hazard ratio; ITT, intention to treat; OS, overall survival.

[a]Median OS follow-up was 11.8 (95% CI, 11.3-12.7) and 11.7 (95% CI, 10.9-12.9) months for Dato-DXd and docetaxel, respectively.

Overall Safety Summary

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)

- The median treatment durations for Dato-DXd and docetaxel were **4.2** and **2.8** months, 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

ILD, interstitial lung disease; TRAE, treatment-related adverse event.
[a]Investigator assessed. Dato-DXd: 2 cases of ILD/pneumonitis and 1 case of sepsis; docetaxel: 1 case of ILD/pneumonitis and 1 case of septic shock.
The safety analysis set included all randomized patients who received ≥1 dose of the study drug.

TRAEs Occurring in ≥10% of Patients

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 (17)	3 (1)
Vomiting	38 (13)	3 (1)	22 (8)	1 (0.3)
Constipation	29 (10)	0	30 (10)	0
Diarrhea	28 (9)	1 (0.3)	55 (19)	4 (1)
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

TRAE, treatment-related adverse event.
[a]This category includes the preferred terms "neutropenia" and "neutrophil count decreased". [b]Includes an event incorrectly reported as grade 3.

- 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, were more common with docetaxel
- No new safety signals were observed with Dato-DXd

Adverse Events of Special Interest

AESI, n (%)	Dato-DXd N=297	Docetaxel N=290
Stomatitis/oral mucositis[a]		
All grades	160 (54)	59 (20)
Grade ≥3	19 (6)	4 (1)
Ocular events[b]		
All grades	57 (19)	27 (9)
Grade ≥3	5 (2)[c]	0
Adjudicated drug-related ILD[d]		
All grades	25 (8)	12 (4)
Grade ≥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 seen 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 was attributed to disease progression by investigator
  - Non-squamous: 4 of 232 patients (1.7%); Squamous: 3 of 65 patients (4.6%)[e]
- IRRs were observed in 24 patients (8%) with either Dato-DXd or docetaxel; all were grade ≤2 with the exception of 1 grade 3 event

AESI, adverse event of special interest; ILD, interstitial lung disease; IRR, infusion-related reaction; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; SMQ, standardized MedDRA query; SOC, system organ class. AESIs listed in this slide are treatment emergent and include all PTs that define the medical concept.

[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 4 cases of keratitis and 1 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.

Conclusions

- Dato-DXd is the first ADC to demonstrate a statistically significant improvement in PFS over docetaxel in patients with previously treated, locally advanced or metastatic NSCLC
- PFS benefit was primarily driven by patients with non-squamous histology
- Fewer grade ≥3 TRAEs and no new safety signals were observed with Dato-DXd
- Grade ≥3 ILD was seen, highlighting the need for careful monitoring and adherence to ILD management guidelines
- The interim OS findings favor Dato-DXd, and the trial is continuing to final analysis

Dato-DXd is a potential new meaningful therapy for patients with previously treated non-squamous NSCLC

ADC, antibody-drug conjugate; ILD, interstitial lung disease; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; TRAE, treatment-related adverse event.

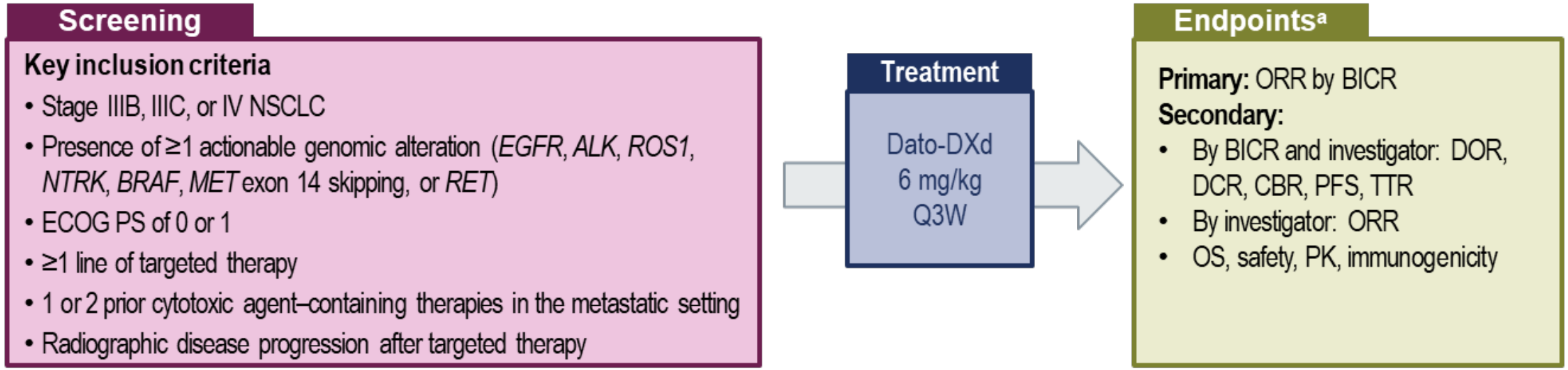
TROPION-Lung05: Datopotamab deruxtecan (Dato-DXd) in previously treated non-small cell lung cancer with actionable genomic alterations

Luis Paz-Ares,[1] Myung-Ju Ahn,[2] Aaron Lisberg,[3] Satoru Kitazono,[4] Byoung Chul Cho,[5] George Blumenschein Jr,[6] Elaine Shum, [7] Elvire Pons Tostivint,[8] Yasushi Goto,[9] Kiyotaka Yoh,[10] Rebecca Heist,[11] Paul Baas,[12] David Planchard,[13] Maurice Pérol,[14] Enriqueta Felip,[15] Wu-Chou Su,[16] Hong Zebger-Gong,[17] Lan Lan,[18] Chelsea Liu,[18] Jacob Sands[19]

[1]Hospital Universitario 12 de Octubre, Madrid, Spain; [2]Samsung Medical Center, Seoul, South Korea; [3]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [4]The Cancer Institute Hospital of JFCR, Tokyo, Japan; [5]Severance Hospital, Seoul, South Korea; [6]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [7]NYU Langone Health Perlmutter Cancer Center, New York, NY, USA; [8]University Hospital of Nantes, Nantes, France; [9]National Cancer Center Hospital, Tokyo, Japan; [10]National Cancer Center Hospital East, Kashiwa, Japan; [11]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [12]The Netherlands Cancer Institute, Amsterdam, the Netherlands; [13]Gustave Rouss, Villejuif, France; [14]Centre Léon Bérard, Lyon, France; [15]Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain; [16]National Cheng Kung University Hospital, Tainan, Taiwan; [17]Daiichi Sankyo Europe GmbH, Munich, Germany; [18]Daiichi Sankyo, Inc, Basking Ridge, NJ, USA; [19]Dana-Farber Cancer Institute, Boston, MA, USA

Introduction and Study Design

- **Dato-DXd** is a TROP2-directed 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]
- In the **phase 1 TROPION-PanTumor01** study, Dato-DXd showed promising efficacy in patients with actionable genomic alterations[2]
- **TROPION-Lung05** (NCT04484142) is a **phase 2**, single-arm study evaluating Dato-DXd in patients with **advanced or metastatic NSCLC with actionable genomic alterations** that progressed on or after targeted therapy and platinum-based chemotherapy



ADC, antibody-drug conjugate; BICR, blinded independent central review; CBR, clinical benefit rate; Dato-DXd, datopotamab deruxtecan; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IgG1, immunoglobulin G1; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; TROP2, trophoblast cell-surface antigen 2; TTR, time to response.

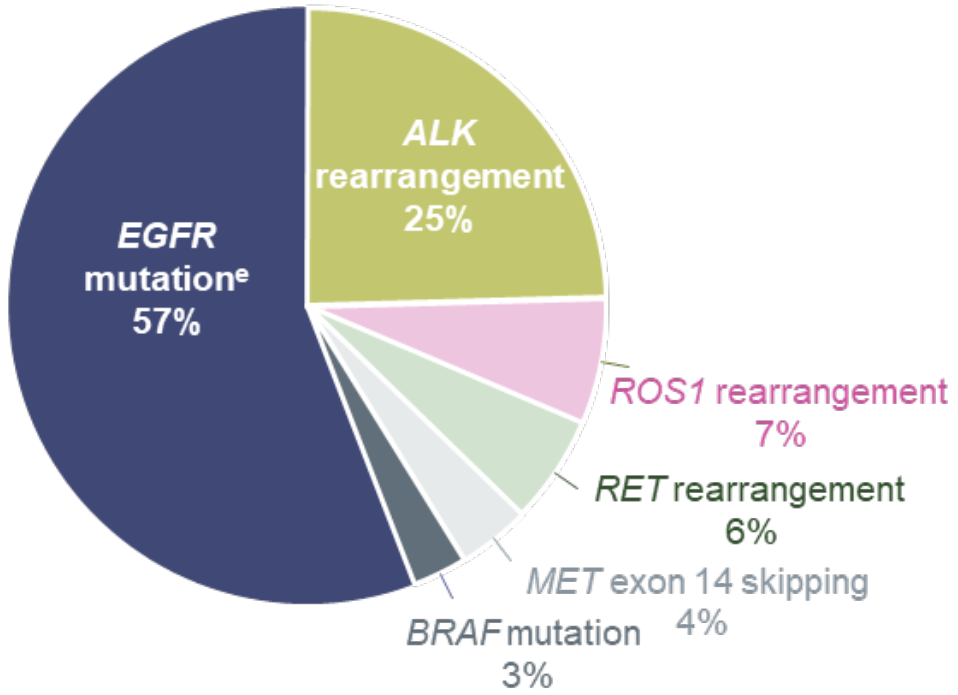
[a]The primary completion date will occur when all patients have had either a minimum of 9 months of follow-up after the start of study treatment or have discontinued from the study.

1. Okajima D, et al. *Mol Cancer Ther*. 2021;20:2329-2340. **2.** Shimizu T, et al. *J Clin Oncol*. Published online June 16, 2023.

Patient Characteristics and Disposition

Demographic characteristics	Dato-DXd (N=137)
Median age (range), years	60 (29-79)
Female, n (%)	83 (61)
Histology, n (%)	
Adenocarcinoma	130 (95)
History of brain metastasis, n (%)[a]	70 (51)
Median prior lines of therapy for adv/met disease	3
Prior lines of therapy, n (%)	137 (100)
≥3 prior lines of therapy for adv/met disease	98 (72)
Prior platinum chemotherapy	137 (100)
Prior anti–PD-1/anti–PD-L1 immunotherapy	49 (36)
≥2 prior lines of targeted therapies for indicated genomic alteration	82 (60)

Relative Frequency of Genomic Alterations[b-d]



Disposition

At the time of data cutoff (December 14, 2022):

- Median (range) treatment duration was 4 (1-21) months
- 60 participants (44%) were ongoing in study
- 20 participants (15%) were ongoing on study treatment

adv/met, advanced/metastatic; Dato-DXd, datopotamab deruxtecan; PD-1, programmed cell death 1 protein; PD-L1, programmed cell death 1 ligand 1.

[a]Patients with clinically inactive brain metastases and patients with treated brain metastases who are no longer symptomatic, require no treatment with corticosteroids or anticonvulsants, and have recovered from radiotherapy may be included in the study. [b]Patients whose tumors harbor *KRAS* mutations, in the absence of the genomic alterations *EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, and *RET*, were excluded from the study. [c]Three patients had tumors with *MET* amplification. [d]Patients had co-occurring alteration types; thus, percentages do not sum to 100%. [e]Protocol requires enrollment of ≈50% of patients with *EGFR*-mutated tumors, among whom 80% should have received prior osimertinib.

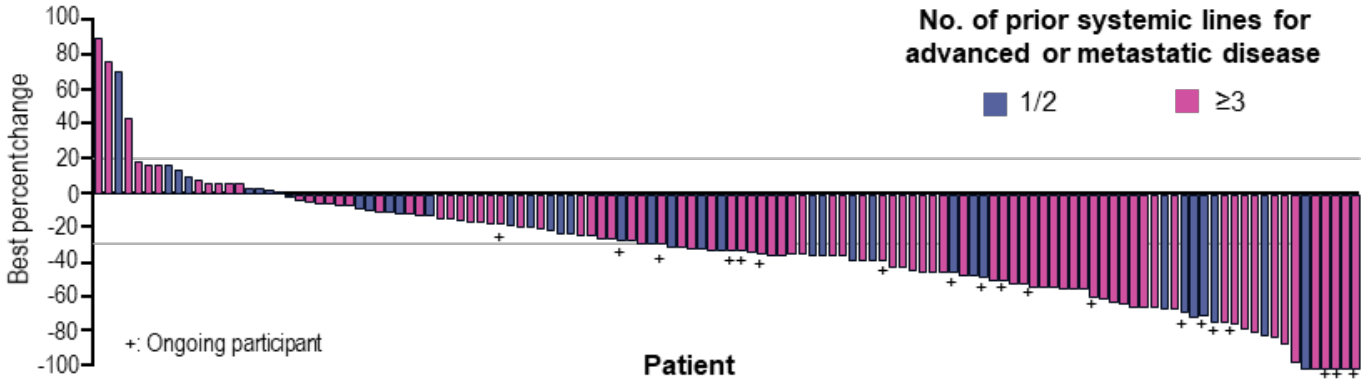
Efficacy Summary

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

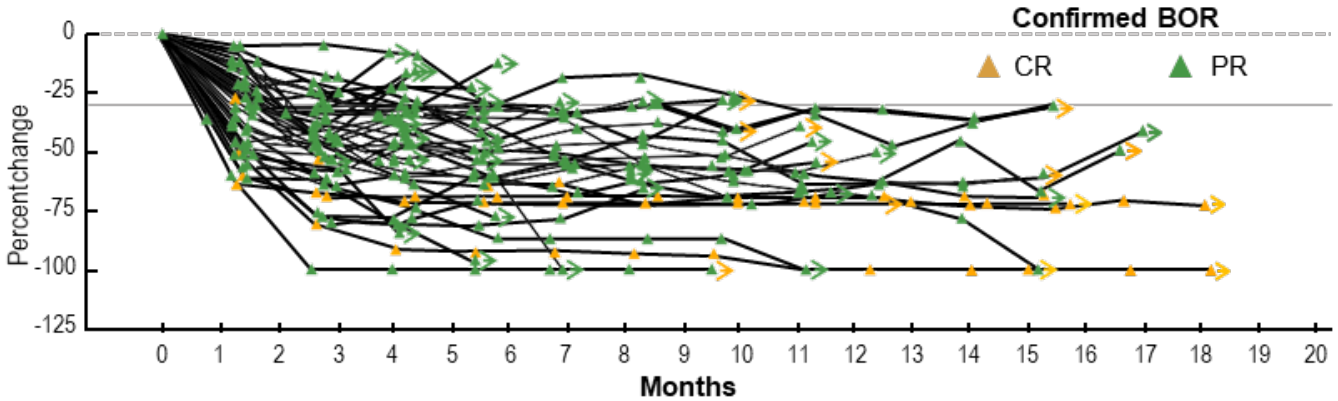
BOR: In the overall population (N=137), 4 patients (3%) achieved a CR and 45 (33%) achieved a PR

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

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



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

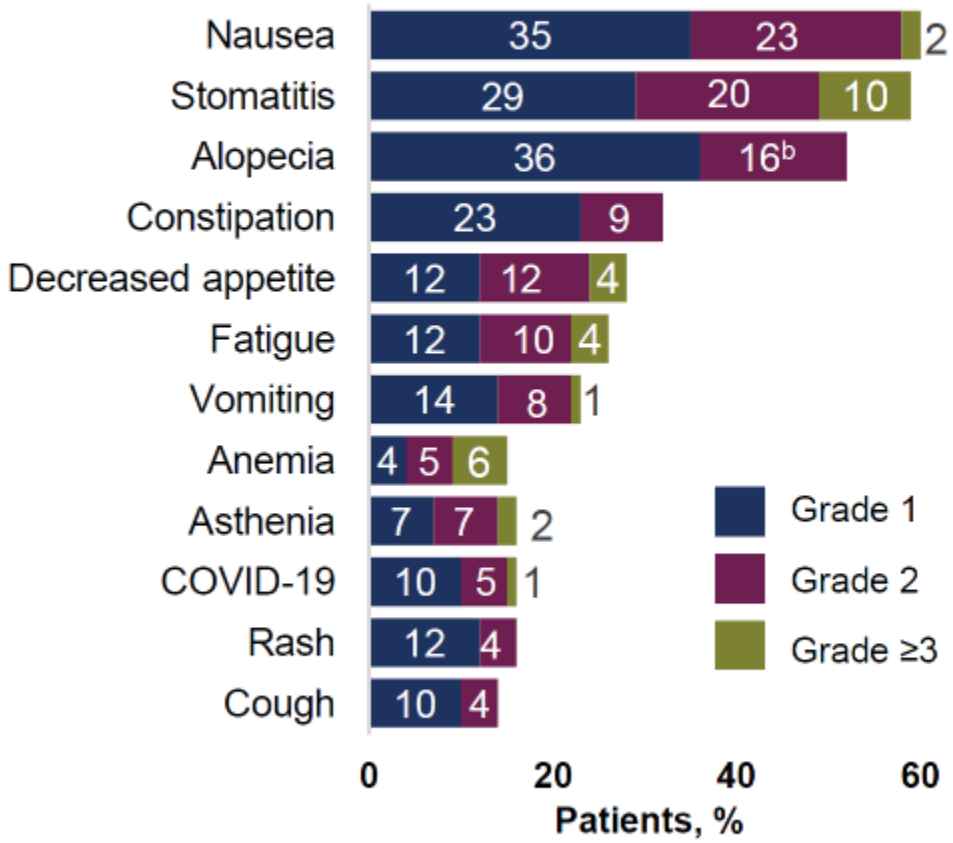


BICR, blinded independent central review; BOR, best overall response; CR, complete response; DCR, disease control rate; DOR, duration of response; ORR, objective response rate; PFS, progression-free survival; PR, partial response.

[a]The 2-sided 95% CIs are based on the Clopper-Pearson exact binomial method. [b]Median PFS and PFS probabilities are based on the Kaplan-Meier method. [c]Per BICR.

Safety Summary

TEAEs Occurring in ≥15% of Patients; All Grades (N=137)[a]



- 137 patients (100%) experienced **TEAEs** (grade ≥3, 47%)
  - 129 (94%) experienced **treatment-related TEAEs** (grade ≥3, 29%)
  - 34 (25%) experienced **serious AEs** (grade ≥3, 5%)
- 30 (22%), 13 (10%), and 2 (2%) patients experienced TEAEs associated with **dose reduction, dose withdrawal, and death**,[c] respectively

AESI Incidence by Grade[d]

n (%)	Total	Grade 1	Grade 2	Grade ≥3
Oral mucositis/stomatitis	90 (66)	45 (33)	30 (22)	15 (11)
Ocular surface toxicity[e]	36 (26)	26 (19)	7 (5)	3 (2)[f]
IRR	22 (16)	15 (11)	7 (5)	0
Adjudicated drug-related ILD	5 (4)	1 (1)	3 (2)	1 (1)[g]

AE, adverse event; AESI, adverse event of special interest; CTCAE, common terminology criteria for adverse event; ILD, interstitial lung disease; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.
[a]Due to rounding, summed rates may not reflect total percentage of TEAEs. [b]Includes an event reported as Grade 3 incorrectly per CTCAE grades. [c]Two deaths were associated with disease progression, unrelated to study drug by investigator. [d]AESIs listed in this slide include all preferred terms defined by the medical concept. [e]Dry eye was the most commonly reported ocular surface toxicity (n=15 [11%]). [f]Patients with grade 3 ocular surface toxicity had corneal disorder, cornea verticillata, and punctate keratitis. [g]One case of ILD was reported as a grade 3 event by investigator, and the patient died due to disease progression per investigator. The same event was adjudicated as a grade 5 event.

Conclusions

Encouraging antitumor activity was observed with **Dato-DXd treatment** in a **heavily pretreated** NSCLC population with **actionable genomic alterations**, including patients with ***EGFR* mutations and *ALK* rearrangements**

Dato-DXd had a **manageable safety profile,** characterized by a low incidence of hematologic or drug-related grade ≥3 toxicities. Nausea and stomatitis were the predominant AEs seen, consistent with previously reported data in NSCLC

The ongoing, randomized, **phase 3 TROPION-Lung01** study (NCT04656652) is assessing Dato-DXd vs docetaxel in patients with pretreated adv/met NSCLC, including those with actionable genomic alterations

adv/met, advanced/metastatic; AE, adverse event; Dato-DXd, datopotamab deruxtecan; NSCLC, non-small cell lung cancer.

Datopotamab deruxtecan (Dato-DXd) vs chemotherapy in previously-treated inoperable or metastatic hormone receptor-positive, HER2-negative (HR+/HER2–) breast cancer: Primary results from the randomised Phase 3 TROPION-Breast01 trial

Aditya Bardia,[1] Komal Jhaveri,[2] Seock-Ah Im,[3] Sonia Pernas,[4] Michelino De Laurentiis,[5] Shusen Wang,[6] Noelia Martínez Jañez,[7] Giuliano Borges,[8] David W. Cescon,[9] Masaya Hattori,[10] Yen-Shen Lu,[11] Erika Hamilton,[12] Qingyuan Zhang,[13] Junji Tsurutani,[14] Kevin Kalinsky,[15] Lu Xu,[16] Neelima Denduluri,[17] Hope S. Rugo,[18] Binghe Xu,[19]* Barbara Pistilli[20]*

*Contributed equally

[1]Massachusetts General Hospital Cancer Center, Boston, MA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA, and Weill Cornell Medical College, New York, NY, USA; [3]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul National University, Seoul, Republic of Korea; [4]Institut Català d'Oncologia, IDIBELL, L'Hospitalet, Barcelona, Spain; [5]Istituto Nazionale Tumori Napoli IRCCS "Fondazione Pascale", Napoli, Italy; [6]Cancer Center of Sun Yet-sen University, Guangzhou, China; [7]Ramón y Cajal University Hospital, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain; [8]Catarina Pesquisa Clínica, Santa Catarina, Brazil; [9]Princess Margaret Cancer Centre/UHN, Toronto, ON, Canada; [10]Aichi Cancer Center, Nagoya, Japan; [11]National Taiwan University Hospital, National Taiwan University College of Medicine, Taipei, Taiwan; [12]Sarah Cannon Research Institute / Tennessee Oncology, Nashville, TN, USA; [13]Harbin Medical University Cancer Hospital, Harbin, China; [14]Showa University Hospital, Tokyo, Japan; [15]Winship Cancer Institute at Emory University, Atlanta, GA, USA; [16]AstraZeneca, New York, NY, USA; [17]AstraZeneca, Arlington, VA, USA; [18]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [19]National Cancer Center / National Clinical Research Center for Cancer / Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [20]Gustave Roussy Cancer Center, Villejuif, France

Background: Unmet Need in HR+/HER2– MBC

- **HR+/HER2– breast cancer** is the **most common subtype** of breast cancer, accounting for 60–70% of all cases[1]
- Despite new therapeutic options becoming available, there remains an **unmet need** after **endocrine therapy** and **one line of systemic therapy** for patients with HR+/HER2– MBC[2–5]
- **Chemotherapy** is utilised widely for management of endocrine-resistant HR+/HER2– MBC, but is associated with **low response rate**, **poor prognosis**, and **significant toxicity** including myelosuppression and peripheral neuropathy[6]
- **TROP2-directed ADCs** can have **significant toxicities** including diarrhoea, neutropenia and thrombocytopenia[7,8]

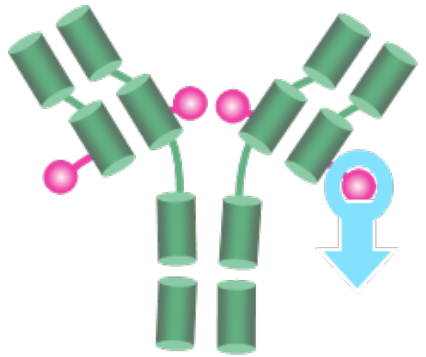
ADC, antibody-drug conjugate; HER2–, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; MBC, metastatic breast cancer; TROP2, trophoblast cell surface antigen 2.

1. Sung H et al. *CA Cancer J Clin* 2021;71:209–49; 2. Gennari A, et al. *Ann Oncol* 2021;32:1475-1495; 3. Wolff AC, et al. *J Clin Oncol* 2023;41:3867–72; 4. Moy B, et al. *J Clin Oncol* 2023;41:1318–20; 5. Moy B, et al. *J Clin Oncol* 2022;40:3088–90; 6. Kuderer NM, et al. *Nat Rev Clin Oncol* 2022;19:681–97; 7. Rugo HS, et al. *J Clin Oncol* 2022;40:3365–76; 8. Yin Y et al. Mini Oral at ESMO 2023; presentation 380MO.

Background: Dato-DXd

- **Dato-DXd** is a **TROP2-directed ADC**, that selectively delivers a potent Topo-I inhibitor payload directly into tumor cells,[1] and has several unique properties*:
  - Optimised drug to antibody ratio ≈ 4
  - Stable linker-payload
  - Tumour-selective cleavable linker
  - Bystander antitumour effect
- Dato-DXd previously demonstrated **promising antitumour activity** and a **manageable safety profile** with a convenient Q3W schedule in pre-treated patients with **metastatic HR+/HER2– breast cancer**[2]

Dato-DXd: Humanised anti-TROP2 IgG1 monoclonal antibody



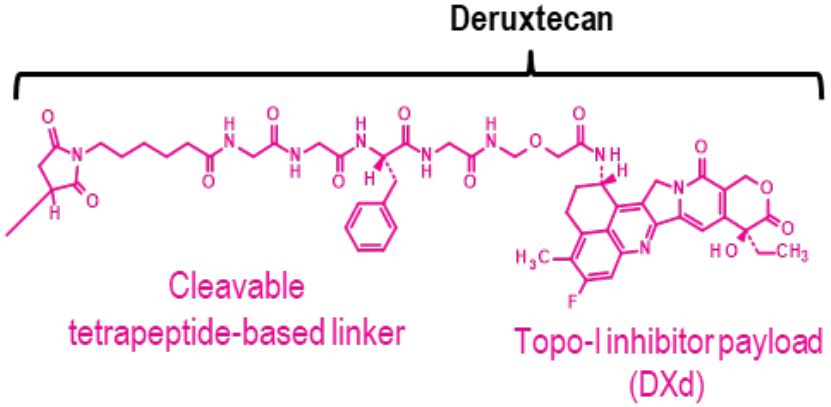


Image is for illustrative purposes only; actual drug positions may vary.

*The clinical relevance of these features is under investigation. Based on animal data.
Dato-DXd, datopotamab deruxtecan; IgG1, immunoglobulin G1; Q3W, every 3 weeks; Topo-I, topisomerase I.

1. Okajima D, et al. *Mol Cancer Ther* 2021;20:2329–40;
2. Meric-Bernstam F, et al. Poster presentation at SABCS 2022: abstract PD13-08.

TROPION-Breast01 Study Design[1]

Randomised, phase 3, open-label, global study (NCT05104866)

Key inclusion criteria:

- Patients with HR+/HER2– breast cancer* (HER2– defined as IHC 0/1+/2+; ISH negative)
- Previously treated with 1–2 lines of chemotherapy (inoperable/metastatic setting)
- Experienced progression on ET and for whom ET was unsuitable
- ECOG PS 0 or 1

1:1

Dato-DXd
6 mg/kg IV Day 1 Q3W
(n=365)

Investigator's choice of chemotherapy (ICC)
as per protocol directions†
(eribulin mesylate D1,8 Q3W; vinorelbine D1,8 Q3W; gemcitabine D1,8 Q3W; capecitabine D1–14 Q3W)
(n=367)

Endpoints:

- **Dual primary:** PFS by BICR per RECIST v1.1, and OS
- **Key secondary:** ORR, PFS (investigator assessed) and safety

Randomisation stratified by:

- **Lines of chemotherapy** in unresectable/metastatic setting (1 vs 2)
- **Geographic location** (US/Canada/Europe vs ROW)
- **Previous CDK4/6 inhibitor** (yes vs no)

- Treatment continued until PD, unacceptable tolerability, or other discontinuation criteria

Detailed description of the statistical methods published previously.[1] *Per American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines. †ICC was administered as follows: eribulin mesylate, 1.4 mg/m² IV on Days 1 and 8, Q3W; capecitabine, 1000 or 1250 mg/m² orally twice daily on Days 1 to 14, Q3W (dose per standard institutional practice); vinorelbine, 25 mg/m² IV on Days 1 and 8, Q3W; or gemcitabine, 1000 mg/m² IV on Days 1 and 8, Q3W. BICR, blinded independent central review; CDK4/6, cyclin-dependent kinase 4/6; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, endocrine therapy; IV, intravenous; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; ROW, rest of world.

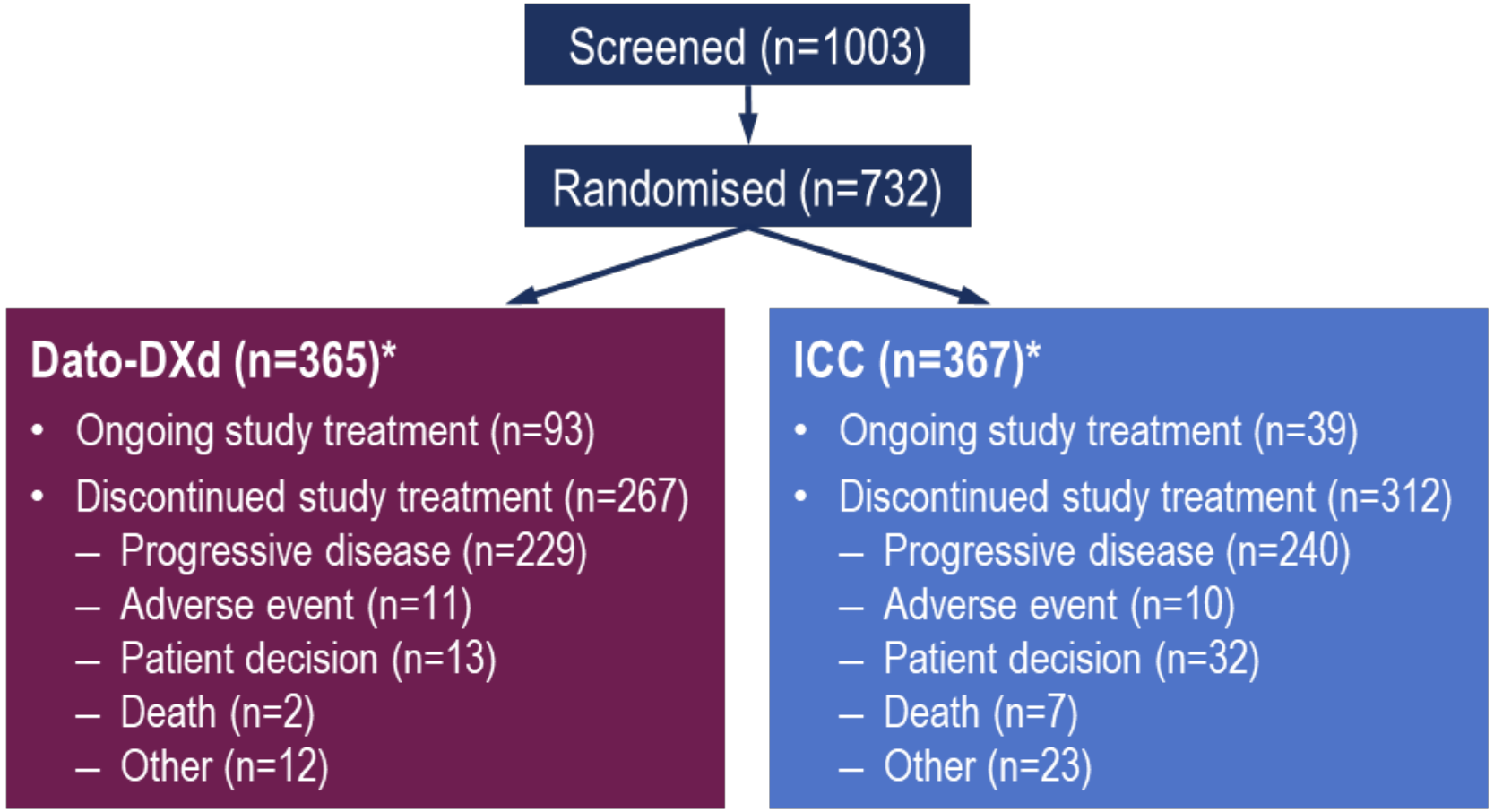
1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

TROPION-Breast01 Statistical Methods[1]

- Primary efficacy analysis performed in intention-to-treat population and analysed by treatment group
- Primary analysis of PFS ~ 419 PFS events
  - Interim OS analysis at the time of the primary PFS analysis
- The final analysis of OS will be conducted at ~ 444 OS events
- PFS analysed using log-rank test utilising stratification factors
- Study considered positive if PFS and/or OS analysis statistically significant

1. Bardia A, et al. *Future Oncol* 2023; doi: 10.2217/fon-2023-0188.

Patient Disposition



ICC:
- Eribulin mesylate: n=220
- Vinorelbine: n=38
- Capecitabine: n=76
- Gemcitabine: n=33

Median study follow-up: 10.8 months

*360 and 351 patients received treatment with Dato-DXd and ICC, respectively.

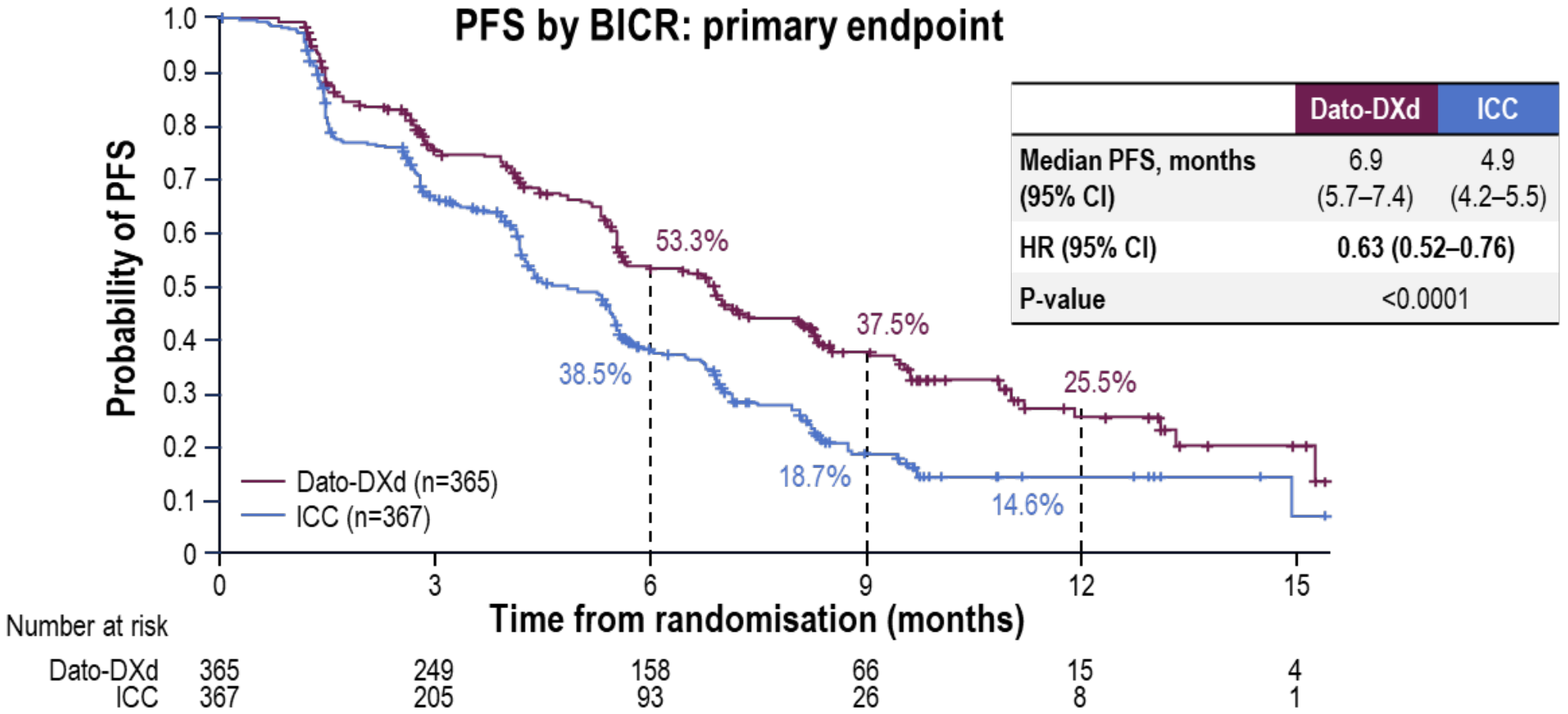
Data cut-off: 17 July 2023.

Demographics and Baseline Characteristics

		Dato-DXd (n=365)	ICC (n=367)
Age, median (range), years		56 (29–86)	54 (28–86)
Female, n (%)		360 (99)	363 (99)
Race, n (%)	Black or African American / Asian / White / Other*	4 (1) / 146 (40) / 180 (49) / 35 (10)	7 (2) / 152 (41) / 170 (46) / 38 (10)
Ethnicity, n (%)	Hispanic or Latino / Not Hispanic or Latino†	40 (11) / 322 (88)	43 (12) / 318 (87)
Prior lines of chemotherapy,‡ n (%)	1 / 2	229 (63) / 135 (37)	225 (61) / 141 (38)
Prior CDK4/6 inhibitor, n (%)	Yes / No	299 (82) / 66 (18)	286 (78) / 81 (22)
Prior taxane and/or anthracycline, n (%)	Taxane and/or Anthracycline	330 (90)	339 (92)
	Neither	35 (10)	28 (8)

*Including not reported. †Ethnicity missing: 3 patients in Dato-DXd group; 6 patients in ICC group.
‡In the inoperable/metastatic setting; one patient in the Dato-DXd group had 3 prior lines of chemotherapy; one patient in the ICC group had 4 prior lines.

Progression-Free Survival



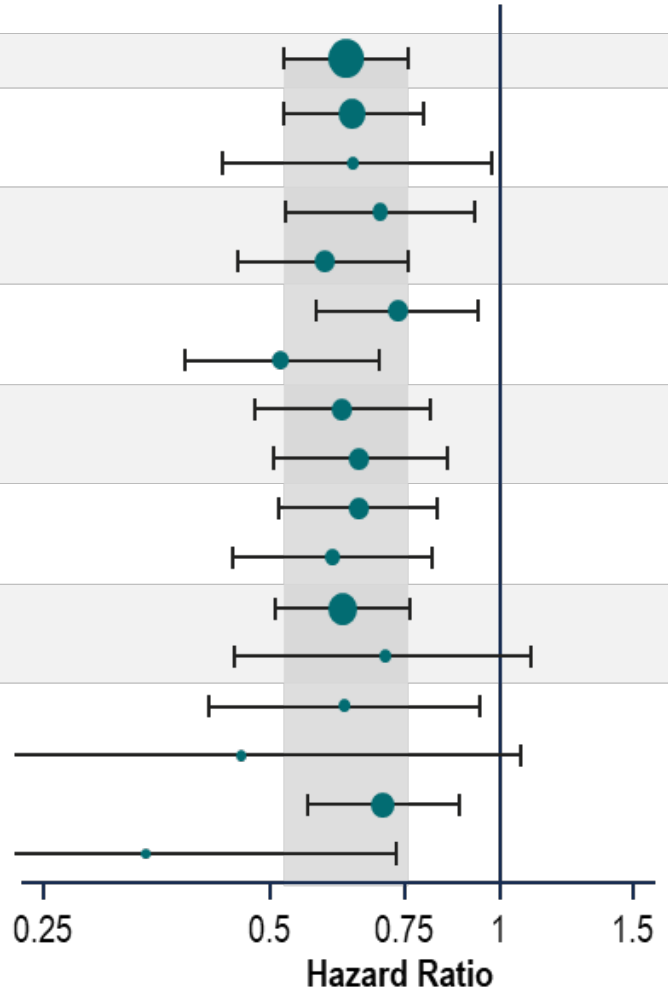
	Dato-DXd	ICC
Median PFS, months (95% CI)	6.9 (5.7–7.4)	4.9 (4.2–5.5)
HR (95% CI)	0.63 (0.52–0.76)	
P-value	<0.0001	

PFS by investigator assessment: Median 6.9 vs 4.5 months; HR 0.64 (95% CI 0.53–0.76)

CI, confidence interval; HR, hazard ratio

PFS by BICR Across Subgroups

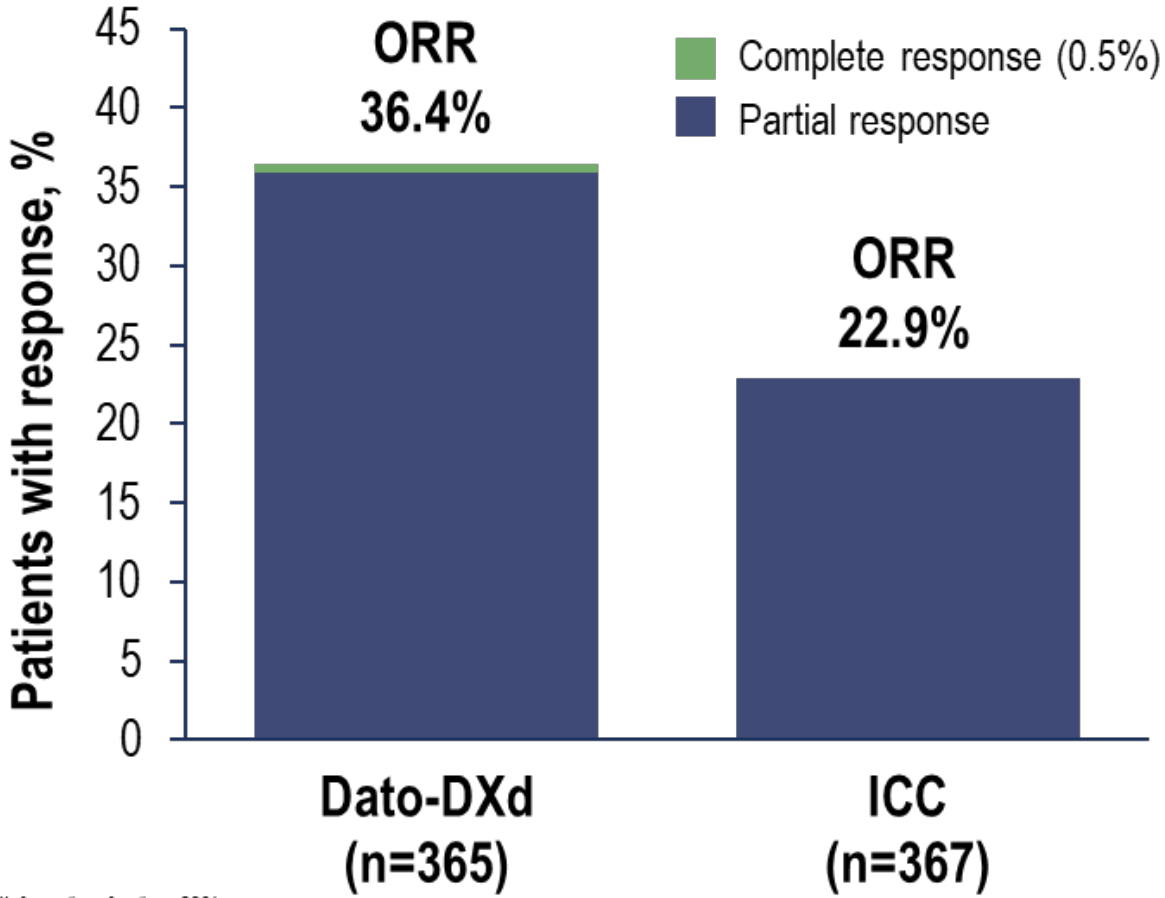
		Events/n Dato-DXd	Events/n ICC	Hazard ratio
All patients		212/365	235/367	0.63
Age at randomisation	<65 years	163/274	190/295	0.64
	≥65 years	49/91	45/72	0.65
Race	Asian	88/146	101/152	0.70
	Non-Asian	109/187	119/183	0.59
ECOG performance status	0	119/197	136/220	0.73
	1	91/165	98/145	0.52
Geographic region	US, Canada, Europe	110/186	112/182	0.62
	Rest of World*	102/179	123/185	0.66
Number of previous lines of chemotherapy	1	128/229	145/225	0.65
	2	84/135	90/141	0.60
Prior use of CDK4/6 inhibitor	Yes	177/299	190/286	0.62
	No	35/66	45/81	0.70
Prior use of taxane and/or anthracycline	Taxane alone	48/80	47/71	0.62
	Anthracycline alone	9/14	16/21	0.46
	Both taxane and anthracycline	141/236	155/247	0.70
	Neither taxane nor anthracycline	14/35	17/28	0.34



Size of circle is proportional to the number of events across both treatment groups.
*Three patients from Canada were incorrectly stratified to Rest of World.

Response and Interim OS

Response Rate



*Information fraction: 39%.
ORR, confirmed objective response rate by BICR

OS: Dual Primary Endpoint

- OS data not mature:*
  - Median follow-up 9.7 months
- A trend favouring Dato-DXd was observed:
  - HR 0.84 (95% CI 0.62–1.14)
- The study is continuing to the next planned analysis for OS

Overall Safety Summary

TRAEs, n (%)	Dato-DXd (n=360)	ICC (n=351)
All grades	337 (94)	303 (86)
Grade ≥3	75 (21)	157 (45)
Associated with dose reduction	75 (21)	106 (30)
Associated with dose interruption	43 (12)	86 (25)
Associated with discontinuation	9 (3)	9 (3)
Associated with death	0	1 (0.3)
Serious TRAEs	21 (6)	32 (9)
Grade ≥3	17 (5)	31 (8)

TRAEs, treatment-related adverse events.

- Median treatment duration was **6.7** months with Dato-DXd and **4.1** months with ICC
- **Rate of grade ≥3 TRAEs in the Dato-DXd group was less than half that in the ICC group**
- Fewer TRAEs leading to dose reductions or interruptions with Dato-DXd compared with ICC

TRAEs Occurring in ≥15% of Patients and AESIs

System Organ Class Preferred term, n (%)	Dato-DXd (n=360)		ICC (n=351)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system				
Anaemia	40 (11)	4 (1)	69 (20)	7 (2)
Neutropenia*	39 (11)	4 (1)	149 (42)	108 (31)
Eye				
Dry eye	78 (22)	2 (1)	27 (8)	0
Gastrointestinal				
Nausea	184 (51)	5 (1)	83 (24)	2 (1)
Stomatitis	180 (50)	23 (6)	46 (13)	9 (3)
Vomiting	71 (20)	4 (1)	27 (8)	2 (1)
Constipation	65 (18)	0	32 (9)	0
General				
Fatigue	85 (24)	6 (2)	64 (18)	7 (2)
Skin and subcutaneous				
Alopecia	131 (36)	0	72 (21)	0

- Most TRAEs were grade 1–2 and manageable

AESIs

- Oral mucositis/stomatitis:† led to treatment discontinuation in one patient in the Dato-DXd group
- Ocular events:‡ most were dry eye; one patient discontinued treatment in the Dato-DXd group
- Adjudicated drug-related ILD:§ rate was low; mainly grade 1/2

Adjudicated drug-related ILD	Dato-DXd	ICC
All grades, n (%)	9 (3)	0
Grade ≥3, n (%)	2 (1)¶	0

*Neutropenia includes the PTs neutropenia and neutrophil count decreased. †Oral stomatitis/mucositis events included PTs of aphthous ulcer, dysphagia, glossitis, mouth ulceration, odynophagia, oral mucosal blistering, oral pain, oropharyngeal pain, pharyngeal inflammation, stomatitis, tongue ulceration; all grade: 59% with Dato-DXd, 17% with ICC; grade 3: 7% with Dato-DXd, 3% with ICC. ‡Ophthalmologic assessments were required at screening, and then every 3 cycles from C1D1 and at end of therapy; ocular events included selected PTs from Corneal Disorder SMQ and select relevant PTs from Eye Disorder SOC; all grade: 49% with Dato-DXd, 23% with ICC; grade 3: 1% with Dato-DXd (one patient with dry eye, one patient with punctate keratitis, and one patient with dry eye and ulcerative keratitis), 0% with ICC. §ILD includes events that were adjudicated as ILD and related to use of Dato-DXd or ICC (includes cases of potential ILD/pneumonitis, based on MedDRA v23.0 for the narrow ILD SMQ, selected terms from the broad ILD SMQ, and PTs of respiratory failure and acute respiratory failure). ¶One adjudicated drug-related grade 5 ILD event: attributed to disease progression by investigator. ILD, interstitial lung disease; PTs, preferred terms; SMQ, standard MedDRA query; SOC, system organ class.

Conclusions

- TROPION-Breast01 demonstrated that Dato-DXd provides both improved efficacy and safety compared with ICC for patients with HR+/HER2– disease
- TROPION-Breast01 met its dual primary PFS endpoint, demonstrating statistically significant and clinically meaningful improvement in PFS with Dato-DXd compared with ICC
  - Consistent PFS benefit observed across subgroups
  - Higher ORR with Dato-DXd and a trend at interim OS favouring Dato-DXd
- Overall, Dato-DXd demonstrated a favourable and manageable safety profile, with no new safety signals
  - Most AESIs were grade 1–2
  - Patients receiving Dato-DXd had fewer grade ≥3 TRAEs (less than half that with ICC), as well as fewer TRAEs leading to dose interruption/reduction compared with ICC

Results support Dato-DXd as a potential new therapeutic option for patients with metastatic HR+/HER2– breast cancer

Datopotamab Deruxtecan (Dato-DXd) + Durvalumab (D) as First-Line (1L) Treatment for Unresectable Locally Advanced/Metastatic Triple-Negative Breast Cancer (a/mTNBC)

Updated Results From BEGONIA, a Phase 1b/2 Study

Professor Peter Schmid, FRCP, MD, PhD

Barts Cancer Institute, Queen Mary University of London, London, UK

P. J. Wysocki,[1] C. X. Ma,[2] Y. H. Park,[3] R. Fernandes,[4] S. Lord,[5] R. D. Baird,[6] C. Prady,[7] K. H. Jung,[8] J. Asselah,[9] R. Huisden,[10] R. Stewart,[10] K. Heider,[10] P. Vukovic,[10] N. Denduluri,[11] Z. Nowecki[12]

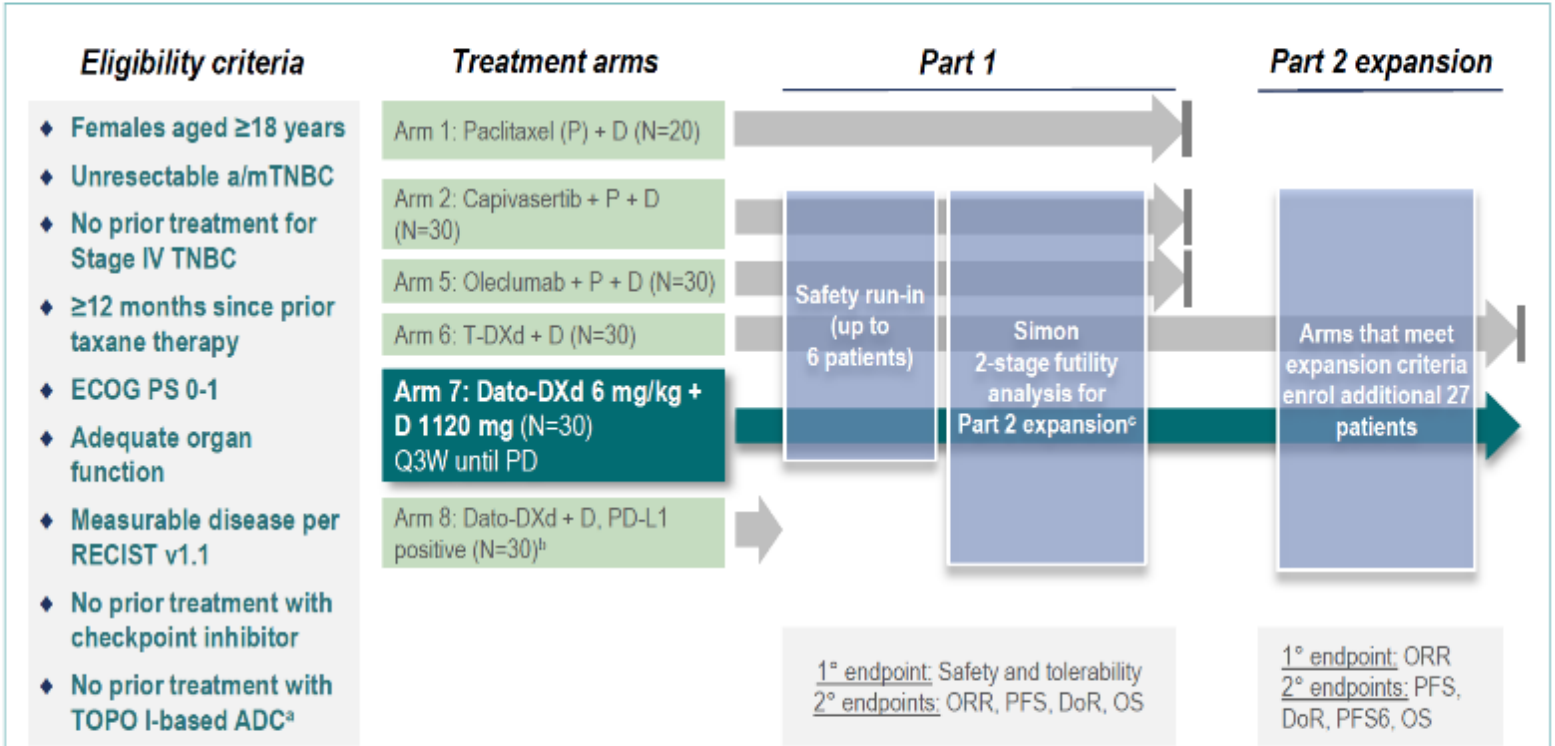
[1]Jagiellonian University Medical College, Krakow, Poland; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [4]Schulich School of Medicine & Dentistry, Western University, London Health Sciences Centre, London, Ontario, Canada; [5]University of Oxford, Oxford, UK; [6]Cancer Research UK Cambridge Centre, Cambridge, UK; [7]Sherbrooke University, Centre intégré de cancérologie de la Montérégie, CISSS Montérégie Centre, Greenfield Park, Quebec, Canada; [8]Asan Medical Center - University of Ulsan, College of Medicine, Seoul, Korea; [9]McGill University Health Centre, Montreal, Quèbec, Canada; [10]AstraZeneca, Cambridge, UK; [11]AstraZeneca, Gaithersburg, MD, USA; [12]Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

The BEGONIA Study (NCT03742102)

Rationale

- Immune checkpoint inhibitors + chemotherapy is the standard of care for patients with PD-L1 positive a/mTNBC; still, most progress within a year (median PFS ~9–10 months)[1,2]
- BEGONIA is evaluating combinations of durvalumab (D), an anti–PD-L1 antibody, with other novel therapies in first-line a/mTNBC
- Dato-DXd is a TROP2-directed ADC with a TOPO I inhibitor payload and a tumour-selective cleavable linker[3]
- At median 7.2 months follow-up, ORR was 74% for patients treated with Dato-DXd + D in BEGONIA[4]

Study Design



We report updated results with longer follow-up for patients from Parts 1 and 2 treated with Dato-DXd + D in BEGONIA Arm 7

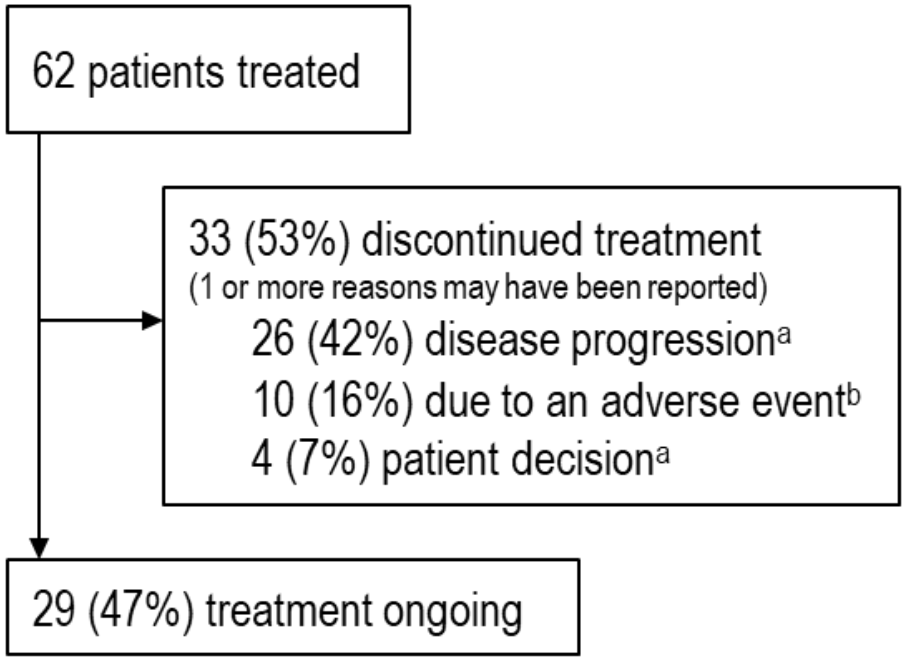
[a]ADC-cohort-specific criteria. [b]Currently enrolling; a safety run-in will not occur for this arm as Dato-DXd + D was already evaluated and found to be tolerable with no dose-limiting toxicities reported. [c]Novel treatment combinations may enter Part 2 expansion if confirmed ORR is at least 57%.

1. Cortes J, et al. *Lancet*. 2020;396(10265):1817-1828. 2. Emens LA, et al. *J Natl Cancer Inst*. 2021;113(8):1005-1016. 3. Bardia A, et al. Presented at SABCS 2022. P6-10-03. 4. Schmid P, et al. Presented at SABCS 2022. PD11-09.

ADC, antibody-drug conjugate; a/mTNBC, advanced/metastatic triple-negative breast cancer; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; D, durvalumab; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-L1, programmed death ligand-1; PFS, progression-free survival; PFS6, progression-free survival at 6 months; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; T-DXd, trastuzumab deruxtecan; TOPO I, topoisomerase I; TROP2, trophoblast cell-surface antigen 2.

BEGONIA Arm 7: Dato-DXd + Durvalumab

Disposition and Baseline Characteristics



Median follow-up: 11.7 (range, 2–20) months

Characteristic	Dato-DXd + D N=62
Age, median (range), years	53 (31–74)
No prior treatment, n (%)	26 (42)
Prior treatments for early-stage disease, n (%)	
Radiotherapy	30 (48)
Cytotoxic chemotherapy	33 (53)
Taxane	26 (42)
Anthracycline	29 (47)
Platinum compound	9 (15)
Hormonal therapy	10 (16)
Targeted therapy	1 (2)
Visceral metastases,[c] n (%)	37 (60)
Lymph node metastases, n (%)	42 (68)
PD-L1 expression,[d] n (%)	
High (TAP ≥10%)	7 (11)
Low (TAP <10%)	54 (87)
Unknown/Missing	1 (2)

[a]Discontinued all study drugs. [b]Discontinued any study drug. [c]Defined as liver/hepatic and/or respiratory metastases. [d]PD-L1 expression was assessed by immunohistochemistry using the VENTANA PD-L1 (SP263) Assay, and expression was defined as the percentage of the tumour area populated by tumour or immune cells with membranous staining (TAP). A sample was considered PD-L1 high if it had ≥10% TAP PD-L1 expression.
Dato-DXd, datopotamab deruxtecan; D, durvalumab; PD-L1, programmed cell death ligand-1; TAP, tumour area positivity.

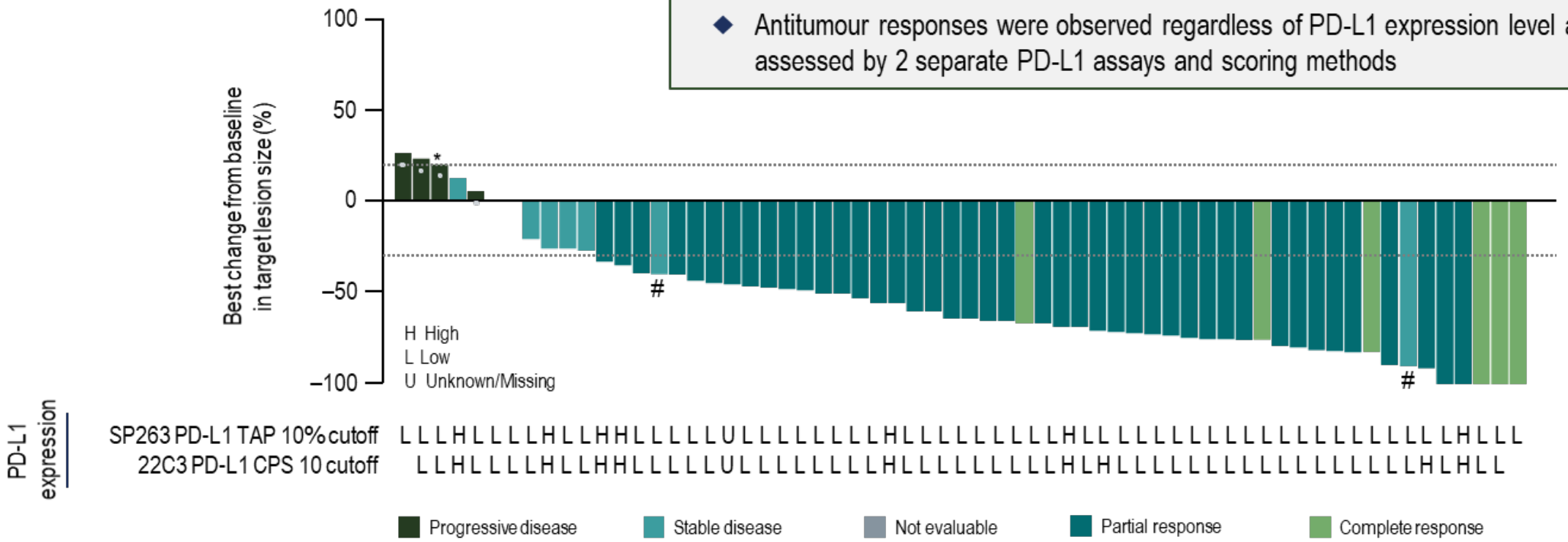
Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Antitumour Responses in 1L a/mTNBC

Confirmed ORR was **79%** (49/62; 95% CI, 66.8–88.3) with 6 CR and 43 PR

- Antitumour responses were observed regardless of PD-L1 expression level as assessed by 2 separate PD-L1 assays and scoring methods



Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%). PD-L1 expression was assessed by 1) immunohistochemistry using the VENTANA PD-L1 (SP263) Assay with expression defined as the percentage of the tumour area populated by tumour or immune cells with membranous staining (TAP), or 2) immunohistochemistry using the 22C3 antibody with expression defined as the number of PD-L1–staining tumour cells, lymphocytes, and macrophages, divided by the total number of viable tumour cells, multiplied by 100 (CPS). *If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%. "•" Patients with PD as best overall response. #Unconfirmed response.

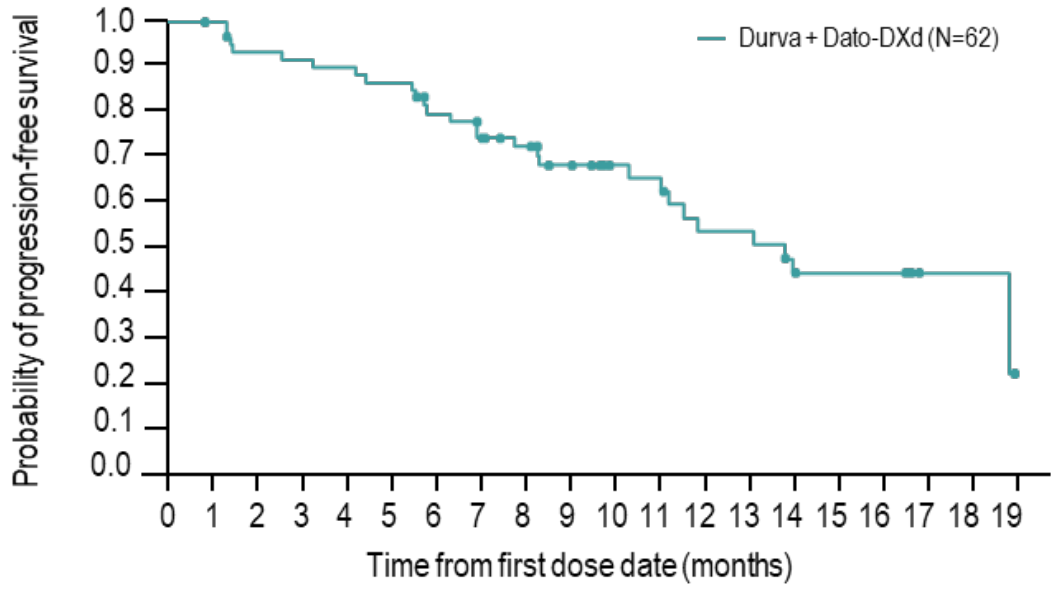
1L, first line; a/m TNBC, advanced/metastatic triple–negative breast cancer; CI, confidence interval; CPS, combined positive score; CR, complete response; Dato-DXd, datopotamab deruxtecan; ORR, objective response rate; PD-L1, programmed cell death ligand-1; PR, partial response; TAP, tumour area positivity.

Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Progression-Free Survival and Duration of Response

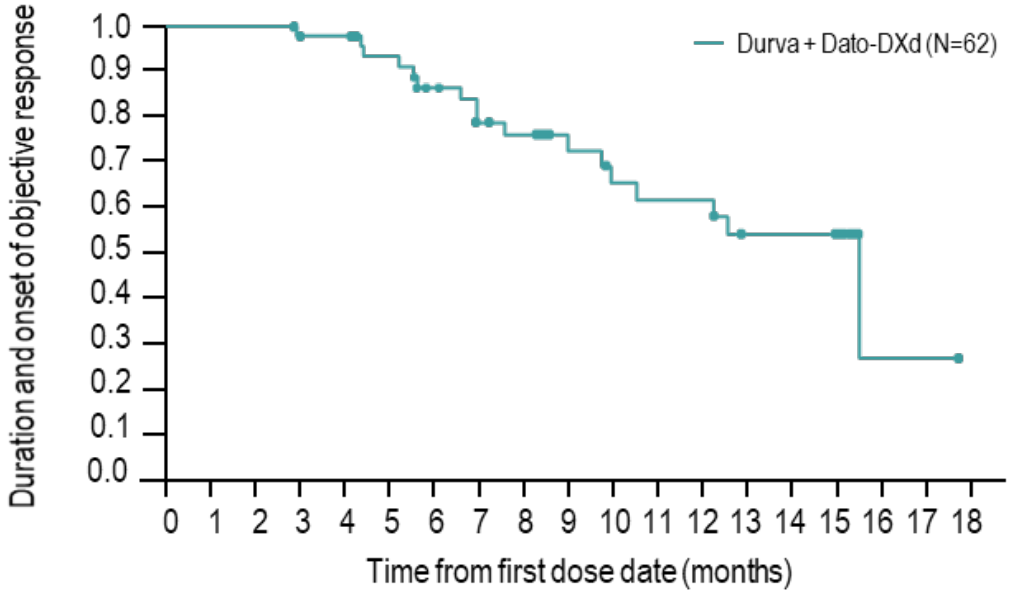
Median PFS was 13.8 months (95% CI, 11.0–NC)



Number of patients at risk

Durva + Dato-DXd	62	61	56	55	54	52	45	40	37	32	24	23	18	18	14	13	13	2	2	0

Median DoR was 15.5 months (95% CI, 9.92–NC)



Number of patients at risk

Durva + Dato-DXd	49	49	49	47	46	42	35	30	28	21	18	17	17	13	13	12	1	1	0

Kaplan-Meier analysis was performed. Circles indicate censored observations.
CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; NC, not calculable; PFS, progression-free survival.

Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Safety Summary

Patients, n (%)	Dato-DXd + D N=62
Any AEs	62 (100)
Grade 3/4	35 (57)
Any treatment-related AEs[a]	62 (100)
Grade 3/4	27 (44)
Any serious AEs	14 (23)
Treatment-related	6 (10)
AEs leading to discontinuation of any treatments	10 (16)
AEs leading to death[b]	1 (2)
Dose adjustments	
Dato-DXd dose reduction	18 (29)
Dato-DXd dose delay	28 (45)
Durvalumab dose delay	31 (50)

[a]Per investigator assessment. [b]Patient died due to dehydration, unrelated to treatment.
AE, adverse event; Dato-DXd, datopotamab deruxtecan; D, durvalumab.

Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Adverse Events

Most frequently reported adverse events (≥15%) (N=62)		
AE preferred term	**Any grade, n (%)**	**Grade 3/4, n (%)**
Nausea	40 (65)	0
Stomatitis	40 (65)	7 (11)
Alopecia	31 (50)	0
Constipation	29 (47)	1 (2)
Fatigue	28 (45)	1 (2)
Rash	20 (32)	0
Vomiting	16 (26)	1 (2)
Amylase increased	13 (21)	11 (18)
COVID-19	13 (21)	0
Dry eye	13 (21)	0
Decreased appetite	12 (19)	1 (2)
Pruritus	10 (16)	0
Cough	10 (16)	0

- The most common AEs were gastrointestinal and generally of low grade (**Table**)
- Stomatitis was the most common AE leading to Dato-DXd dose reduction (11 patients)
- There were 3 (5%) adjudicated treatment-related ILD/pneumonitis events (2 grade 2 events, 1 grade 1 event)
- Limited rates of diarrhea (13% any grade, 1 grade 3 event) and neutropenia (5% any grade, 1 grade 3 event) were reported
- The most frequent AESIs for Arm 7 were stomatitis (65%), rash (32%), dry eye (21%), hypothyroidism (14.5%), and keratitis (14.5%)

AE, adverse event; AESI, adverse event of special interest; ILD, interstitial lung disease.

Data cutoff: 02 Feb 2023

BEGONIA Arm 7: Dato-DXd + Durvalumab

Conclusions

Dato-DXd + durvalumab continues to demonstrate robust, durable responses in first-line a/mTNBC in a biomarker-unselected population with median 11.7 months of follow-up

- Confirmed ORR was 79% (95% CI, 66.8–88.3), responses observed regardless of PD-L1 expression
- Median DoR was 15.5 months (95% CI, 9.92–NC)
- Median PFS was 13.8 months (95% CI, 11.0–NC)

The combination of Dato-DXd + durvalumab had a tolerable and manageable safety profile, with no new safety signals

- Comprehensive toxicity management guidelines were implemented during the course of the study

BEGONIA is currently enrolling for Arm 8, Dato-DXd + durvalumab in a PD-L1–high population

a/mTNBC, advanced/metastatic triple-negative breast cancer; CI, confidence interval; Dato-DXd, datopotamab deruxtecan; DoR, duration of response; NC, not calculable; ORR, objective response rate; PD-L1, programmed death ligand-1; PFS, progression-free survival.

Trastuzumab deruxtecan (T-DXd) for pretreated patients withHER2-expressing solid tumors: primary analysis from the DESTINY-PanTumor02 (DP-02) study

Funda Meric-Bernstam, MD;[a] Vicky Makker; Ana Oaknin; Do-Youn Oh; Susana Banerjee; Antonio González-Martín; Kyung Hae Jung; Iwona Ługowska; Luis Manso; Aránzazu Manzano; Bohuslav Melichar; Salvatore Siena; Daniil Stroyakovskiy; Anitra Fielding; Yan Ma; Soham Puvvada; Jung-Yun Lee

On behalf of the DESTINY-PanTumor02 investigators
[a]University of Texas MD Anderson Cancer Center, Houston, TX, USA
October 23, 2023 | 16:40–16:45 CEST

DESTINY-PanTumor02: a Phase 2 study of T-DXd for HER2-expressing solid tumors

An open-label, multicenter study (NCT04482309)

Key eligibility criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd
5.4 mg/kg Q3W

40 per cohort[b]

- Endometrial cancer
- Cervical cancer
- Ovarian cancer
- Bladder cancer
- Other tumors[c]
- Biliary tract cancer
- Pancreatic cancer

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR, DCR, PFS, OS
- Safety

Exploratory analysis

- Subgroup analyses by HER2 status

Primary analysis
data cutoff: Jun 8, 2023
Median follow up: 12.75 mo

Baseline characteristics

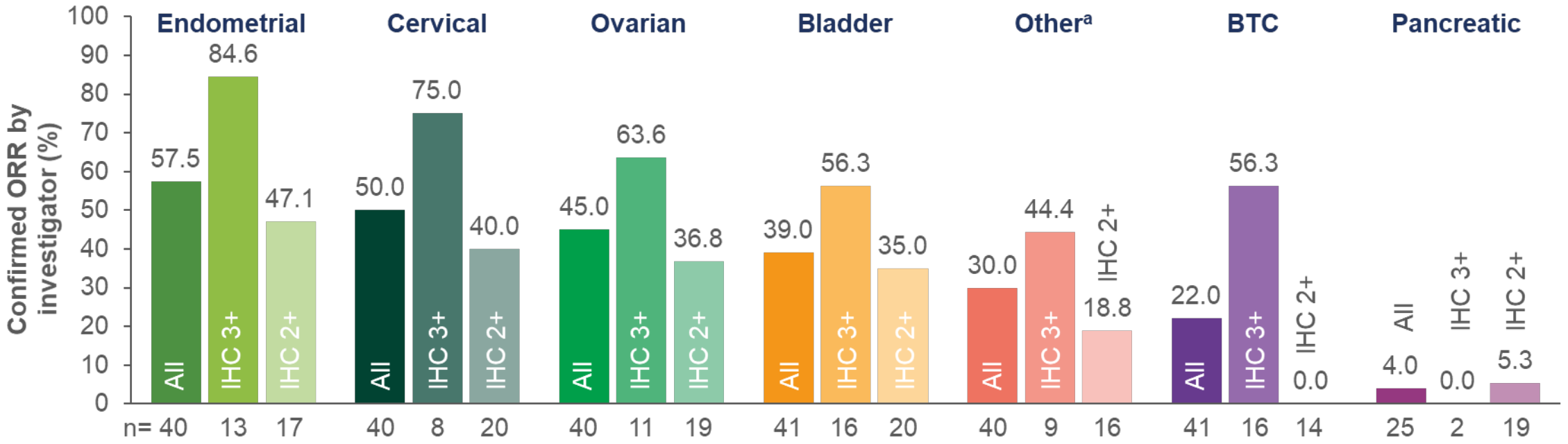
- 267 patients received treatment; 202 (75.7%) based on local HER2 testing
  - 111 (41.6%) patients were IHC 3+ based on HER2 test (local or central) at enrollment, primary efficacy analysis (all patients)
  - **75 (28.1%) patients were IHC 3+ on central testing**, sensitivity analysis on efficacy endpoints (subgroup analyses)
- Median age was 62 years (23–85) and **109 (40.8%) patients had received ≥3 lines of therapy**

[a]Patients were eligible for either test. All patients were centrally confirmed; [b]planned recruitment, cohorts with no objective responses in the first 15 patients were to be closed; [c]patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer

2L, second-line; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization

1. Hofmann M, et al. *Histopathology*. 2008;52:797–805

Objective response and duration of response



Median DOR, months (95% CI)[b]	NR (9.9, NR)	14.2 (4.1, NR)	11.3 (4.1, 22.1)	8.7 (4.3, 11.8)	22.1 (4.1, NR)	8.6 (2.1, NR)	5.7 (NR, NR)

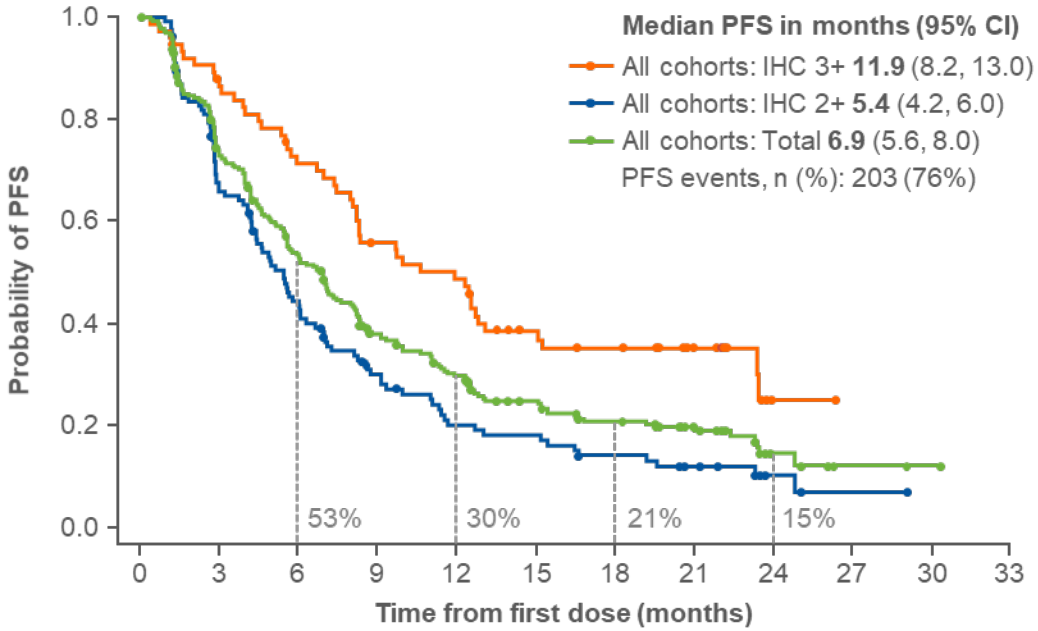
	All patients (N=267)	IHC 3+ (n=75)	IHC 2+ (n=125)
ORR, % (95% CI)	37.1 (31.3, 43.2)	61.3 (49.4, 72.4)	27.2 (19.6, 35.9)
Median DOR, months (95% CI)[b]	11.3 (9.6, 17.8)	22.1 (9.6, NR)	9.8 (4.3, 12.6)

Analysis of ORR by investigator was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer; [b]includes patients with a confirmed objective response only

BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; ORR, objective response rate; T-DXd, trastuzumab deruxtecan

Efficacy endpoint: PFS and OS by HER2 status

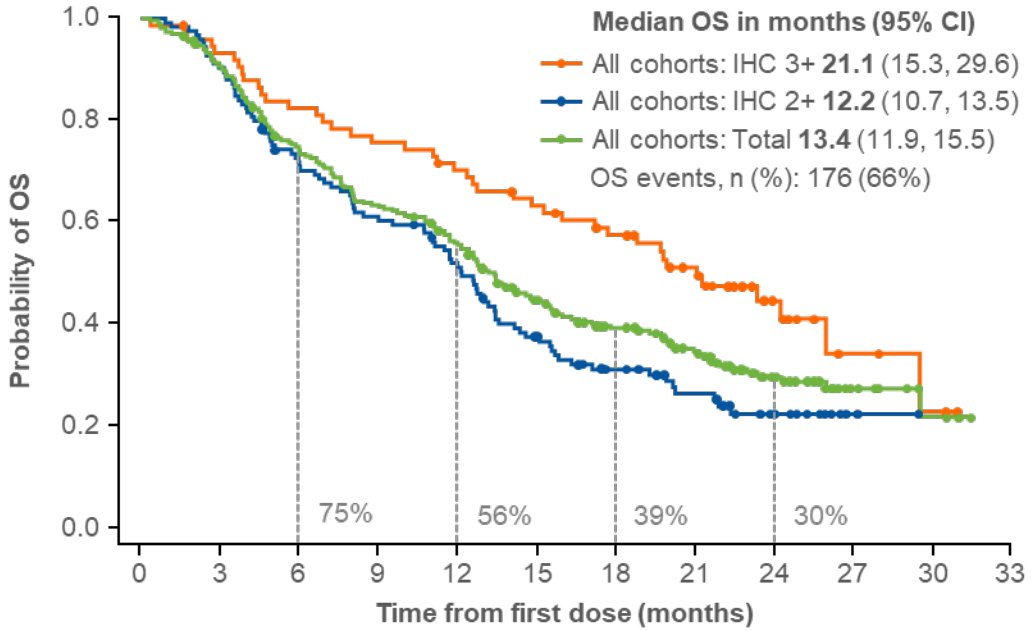
K-M estimates of PFS by investigator assessment (All cohorts)



Number at risk, month

All cohorts: IHC 3+	75	63	51	39	34	23	19	12	1	0		
All cohorts: IHC 2+	125	78	50	31	20	18	13	9	3	1	0	
All cohorts: Total	267	185	132	89	68	51	39	25	6	2	1	0

K-M estimates of OS (All cohorts)



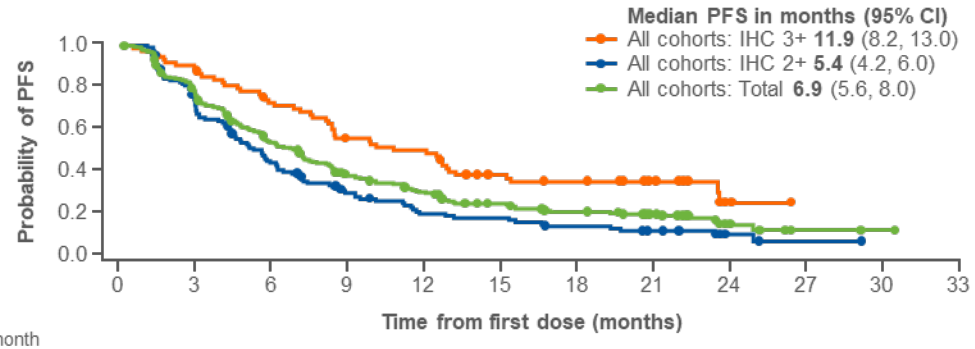
Number at risk, month

All cohorts: IHC 3+	75	69	61	56	51	45	39	29	13	4	2	0
All cohorts: IHC 2+	125	113	88	75	62	43	31	22	12	2	0	
All cohorts: Total	267	239	194	165	143	108	86	65	34	10	4	0

Circle indicates a censored observation
CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; K-M, Kaplan-Meier; OS, overall survival; PFS, progression-free survival

Efficacy endpoint: PFS by HER2 status per cohort

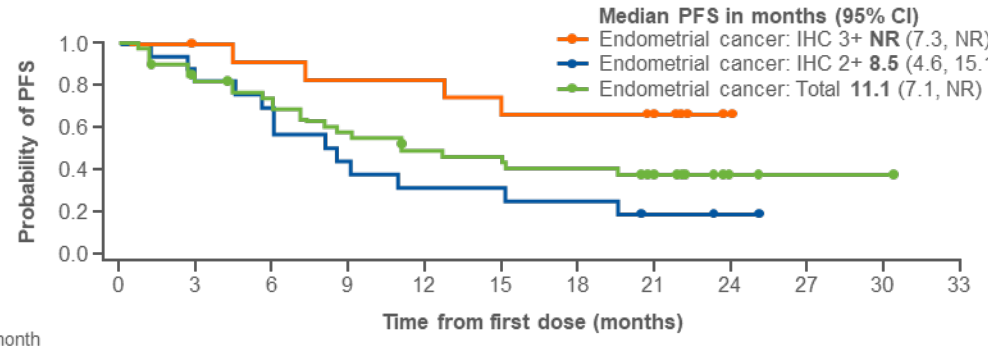
All cohorts



Number at risk, month

All cohorts: IHC 3+	75	63	51	39	34	23	19	12	1	0	
All cohorts: IHC 2+	125	78	50	31	20	18	13	9	3	1	0
All cohorts: Total	267	185	132	89	68	51	39	25	6	2	1	0

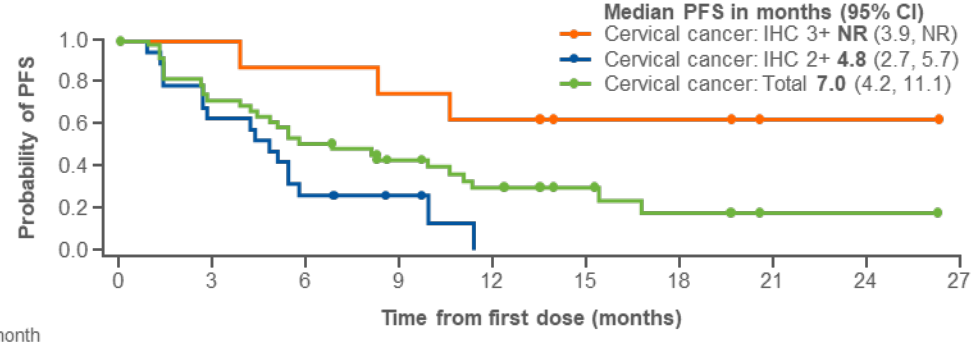
Endometrial cancer



Number at risk, month

Endometrial cancer: IHC 3+	13	12	11	10	10	9	8	5	0		
Endometrial cancer: IHC 2+	17	14	11	7	5	5	4	2	1	0	
Endometrial cancer: Total	40	31	27	21	17	16	14	8	2	1	1	0

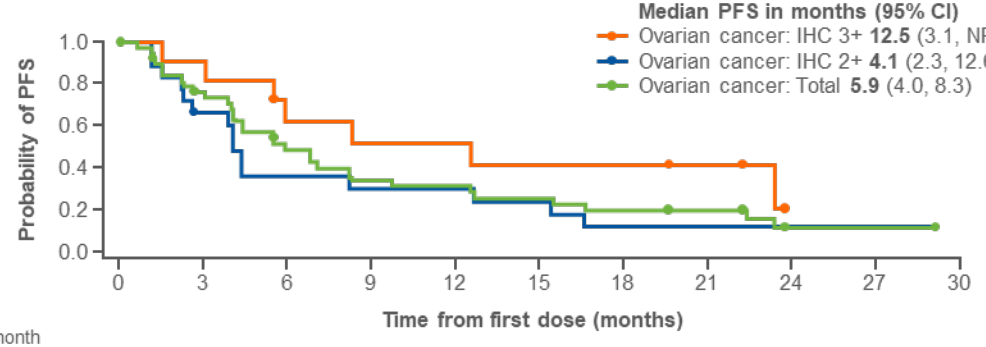
Cervical cancer



Number at risk, month

Cervical cancer: IHC 3+	8	8	7	6	5	3	3	1	1	0
Cervical cancer: IHC 2+	20	12	5	3	0					
Cervical cancer: Total	40	28	20	14	9	6	3	1	1	0

Ovarian cancer



Number at risk, month

Ovarian cancer: IHC 3+	11	10	6	5	5	4	4	3	0	
Ovarian cancer: IHC 2+	19	11	6	5	5	4	2	2	1	1	0
Ovarian cancer: Total	40	28	17	12	11	9	7	6	1	1	0

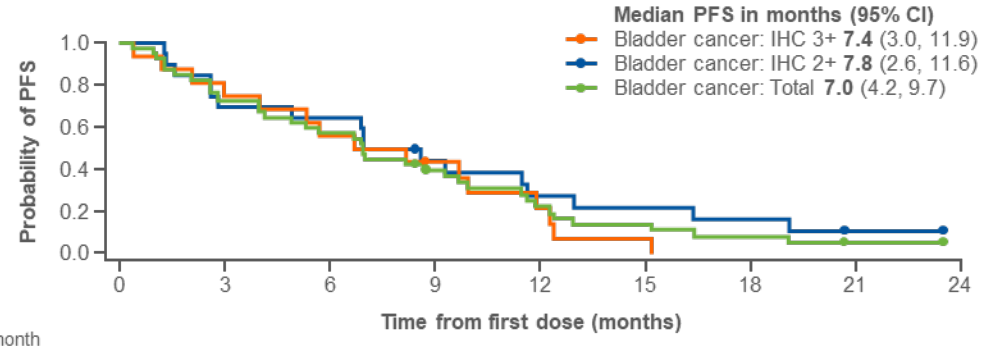
Circle indicates a censored observation
CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; PFS, progression-free survival

Skip in ESMO Highlight presentation

Daiichi-Sankyo

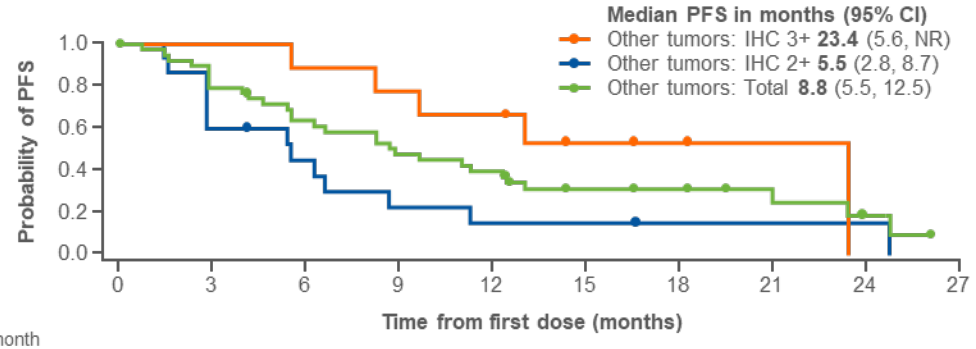
Efficacy endpoint: PFS by HER2 status per cohort

Bladder cancer



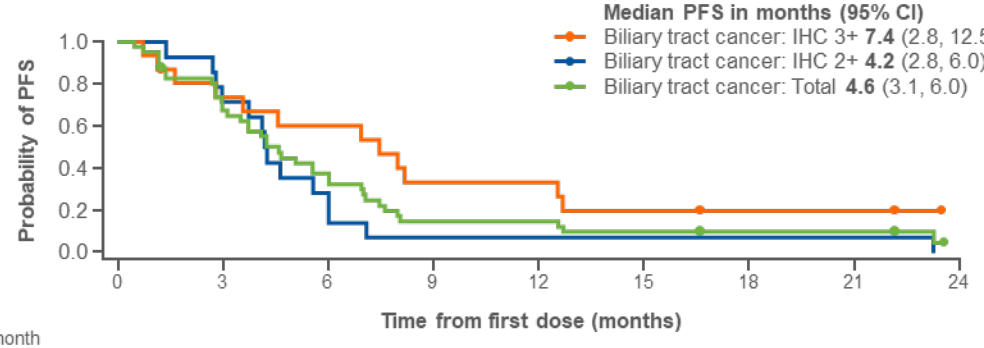
Number at risk, month									
Bladder cancer: IHC 3+	16	12	9	6	3	1	0		
Bladder cancer: IHC 2+	20	14	13	8	5	4	3	1	0
Bladder cancer: Total	41	29	23	14	8	5	3	1	0

Other tumors



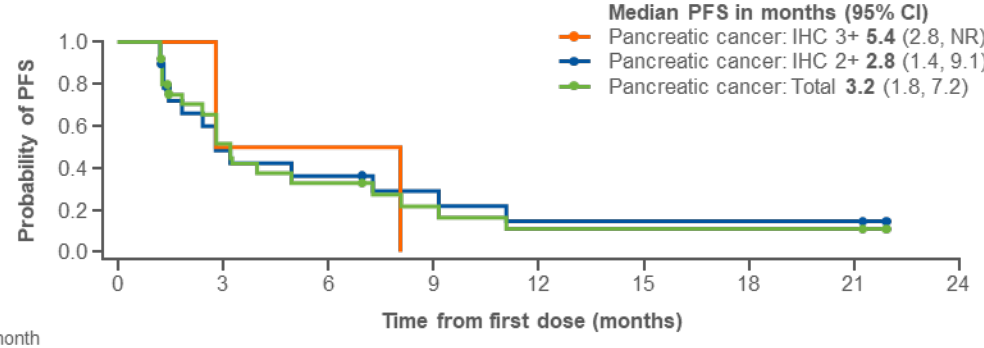
Number at risk, month									
Other tumors: IHC 3+	9	9	8	7	6	3	2	1	0
Other tumors: IHC 2+	16	9	6	3	2	2	1	1	1	0
Other tumors: Total	40	31	24	18	15	9	7	4	2	0

Biliary tract cancer



Number at risk, month									
Biliary tract cancer: IHC 3+	16	11	9	5	5	3	2	2	0
Biliary tract cancer: IHC 2+	14	10	3	1	1	1	1	1	0
Biliary tract cancer: Total	41	27	14	6	6	4	3	3	0

Pancreatic cancer

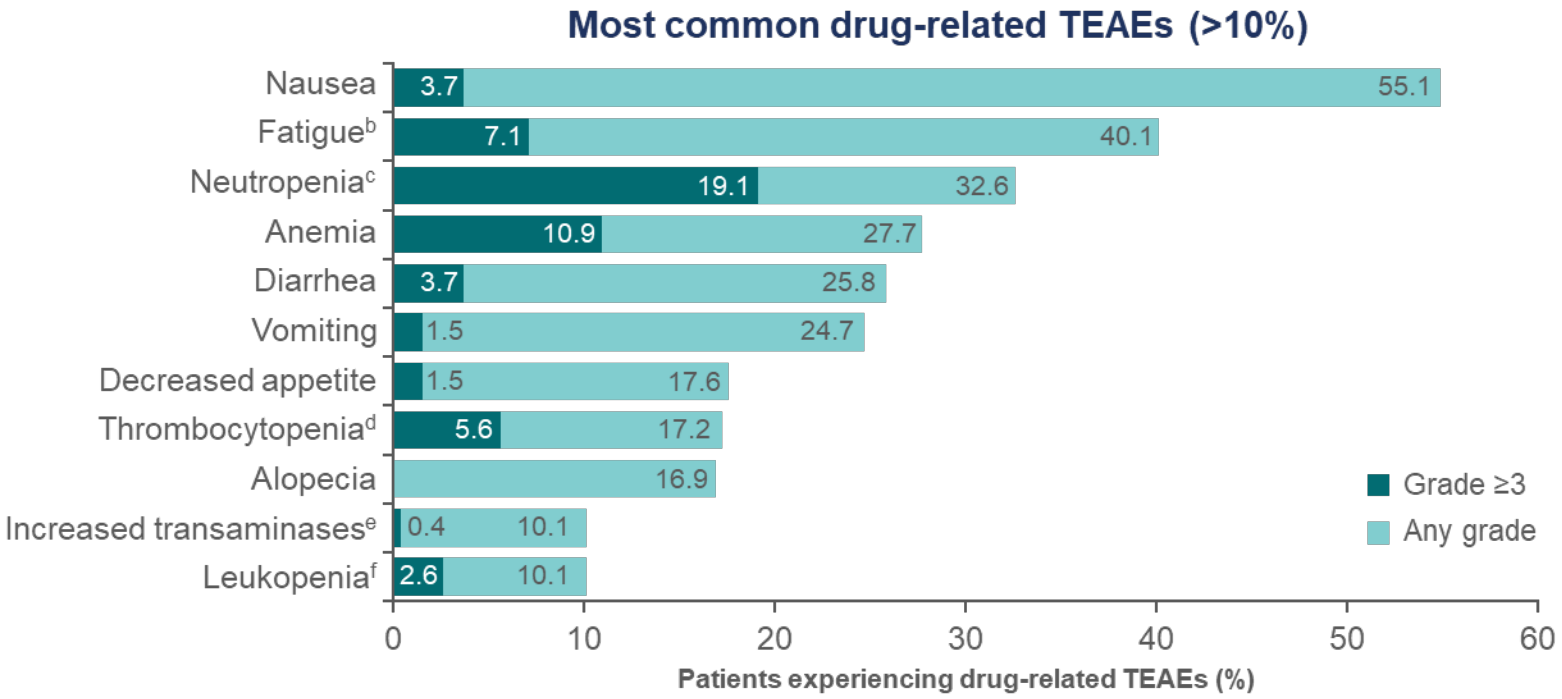


Number at risk, month									
Pancreatic cancer: IHC 3+	2	1	1	0					
Pancreatic cancer: IHC 2+	19	8	6	4	2	2	2	2	0
Pancreatic cancer: Total	25	11	7	4	2	2	2	2	0

Circle indicates a censored observation
CI, confidence interval; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; NR, not reached; PFS, progression-free survival

Safety summary

n (%)	All patients (N=267)
Any drug-related TEAEs	226 (84.6)
Drug-related TEAEs Grade ≥3	109 (40.8)
Serious drug-related TEAEs	36 (13.5)
Drug-related TEAEs associated with dose discontinuations	23 (8.6)
Drug-related TEAEs associated with dose interruptions	54 (20.2)
Drug-related TEAEs associated with dose reductions	54 (20.2)
Drug-related TEAEs associated with deaths	4 (1.5)[a]



ILD/pneumonitis adjudicated as T-DXd related, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N=267)	7 (2.6)	17 (6.4)	1 (0.4)	0	3 (1.1)	28 (10.5)

Analyses were performed in patients who received ≥1 dose of T-DXd (N=267); median total treatment duration 5.6 months (range 0.4–31.1)
[a]Included pneumonia (n=1), organizing pneumonia (n=1), pneumonitis (n=1), and neutropenic sepsis (n=1); [b]category includes the preferred terms fatigue, asthenia, and malaise; [c]category includes the preferred terms neutrophil count decreased and neutropenia; [d]category includes the preferred terms platelet count decreased and thrombocytopenia; [e]category includes the preferred terms aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, hypertransaminasemia; [f]category includes the preferred terms white blood cell count decreased and leukopenia
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event

Conclusions

The robust response rates and survival outcomes are encouraging and were observed across tumor types in heavily pretreated patients

T-DXd demonstrated clinically meaningful activity across a broad range of HER2-expressing solid tumors:

- **ORR:** 37.1% in all patients and 61.3% in patients with IHC 3+
- **Durable responses:** median DOR 11.3 months in all patients and 22.1 months in patients with IHC 3+

Durable responses led to clinically meaningful progression-free and overall survival outcomes:

- **PFS:** 6.9 months in all patients and 11.9 months in patients with IHC 3+
- **OS:** 13.4 months in all patients and 21.1 months in patients with IHC 3+

The safety of T-DXd was consistent with the known profile

DESTINY-PanTumor02 supports the potential role of T-DXd as a tumor-agnostic therapy for patients with HER2-expressing solid tumors

DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan

Raludotatug deruxtecan (R-DXd; DS-6000) monotherapy in patients with previously treated ovarian cancer (OVC): subgroup analysis of a first-in-human Phase 1 study

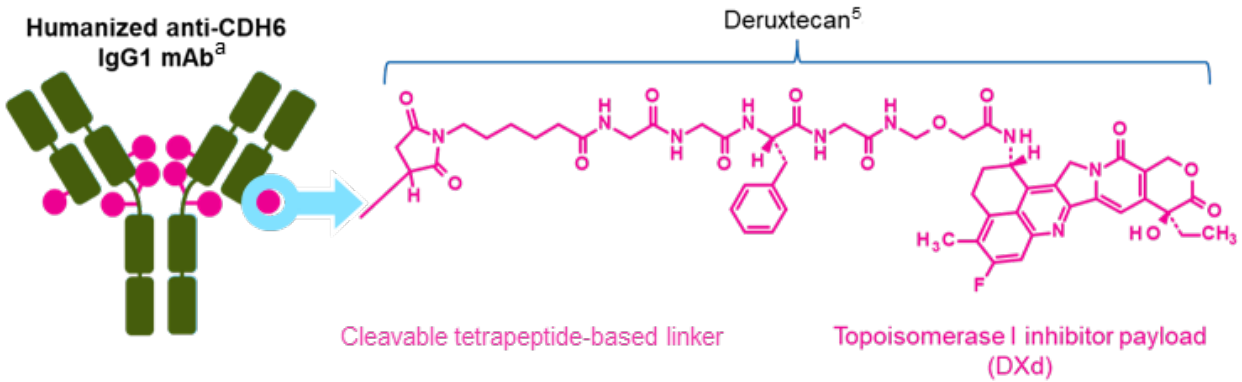
Kathleen Moore,[1,2] Alexander Philipovskiy,[2,3] Kenichi Harano,[4] Brian Rini,[5] Kazuki Sudo,[6] Shigehisa Kitano,[7] David R. Spigel,[2,8] Jie Lin,[9] Madan G. Kundu,[9] Amine Bensmaine,[10] Yusuke Myobatake,[9] Erika Hamilton[2,8]

[1]Oklahoma University, Oklahoma City, OK, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]Florida Cancer Specialists, Lake Mary, FL, USA; [4]National Cancer Center Hospital East, Kashiwa, Japan; [5]Vanderbilt-Ingram Cancer Center, Nashville, TN, USA; [6]National Cancer Center Hospital, Tokyo, Japan; [7]Japanese Foundation for Cancer Research, Tokyo, Japan; [8]Tennessee Oncology, PLLC, Nashville, TN, USA; [9]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA; [10]Daiichi Sankyo, Inc., Rueil-Malmaison, France.

Background

- The emergence of platinum resistance in recurrent OVC is inevitable; these patients have a clear need for novel treatments[1]
- Mirvetuximab soravtansine-gynx received accelerated approval from the FDA for the treatment of patients with platinum-resistant, FRα-positive OVC (ORR: 31.7%, median DOR: 6.9 months)[2]
- Expression of CDH6 is observed in ~65–85% of patients with OVC[3,4]
- Raludotatug deruxtecan (R-DXd; DS-6000) is a CDH6-directed ADC composed of three parts: a humanized anti-CDH6 IgG1 mAb, covalently linked to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker[5]

R-DXd was designed with 7 key attributes



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

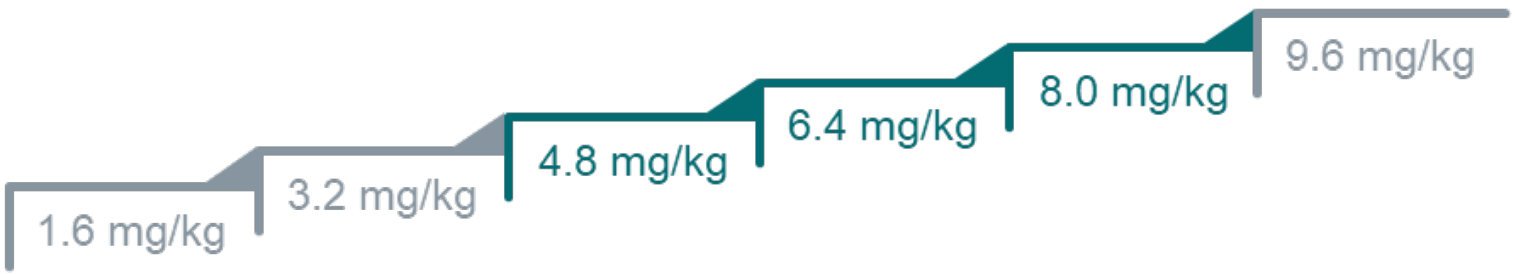
[a]Image is for illustrative purposes only; actual drug positions may vary. [b]The clinical relevance of these features is under investigation. [c]Based on animal data.
ADC, antibody–drug conjugate; CDH6, cadherin 6; DOR, duration of response; DXd, deruxtecan; FDA, United States Food and Drug Administration; FRα, folate receptor alpha; IgG1, immunoglobulin G1; mAb, monoclonal antibody; ORR, objective response rate; OVC, ovarian cancer.

1. Richardson DL, et al. *JAMA Oncol*. 2023;9:851–859; 2. ELAHERE™ (mirvetuximab soravtansine-gynx) prescribing information. Accessed September 1, 2023; 3. Bartolomé RA, et al. *Mol Oncol*. 2021;15:1849–1865; 4. Shintani D, et al. *Gynecol Oncol*. 2022;166(Suppl. 1):S116; 5. Suzuki H, et al. *Ann Oncol*. 2021;32(Suppl. 5):S361–S375; 6. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67:173–185.

First-in-human phase 1 study of R-DXd (NCT04707248)[1,2]

Subgroup analysis of patients with OVC who received R-DXd at 4.8–8.0 mg/kg[a]

Part A
Dose escalation: R-DXd IV Q3W



Part B
Dose expansion: R-DXd IV Q3W

- OVC cohort: 4.8 mg/kg
- OVC cohort: 6.4 mg/kg
- OVC cohort: 5.6 mg/kg
- OVC cohort: 8.0 mg/kg

Enrollment criteria:

- Advanced/metastatic OVC not amenable to SOC therapy
- ECOG PS 0–1
- Prior taxane and platinum-based chemotherapy
- No previous CDH6-targeting agents or ADCs with a linked topoisomerase I inhibitor
- Patients were not selected based on tumor CDH6 expression

Key primary objectives:

- Safety and tolerability
- Determine MTD and RDEs for dose expansion
- Determine ORR per RECIST v1.1 for dose expansion

Key secondary objectives:

- PK: ADC, total anti-CDH6 antibody, and the DXd payload
- Antitumor activity per RECIST v1.1
- Immunogenicity

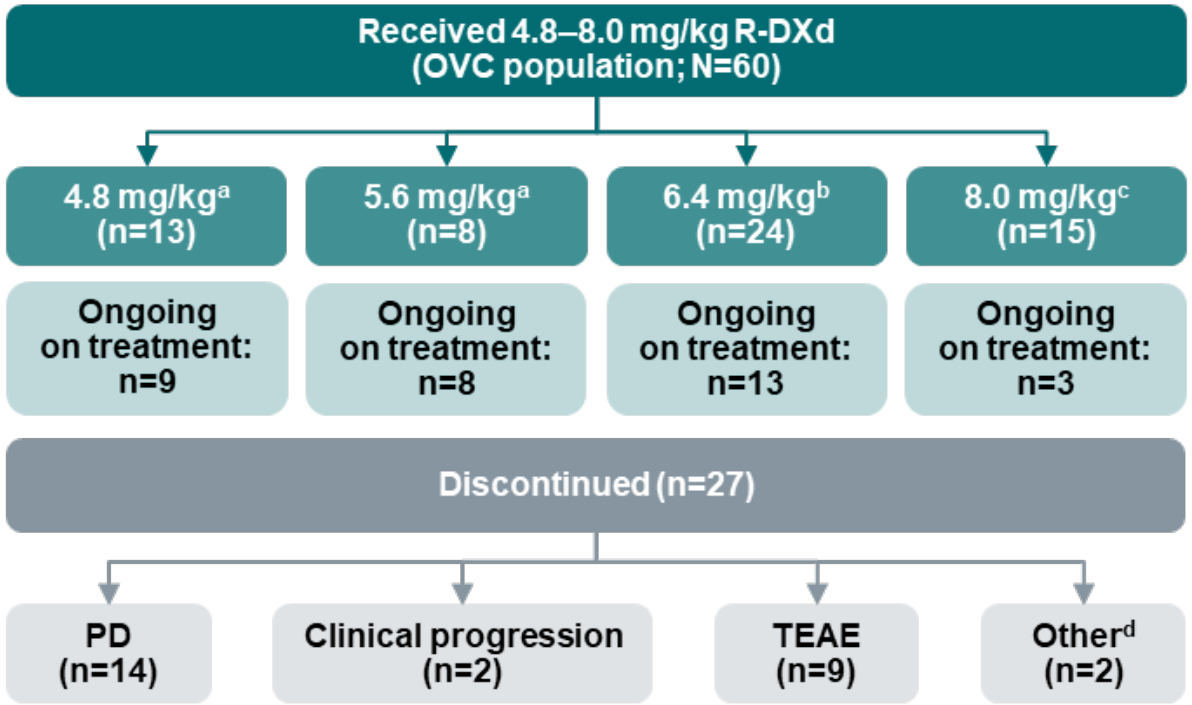
[a]4.8–8.0 mg/kg R-DXd dose cohorts were initially prioritized for dose expansion due to a favorable benefit/risk profile.

ADC, antibody–drug conjugate; CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; ORR, objective response rate; OVC, ovarian cancer; PK, pharmacokinetics; Q3W, every 3 weeks; RDE, recommended doses for expansion; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard of care.

1. ClinicalTrials.gov. https://classic.clinicaltrials.gov/ct2/show/NCT04707248. Accessed July 20, 2023; 2. Data on file. Daiichi Sankyo, Inc. DS6000-A-U101 protocol, version 3; 2020.

Baseline demographics and disease characteristics

Data cutoff: July 14, 2023



- Median treatment duration: 18 weeks (range: 3–115)
- 12 (20%) patients received treatment for ≥6 months
- 3 (5%) patients received treatment for ≥18 months

	OVC (4.8–8.0 mg/kg) N=60
Age, median years (range)	66 (42–82)
ECOG PS, n (%)	
0	22 (36.7)
1	38 (63.3)
Platinum-resistant disease[e], n (%)	55 (91.7)
Number of prior systemic regimens, median (range)	4 (1–13)
Received prior systemic therapy, n (%)	
Bevacizumab	41 (68.3)
PARP inhibitor	39 (65.0)
Baseline tumor CDH6 expression H-score, median (range)	125 (0–250)

[a]Enrollment ongoing. [b]Enrollment completed. [c]As of October 2022, the patients who were still receiving R-DXd at 8.0 mg/kg were dose-reduced to receive R-DXd 6.4 mg/kg. [d]Death (n=1) and informed consent withdrawn (n=1). [e]Defined as tumor progression during or within 6 months after completion of prior platinum therapy. Five patients had tumor progression 6 months after platinum therapy.

CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; OVC, ovarian cancer; PARP, poly adenosine diphosphate-ribose polymerase; PD, progressive disease; TEAE, treatment-emergent adverse event.

Safety profile of R-DXd is manageable

Patients with OVC who received R-DXd at 4.8–8.0 mg/kg

Overview of TEAEs

	n (%) N=60
Any TEAEs	57 (95.0)
TEAE with CTCAE Grade ≥3	31 (51.7)
TEAE associated with drug discontinuation	9 (15.0)
TEAE associated with dose interruption	22 (36.7)
TEAE associated with dose reduction	15 (25.0)
Any treatment-related CTCAE Grade ≥3 TEAE	22 (36.7)
Treatment-related TEAE associated with death	2 (3.3)[a]

- 3.3% (2/60) of patients in the 4.8–8.0 mg/kg cohort experienced Grade 5 ILD; both occurred in the 8.0 mg/kg cohort and were adjudicated as treatment-related
- 8.9% (4/45) of patients in the 4.8–6.4 mg/kg cohort experienced ILD (all Grade 2), of which 2 were adjudicated as treatment-related
- As of October 2022, the 8.0 mg/kg cohort was closed due to a higher incidence of serious and Grade ≥3 TEAEs and lack of a favorable benefit/risk ratio[b]
- Further dose assessment is ongoing at three doses: 4.8, 5.6 and 6.4 mg/kg

Data cutoff: July 14, 2023.

[a]Grade 5 ILD. [b]6/15 (40.0%) patients in the 8.0-mg/kg OVC cohort experienced serious and Grade ≥3 TEAEs.

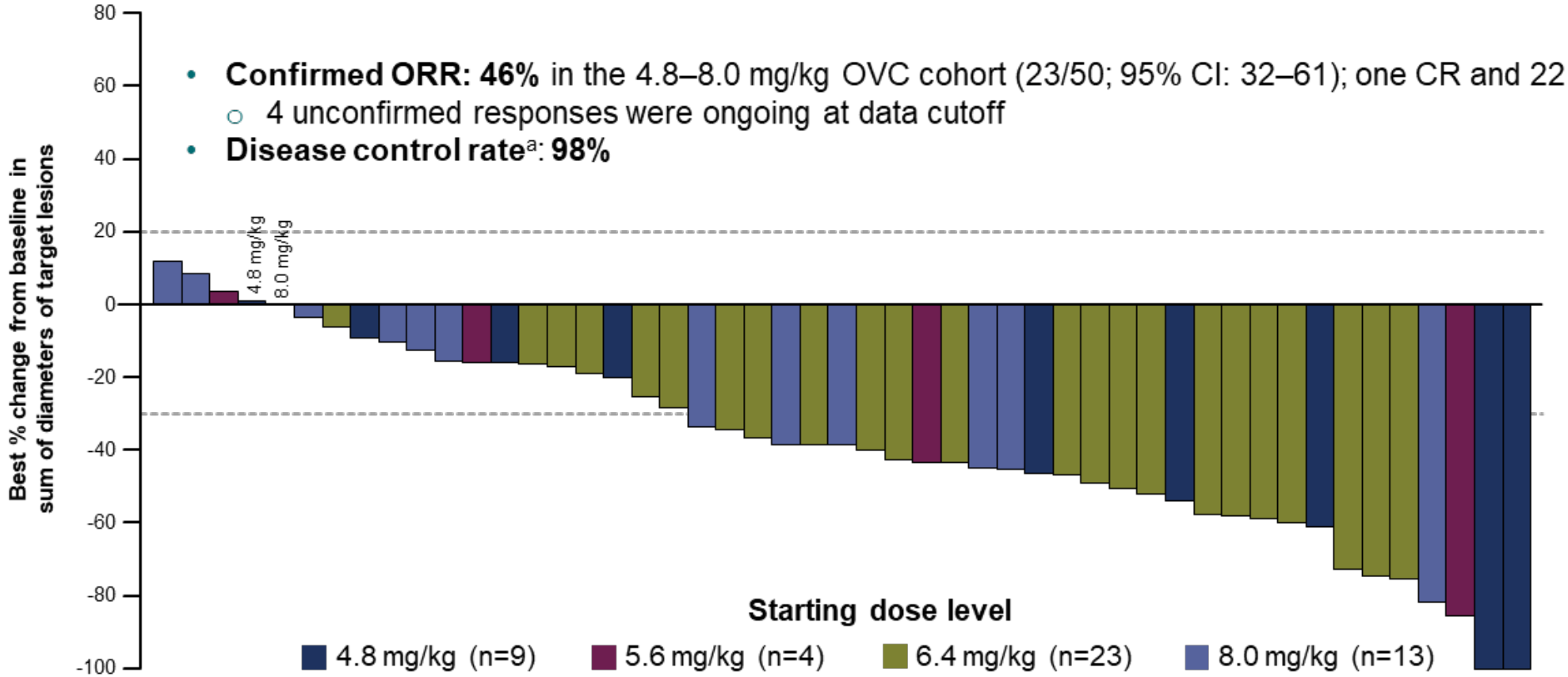
CTCAE, Common Terminology Criteria for Adverse Events; ILD, interstitial lung disease; OVC, ovarian cancer; TEAE, treatment-emergent adverse event.

Most common (≥10%) treatment-related TEAEs

Preferred term	n (%) N=60	
	All grades	Grade ≥3
Nausea	35 (58.3)	1 (1.7)
Fatigue	27 (45.0)	2 (3.3)
Vomiting	20 (33.3)	1 (1.7)
Anemia	17 (28.3)	11 (18.3)
Decreased neutrophil count	15 (25.0)	7 (11.7)
Diarrhea	16 (26.7)	1 (1.7)
Decreased appetite	15 (25.0)	1 (1.7)
Decreased platelet count	10 (16.7)	3 (5.0)
Alopecia	7 (11.7)	0
Malaise	6 (10.0)	0

Preliminary efficacy data for R-DXd are promising in pretreated OVC patients

- **Confirmed ORR: 46%** in the 4.8–8.0 mg/kg OVC cohort (23/50; 95% CI: 32–61); one CR and 22 PRs
  - 4 unconfirmed responses were ongoing at data cutoff
- **Disease control rate**[a]: **98%**



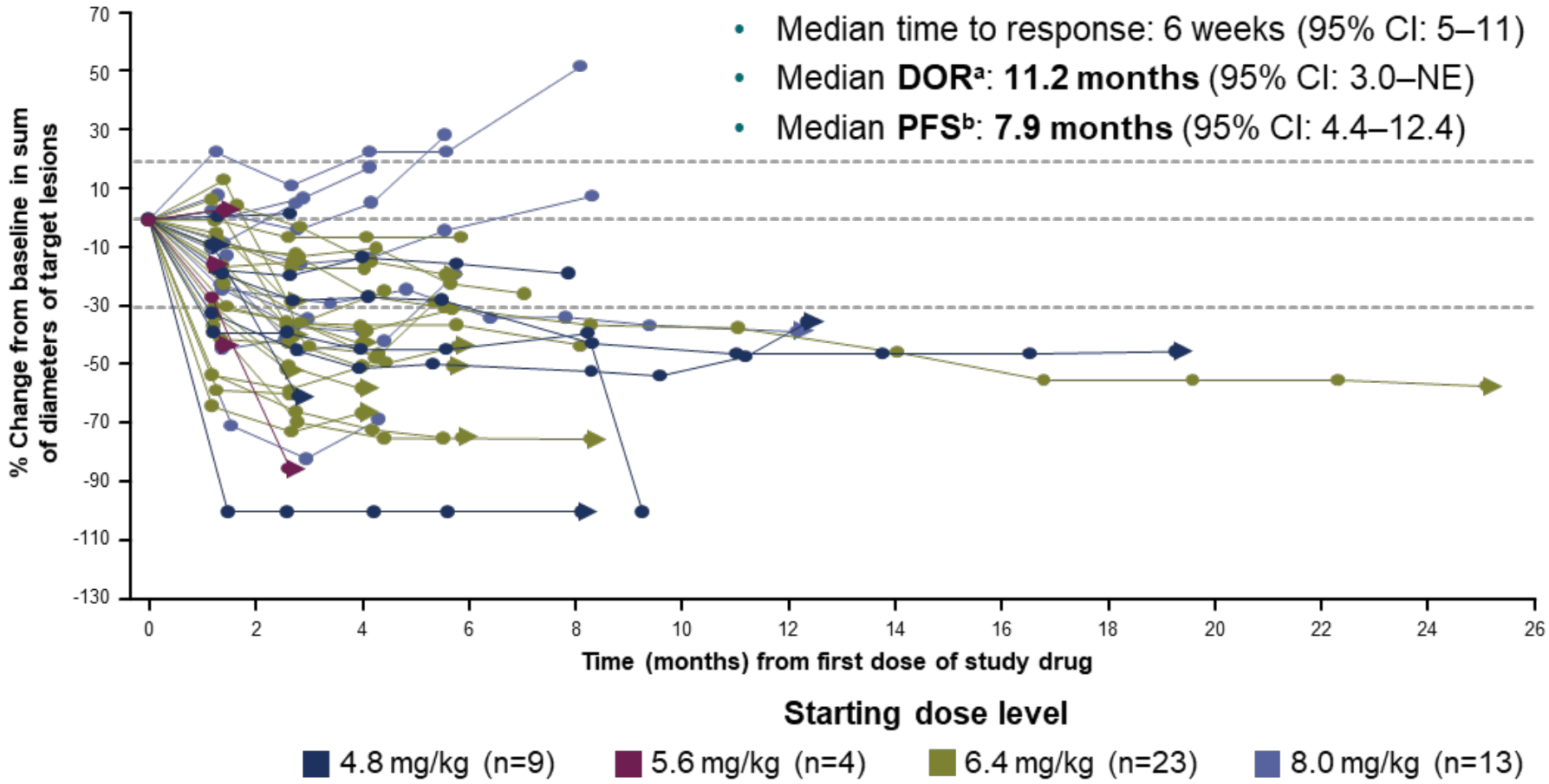
Data cutoff: July 14, 2023.

[a]CR + PR + stable disease.

The efficacy evaluable population included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason. Change from baseline in target tumor size was assessed per RECIST v1.1. Two patients with no measurable lesions at baseline and one patient who discontinued and did not have a post-baseline tumor assessment were not included in the waterfall plot.

CI, confidence interval; CR, complete response; ORR, objective response rate; OVC, ovarian cancer; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Preliminary efficacy data for R-DXd are promising in pretreated OVC patients



Data cutoff: July 14, 2023.

[a]Median follow-up for DOR: 5.8 months (range: 1.4–16.8). [b]Median follow-up for PFS: 5.6 months (range: 0.03–25.1).

The efficacy evaluable population included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason. Change from baseline in target tumor size was assessed per RECIST v1.1. Two patients with no measurable lesions at baseline and one patient who discontinued and did not have a post-baseline tumor assessment were not included in the spider plot.

CI, confidence interval; DOR, duration of response; NE, not estimable; OVC, ovarian cancer; PFS, progression-free survival; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

Conclusions

- R-DXd is the first CDH6-directed ADC to demonstrate promising efficacy in patients with heavily pretreated platinum-resistant OVC who were not selected based on tumor CDH6 expression
  - ORR: 46% in the 4.8–8.0 mg/kg OVC cohort; one CR and 22 PRs
  - Median DOR: 11.2 months[a]
  - Median PFS: 7.9 months[b]
- Safety profile is manageable, and toxicities are consistent with those observed with other DXd ADCs[1,2]
- Based on the accumulated overall safety, tolerability, PK and efficacy profile of R-DXd, the 8.0 mg/kg cohort was closed, and further assessment is ongoing at three dose levels: 4.8 mg/kg, 5.6 mg/kg and 6.4 mg/kg
- These data support further clinical evaluation of R-DXd in a late-phase study in patients with OVC

[a]Median follow-up for DOR: 5.8 months (range: 1.4–16.8). [b]Median follow-up for PFS: 5.6 months (range: 0.03–25.1).

ADC, antibody–drug conjugate; CDH6, cadherin 6; CI, confidence interval; CR, complete response; DOR, duration of response; DXd, deruxtecan; ORR, objective response rate; OVC, ovarian cancer; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response.

1. Guo Z, et al. *J Clin Pharm Ther*. 2022;47:1837–1844; 2. Jänne PA, et al. *Cancer Discov*. 2022;12:74–89.

A few data from poster presentation

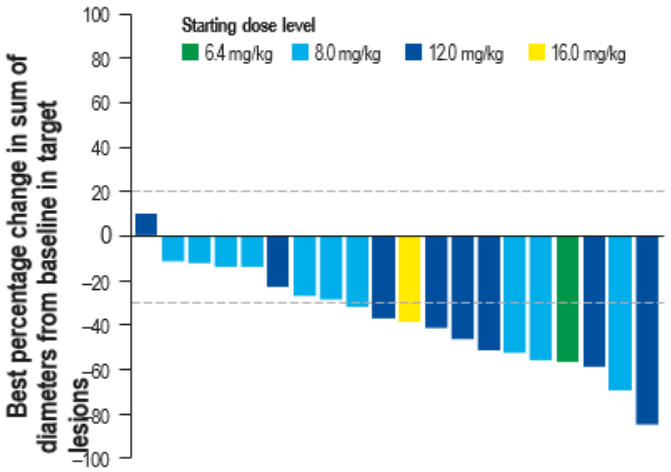
Ifinatamab Deruxtecan (I-DXd; DS-7300) in patients with advanced solid tumors: Updated clinical and biomarker results from a phase 1/2 study

Manish R. Patel,[1,2] Toshihiko Doi,[3] Takafumi Koyama,[4] Gerald S. Falchook,[5] Claire Friedman,[6] Sarina A. Piha-Paul,[7] Martin Gutierrez,[8] Mark Awad,[9] Ahmad Mattour,[10] Taroh Satoh,[11] Naoko Okamoto,[12] Jasmeet Singh,[12] Naoto Yoshizuka,[12] Meng Qian,[12] Xiaozhong Qian,[12] Brittany P. Tran,[12] Ololade Dosunmu,[2] Pengcheng Lu,[2] Melissa L. Johnson[2]

[1]Florida Cancer Specialists and Research Institute, Sarasota, FL, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]National Cancer Center Hospital East, Chiba, Japan; [4]National Cancer Center Hospital, Tokyo, Japan; [5]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; [6]Memorial Sloan Kettering Cancer Center, New York, NY, USA;
[7]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [8]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ, USA; [9]Dana-Farber Cancer Institute, Boston, MA, USA; [10]Henry Ford Health System, Detroit, MI, USA; [11]Osaka University Hospital, Osaka, Japan; [12]Daiichi Sankyo, Inc., Basking Ridge, NJ, USA

Efficacy Analysis in Select Tumor Types (≥4.8 mg/kg cohort)

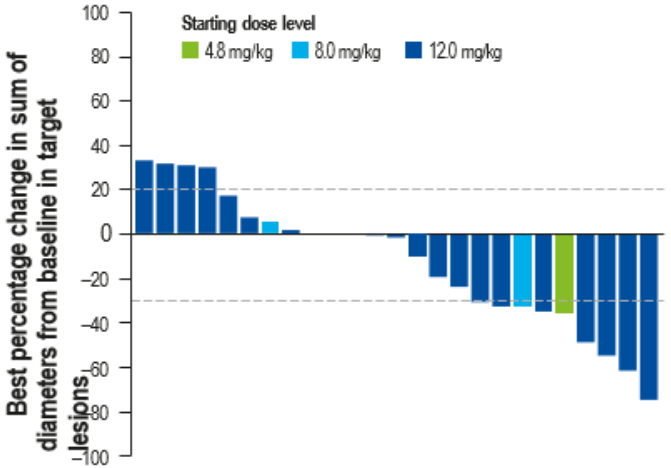
A) SCLC[3]



	SCLC
Efficacy population (≥4.8 mg/kg)	**n=21**
Confirmed ORR, n (%; 95% CI)	11 (52.4; 29.8–74.3)
Confirmed CR, n (%)	1 (4.8)
Confirmed PR, n (%)	10 (47.6)
TTR, median (95% CI), months	1.2 (1.2–1.4)
DOR, median (95% CI), months	5.9 (2.8–7.5)
Median PFS, months (95% CI)	5.6 (3.9–8.1)
Median OS, months (95% CI)	12.2 (6.4–NE)
Follow-up, median (95% CI), months	11.7 (4.6–12.9)
Safety population (all doses)	**n=22**
Number of prior systemic regimens, median (range)	2 (1–7)
Platinum-based chemotherapy, n (%)	22 (100)
Immunotherapy, n (%)	18 (81.8)
Irinotecan or topotecan, n (%)	5 (22.7)[a]
Topotecan, n (%)	3 (13.6)

[a]One patient received both.
Change from baseline in target lesions was assessed per RECIST v1.1. All 21 patients were evaluable at baseline, but one did not have any post-baseline tumor assessments, and so was not included in the waterfall plot.

B) ESCC



	ESCC
Efficacy population (≥4.8 mg/kg)	**n=28**
Confirmed ORR, n (%; 95% CI)	6 (21.4; 8.3–41.0)
Confirmed PR, n (%)	6 (21.4)
TTR, median (95% CI), months	1.4 (1.2–NE)
DOR, median (95% CI), months	3.5 (2.4–NE)
Median PFS, months (95% CI)	2.8 (2.1–5.5)
Median OS, months (95% CI)	7.0 (4.8–12.2)
Follow-up, median (95% CI), months	14.9 (6.3–NE)
Safety population (all doses)	**n=29**
Number of prior systemic regimens, median (range)	4 (1–7)
Cisplatin/carboplatin/oxaliplatin, n (%)	29 (100)
Taxane, n (%)	21 (72.4)
Immunotherapy, n (%)	27 (93.1)

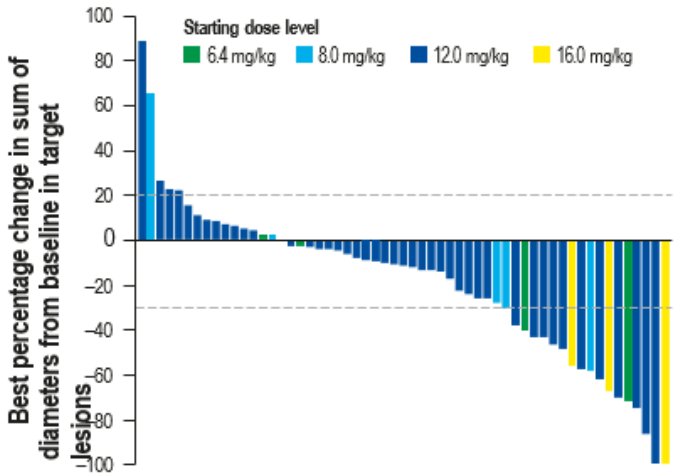
Change from baseline in target lesions was assessed per RECIST v1.1. Of 28 patients with measurable disease at baseline, three did not have post-baseline tumor the assessments, and so were not included in the waterfall plot.

- In the ≥4.8 mg/kg population, the confirmed ORR was 27.3% (38/139; 95% CI: 20.1%–35.5%)
- ORRs in the tumor types selected in this analysis were as follows:
  - –SCLC: 11/21 (52%) patients achieved a PR (n=10) or CR (n=1)
  - –ESCC: 6/28 (21%) patients achieved a PR

See next slide for mCRPC and sqNSCLC

Efficacy Analysis in Select Tumor Types (≥4.8 mg/kg cohort)

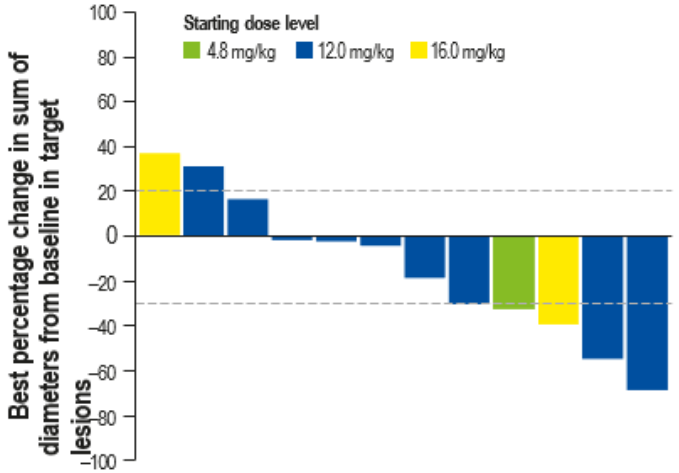
C) mCRPC



	mCRPC
Efficacy population (≥4.8 mg/kg)	**n=73**
Confirmed ORR, n (%; 95% CI)[a]	15 (25.4; 15.0–38.4)
Confirmed PR, n (%)	15 (25.4)
Confirmed ORR in patients with liver mets at baseline (27/59, 45.8% of mCPRC efficacy population ≥4.8 mg/kg), n (%)	9 (33.3)
TTR, median (95% CI), months[a]	1.4 (1.2–2.6)
DOR, median (95% CI), months[a]	6.4 (3.0–10.0)
Median PFS, months (95% CI)[b]	5.3 (4.1–6.9)
Median OS, months (95% CI)[b]	13.0 (10.3–16.0)
Follow-up, median (95% CI), months[b]	16.6 (14.5–18.6)
Safety population (all doses)	**n=75**
Number of prior systemic regimens, median (range)	6 (1–11)
Taxane, n (%)	61 (81.3)
NHA, n (%)	72 (96.0)

[a]The ORR is calculated based on 59 patients who received ≥1 dose ≥4.8 mg/kg, had measurable disease at baseline, ≥2 postbaseline scans, and/or discontinued treatment for any reason at data cutoff. [b]n=73, including patients with bone metastases who were not evaluable for ORR.
Change from baseline in target lesions was assessed per RECIST v1.1. Two patients did not have any post-baseline tumor assessments and were not included in the waterfall plot.

D) sqNSCLC



	sqNSCLC
Efficacy population (≥4.8 mg/kg)	**n=13**
Confirmed ORR, n (%; 95% CI)	4 (30.8, 9.1–61.4)
Confirmed PR, n (%)	4 (30.8)
TTR, median (95% CI), months	1.3 (0.7–NE)
DOR, median (95% CI), months	4.1 (2.8–NE)
Follow-up, median (95% CI), months	5.2 (1.7–NE)
Safety population (all doses)	**n=18**
Number of prior systemic regimens, median (range)	3 (1–12)
Platinum-based chemotherapy, n (%)	18 (100)
Immunotherapy, n (%)	18 (100)
Taxane, n (%)	16 (88.9)

Change from baseline in target lesions was assessed per RECIST v1.1. One patient did not have any post-baseline tumor assessments and was not included in waterfall plot. Since enrollment in the sqNSCLC cohort is ongoing, analyses of PFS and OS in this cohort are not yet mature.

- The sqNSCLC expansion cohort was the latest expansion cohort to open and is ongoing, hence the relatively short duration of follow-up
- ORRs in the tumor types selected in this analysis were as follows:
  - mCRPC: 15/59 (25%) patients achieved a PR
  - sqNSCLC: 4/13 (31%) patients achieved a PR

Most Common (>15% of Study Total) TEAEs, Regardless of Causality

System organ class preferred term, n (%)[a]	SCLC (n=22)		ESCC (n=29)		mCRPC (n=75)		sqNSCLC (n=18)		Study total (N=174)[b]	
	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3	All grades	Grade ≥3
Nausea[c]	13 (59.1)	1 (4.5)	13 (44.8)	1 (3.4)	51 (68.0)	2 (2.7)	11 (61.1)	2 (11.1)	105 (60.3)	6 (3.4)
Anemia	6 (27.3)	1 (4.5)	12 (41.4)	8 (27.6)	27 (36.0)	15 (20.0)	4 (22.2)	3 (16.7)	57 (32.8)	33 (19.0)
IRR[c,d]	3 (13.6)	0	11 (37.9)	0	25 (33.3)	0	5 (27.8)	0	57 (32.8)	0
Decreased appetite	5 (22.7)	1 (4.5)	11 (37.9)	2 (6.9)	24 (32.0)	0	4 (22.2)	0	56 (32.2)	3 (1.7)
Fatigue	11 (50.0)	0	6 (20.7)	0	32 (42.7)	1 (1.3)	1 (5.6)	0	55 (31.6)	1 (0.6)
Vomiting[c]	6 (27.3)	0	2 (6.9)	0	33 (44.0)	2 (2.7)	5 (27.8)	1 (5.6)	54 (31.0)	3 (1.7)
Diarrhea	3 (13.6)	0	2 (6.9)	0	21 (28.0)	2 (2.7)	3 (16.7)	1 (5.6)	30 (17.2)	3 (1.7)
Pyrexia	4 (18.2)	0	6 (20.7)	0	11 (14.7)	0	3 (16.7)	0	30 (17.2)	0
Constipation	4 (18.2)	1 (4.5)	6 (20.7)	1 (3.4)	13 (17.3)	0	3 (16.7)	0	29 (16.7)	2 (1.1)

- No new safety signals were observed; the safety profile was consistent with previous reports
- The most common TEAEs associated with drug discontinuation were pneumonitis (n=3) and ILD (n=2)
- The most common (≥3%) Grade ≥3 TEAEs were anemia (19.0%), neutropenia (4.0%), and nausea and lymphocyte count decreased (3.4% each)
- Overall, 10/174 patients (5.7%) had confirmed ILD that was adjudicated as drug- related; 5 of these cases led to drug discontinuation. Most cases of ILD were Grade 1 or 2 (n=8); one Grade 4 ILD occurred in the 12 mg/kg cohort, and one Grade 5 ILD occurred in the 16 mg/kg cohort

[a]Adverse events were coded using MedDRA, version 25.1. [b]Includes patients with SCLC, ESCC, mCRPC, sqNSCLC and other tumor types.
[c]Prophylactic premedication for nausea, vomiting, and IRR was not permitted for primary prophylaxis during Cycle 1 of dose escalation.
[d]For Grade 2 IRRs, prophylactic medication (with or without corticosteroids) was administered for ≤24 hours at the discretion of the investigator before subsequent administration of I-DXd.

ESMO Highlights 2023

Agenda

1 ESMO presentations

- ✓ TROPION-Lung01 study TLR
- ✓ TROPION-Lung05 Ph2 study results
- ✓ TROPION-Breast01 study TLR
- ✓ BEGONIA study longer follow-up data
- ✓ DESTINY-PanTumor02 primary analysis data
- ✓ DS-6000 Ph1 study OVC subgroup analysis data
- ✓ DS-7300 Ph1/2 study updated data (extract)

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

Contact address regarding this material

Daiichi Sankyo Co., Ltd.
Corporate Communications Department

TEL: +81-3-6225-1125
Email: DaiichiSankyoIR@daiichisankyo.co.jp