Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

欧州臨床腫瘍学会 (ESMO) 2021 ハイライト

第一三共株式会社

グローバル研究開発ヘッド
竹下　健一

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1 はじめに

2 ESMO ハイライト

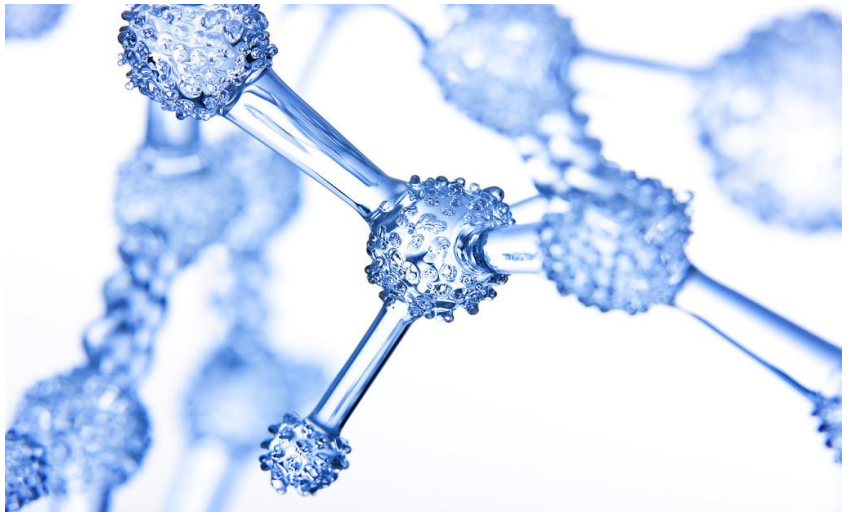
3 ESMO 発表

DESTINY-Breast03
DESTINY-Lung01
DS-7300 Ph1/2

4 添付資料

はじめに

- **今年の ESMO は、第一三共が、がん領域のグローバルリーダーに変革する大きな転換点となった**
  - 4つの late-breakingセッションでの発表、ここには Presidential Symposium のオープニング演題も含まれる
  - 臨床入りした4つ目の DXd-ADCであるDS-7300の臨床試験データを初めて発表
- **本日発表するデータは、がん患者さんの治療を変革する医薬品の創出において当社のリーダーシップが強まっていることを示すと共に、複数のがんに対する当社独自のADC技術の強みを実証し続けている。**



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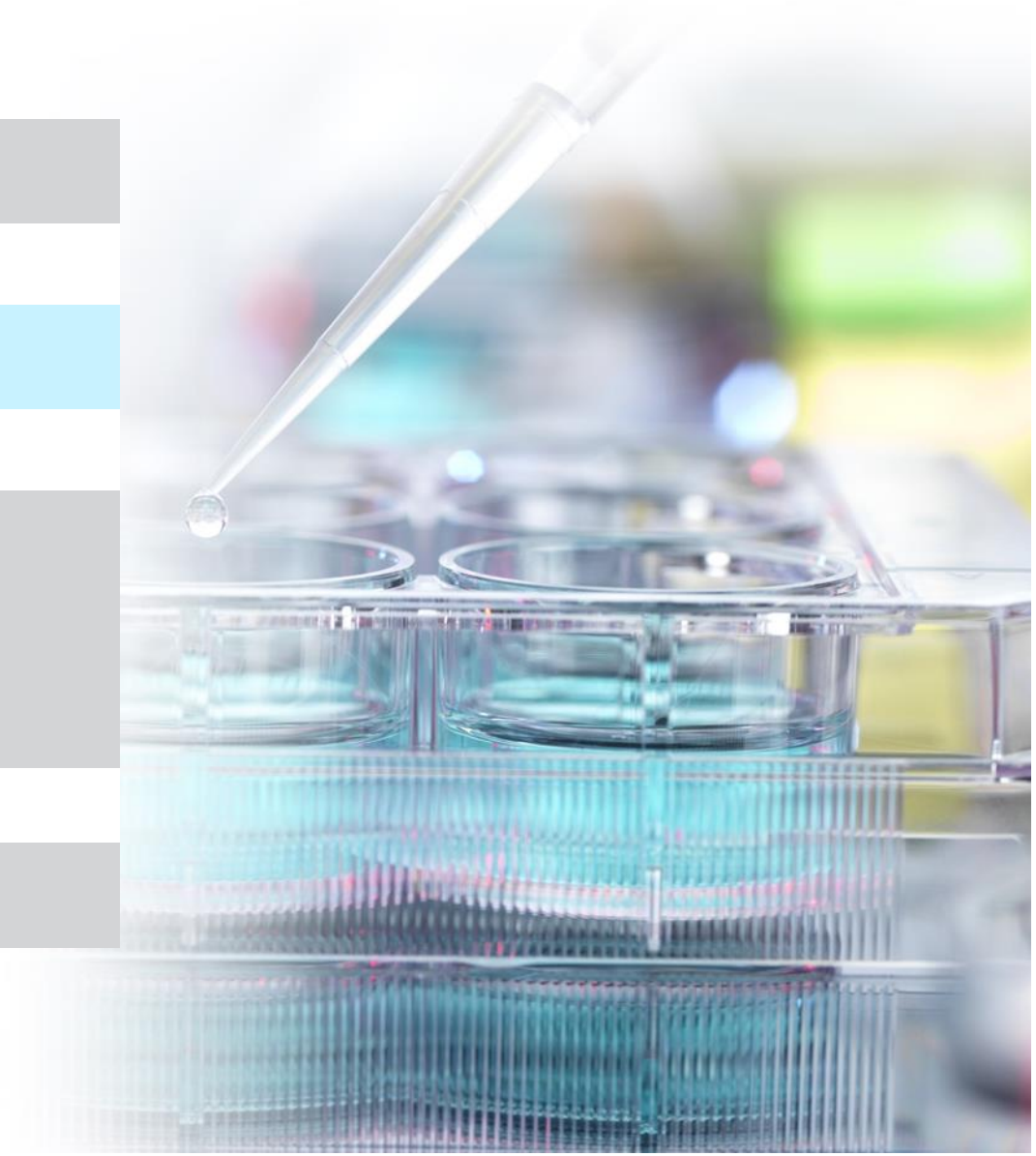
2 **ESMO ハイライト**

3 ESMO 発表演題

DESTINY-Breast03
DESTINY-Lung01
DS-7300 Ph1/2

4 添付資料



4つの late breaking 発表におけるハイライト

1. エンハーツ® DESTINY-Breast03
（HER2陽性 乳がん、2次治療、フェーズ3）

- **Presidential Symposium** におけるオープニング発表
- **乳がんでの最初の直接比較グローバルフェーズ3試験**、エンハーツ®は、**T-DM1**に対し優れた有効性を示した
- **PFSにおいて、**統計的に有意かつ臨床的に意義ある、**前例のない改善**を示した

→ **HER2陽性乳がんの2次治療における新たな標準治療となる決定的かつ確証的なエビデンスを示すと共に、エンハーツ®のHER2陽性乳がんにおける全ての臨床試験への自信が大幅に高まった**

HER2陽性乳がんの治療におけるパラダイムシフト

BC: breast cancer, PFS: progression free survival

4つの late breaking 発表におけるハイライト

2. エンハーツ® DESTINY-Lung01
（HER2変異 非小細胞肺がん、2次治療、フェーズ2）

- 未だ承認された薬がないHER2変異非小細胞肺がんにおいて、**HER2を標的とする治療が堅牢で持続的な有効性を示す可能性**を示した
- データは、**the New England Journal of Medicine** に同時に掲載された

→HER2変異非小細胞肺がん患者の転帰に変革をもたらし、新たな標準治療となる可能性

エンハーツ®がHER2が標的になりうる多様ながんの治療にも変革をもたらす可能性

NSCLC: non small cell lung cancer

4つの late breaking 発表におけるハイライト

3. エンハーツ® DESTINY-Gastric02
（HER2陽性 胃がん、2次治療、フェーズ2）

- **単群**で実施したHER2陽性胃がん患者の2次治療における**西洋人**を含む**最初の試験**で、エンハーツ®は、**素晴らしい持続的な有効性**を示した

4. Dato-DXd TROPION-PanTumor01
（サブグループ解析：アクショナブル遺伝子変異を有する非小細胞肺がん）

- アクショナブル遺伝子変異を有する非小細胞肺がん患者群での**最初のサブグループ解析**であり、**有望な有効性**のデータから本患者層での開発への**自信を得た**

AGA: actionable genomic alterations, GC: gastric cancer, NSCLC: non small cell lung cancer

DS-7300 口頭発表のハイライト

◆ DS-7300 固形がんに対するフェーズ1/2試験

- **4番目のDXd-ADC**であるDS-7300における**最初の臨床データ**となるfirst-in-human用量漸増試験での中間結果
- DS-7300は、**B7-H3を標的としたADC** であり、これまでにB7-H3を標的として承認された抗がん剤はない
- DS-7300は、多数の前治療を受けた複数の進行固形がんに対し、**有望な初期の有効性および忍容性を示し、**かつ用量制限毒性は出ていない

→ B7-H3を標的とするDS-7300は、現在、治療オプションが限られているいくつかのがん種に対する新しい効果的な治療戦略となりうる予備的なエビデンスを示した。

複数のがんに対する
第一三共のADC技術の強みがさらに示された

DLT: dose limiting toxicity

本日の発表

ESMO 2021では 全部で18の抄録が発表された

- Presidential Symposiumでの発表：1演題
- 口頭発表：3演題
- ミニ口頭発表： 2演題
- e-ポスター：12発表

本日お話しする3つの発表

- エンハーツ® DESTINY-Breast03 フェーズ3 データ
- エンハーツ® DESTINY-Lung01 フェーズ2 HER2変異コホート データ
- DS-7300 フェーズ1/2 試験 中間データ

全てのスライドを 添付資料に掲載しています

- ENHERTU® DESTINY-Breast03
- ENHERTU® DESTINY-Lung01
- ENHERTU® DESTINY-Gastric02
- ENHERTU® DESTINY-Breast01
- Dato-DXd TROPION-PanTumor01 非小細胞肺がん コホート
- Dato-DXd TROPION-PanTumor01 アクショナブル遺伝子変異を有する 非小細胞肺がん サブ解析
- DS-7300 Ph1/2

AGA: actionable genomic alterations, NSCLC: non small cell lung cancer

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DESTINY-Breast03
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4 添付資料

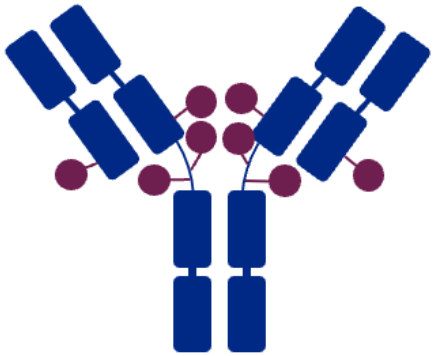
Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients With HER2+ Metastatic Breast Cancer: Results of the Randomized, Phase 3 Study DESTINY-Breast03

Javier Cortés, MD[a], Sung-Bae Kim, Wei-Pang Chung,
Seock-Ah Im, Yeon Hee Park, Roberto Hegg, Min-Hwan Kim, Ling-Ming Tseng, Vanessa Petry, Chi-Feng Chung,
Hiroji Iwata, Erika Hamilton, Giuseppe Curigliano, Binghe Xu, Caleb Lee,
Yali Liu, Jillian Cathcart, Emarjola Bako, Sunil Verma, Sara Hurvitz
On behalf of the DESTINY-Breast03 investigators

[a]Medical Oncology, International Breast Cancer Center (IBCC), Quironsalud Group, and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain.

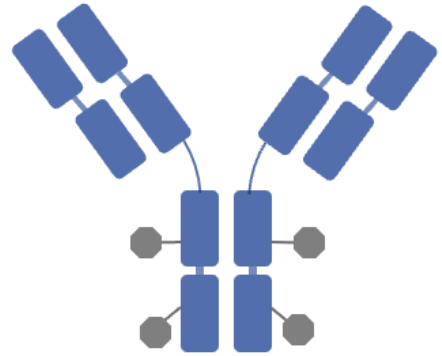
ADC Characteristic Differences Between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



ADC, antibody-drug conjugate; MoA, mechanism of action.

[a]The clinical relevance of these features is under investigation.

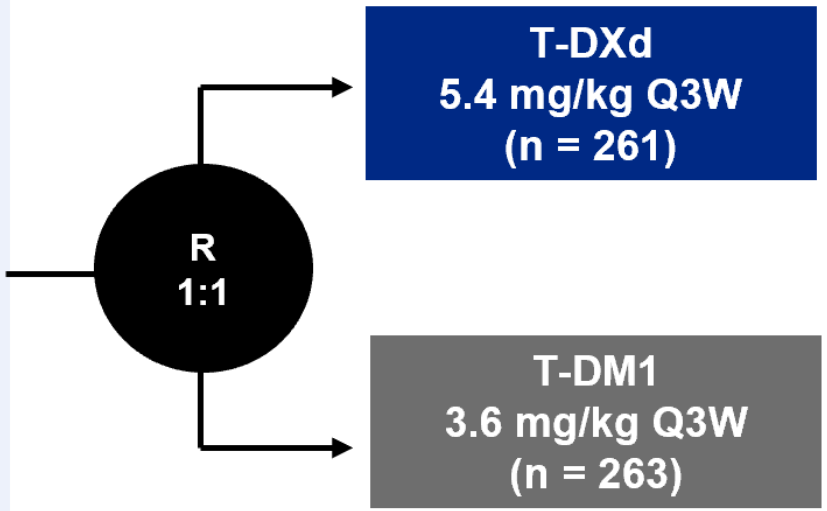
1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42. 4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

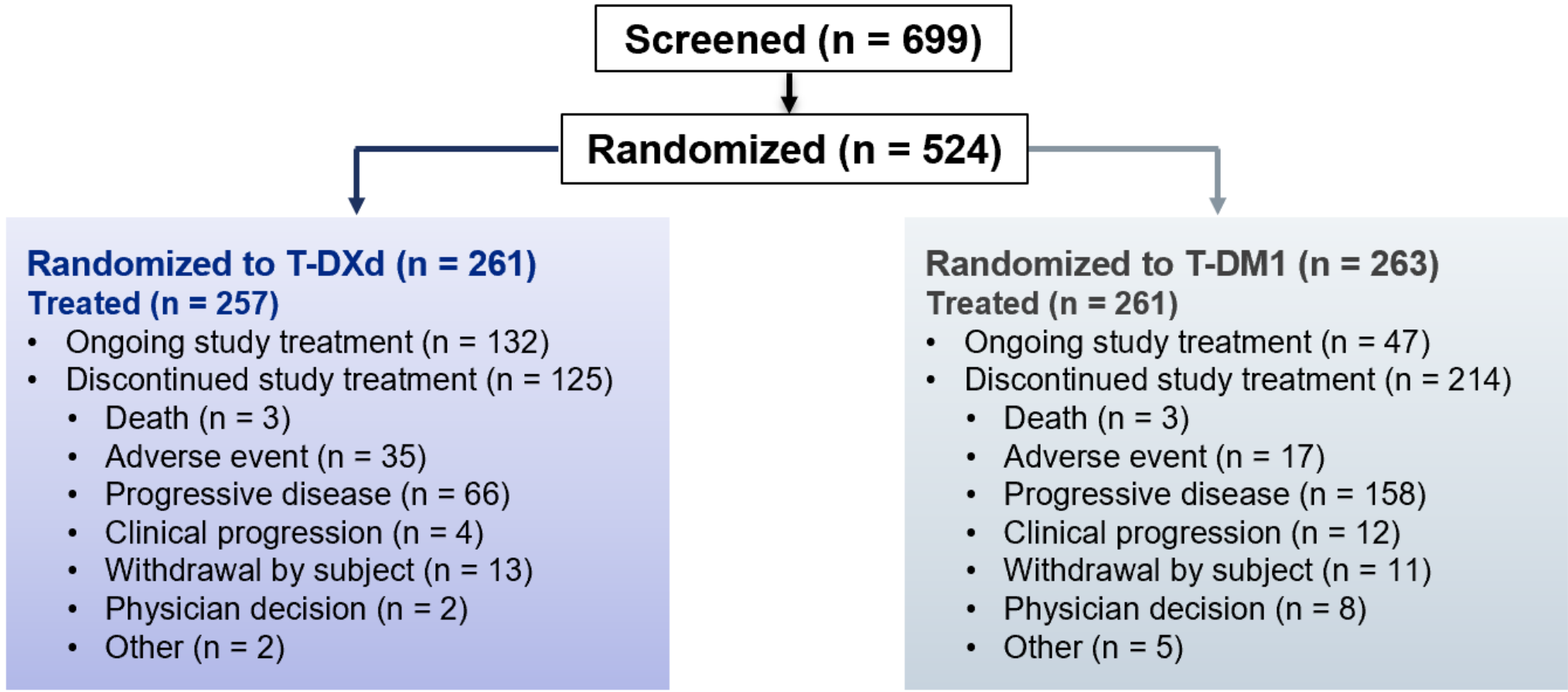
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Patient Disposition



Median follow up for T-DXd was 16.2 months and for T-DM1 was 15.3 months

Baseline Characteristics

	T-DXd (n = 261)	T-DM1 (n = 263)
Age, median (range), years	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Female, %	99.6	99.6
Region, %		
Europe	20.7	19.0
Asia	57.1	60.8
North America	6.5	6.5
Rest of world	15.7	13.7
HER2 status (IHC[a], %)		
3+	89.7	88.2
2+ (ISH amplified)	9.6	11.4
1+ | Not Evaluable | Not Examined	0.4 | 0.4 | 0	0 | 0.4 | 0
ECOG PS, %		
0 | 1 | Missing	59.0 | 40.6 | 0.4	66.5 | 33.1 | 0.4
Hormone receptor, %		
Positive | Negative	50.2 | 49.8	51.0 | 49.0
Brain metastases, %		
Yes | No	23.8 | 76.2	19.8 | 80.2
Visceral disease, %		
Yes | No	70.5 | 29.5	70.3 | 29.7

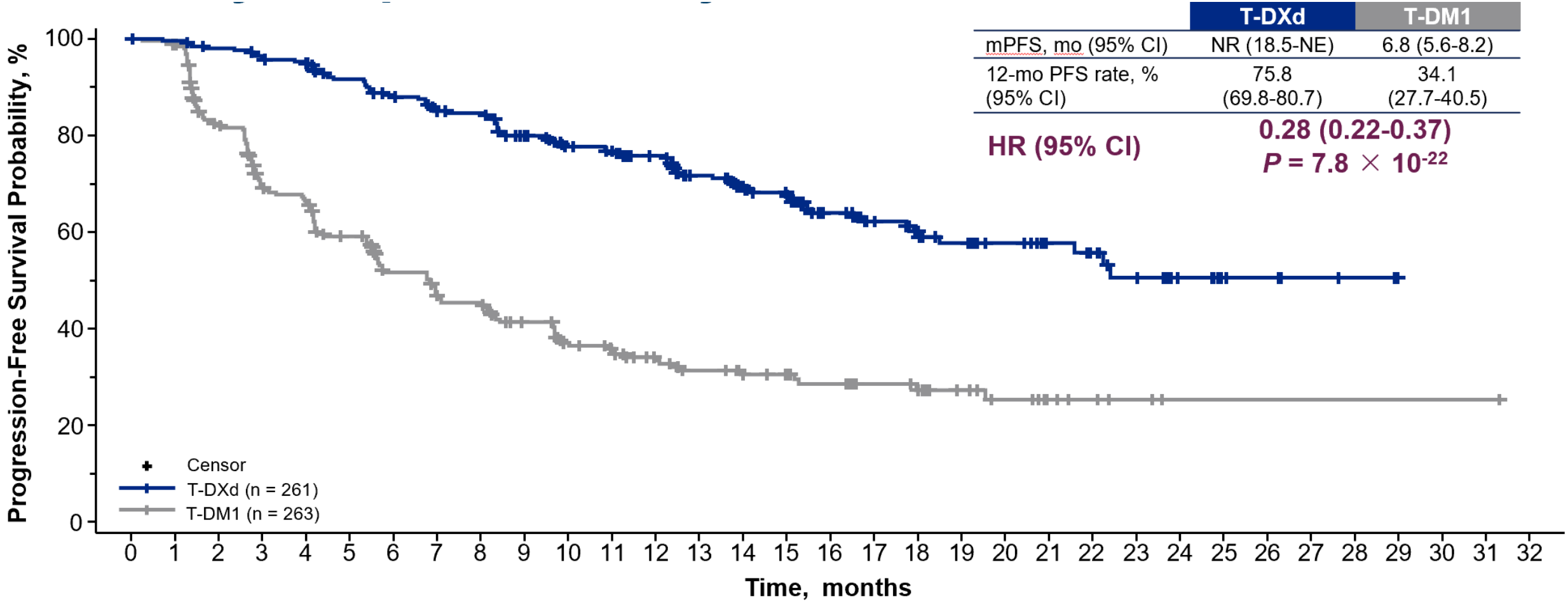
ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ISH, in situ hybridization.
[a]HER2-status as evaluated by central lab.

Prior Therapies

	T-DXd (n = 261)	T-DM1 (n = 263)
Prior Treatment for mBC, n (%)		
No	21 (8.0)	29 (11.0)
Yes	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting (includes rapid progressors as one line of treatment)[a], n (%)		
0	2 (0.8)	3 (1.1)
1	130 (49.8)	123 (46.8)
2	56 (21.5)	65 (24.7)
3	35 (13.4)	35 (13.3)
4	15 (5.7)	19 (7.2)
≥5	23 (8.8)	18 (6.8)
Prior cancer therapy[b], %		
Trastuzumab	99.6	99.6
Pertuzumab	62.1	60.1
Other anti-HER2		
Anti-HER2 TKI	16.1	13.7
Other anti-HER2 antibody or ADC	0.8	1.1

TKI, tyrosine-kinase inhibitor.
[a]Rapid progressors defined as progression within 6 mo of (neo)adjuvant therapy) or 12 mo if regimen contained pertuzumab. Line of therapy does not include endocrine therapy.
[b]All patients received at least 1 prior cancer therapy. One patient with prior T-DM1 treatment was enrolled in error in the T-DXd arm.

Primary Endpoint: PFS by BICR



	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

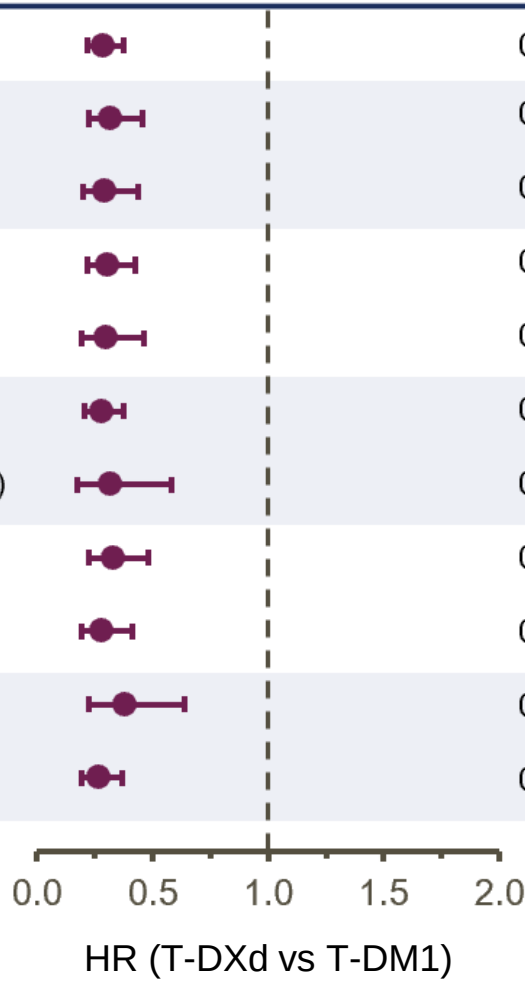
Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0			
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1)
HR, hazard ratio; INV, investigator; mo, month; NE, not estimable; NR, not reached.

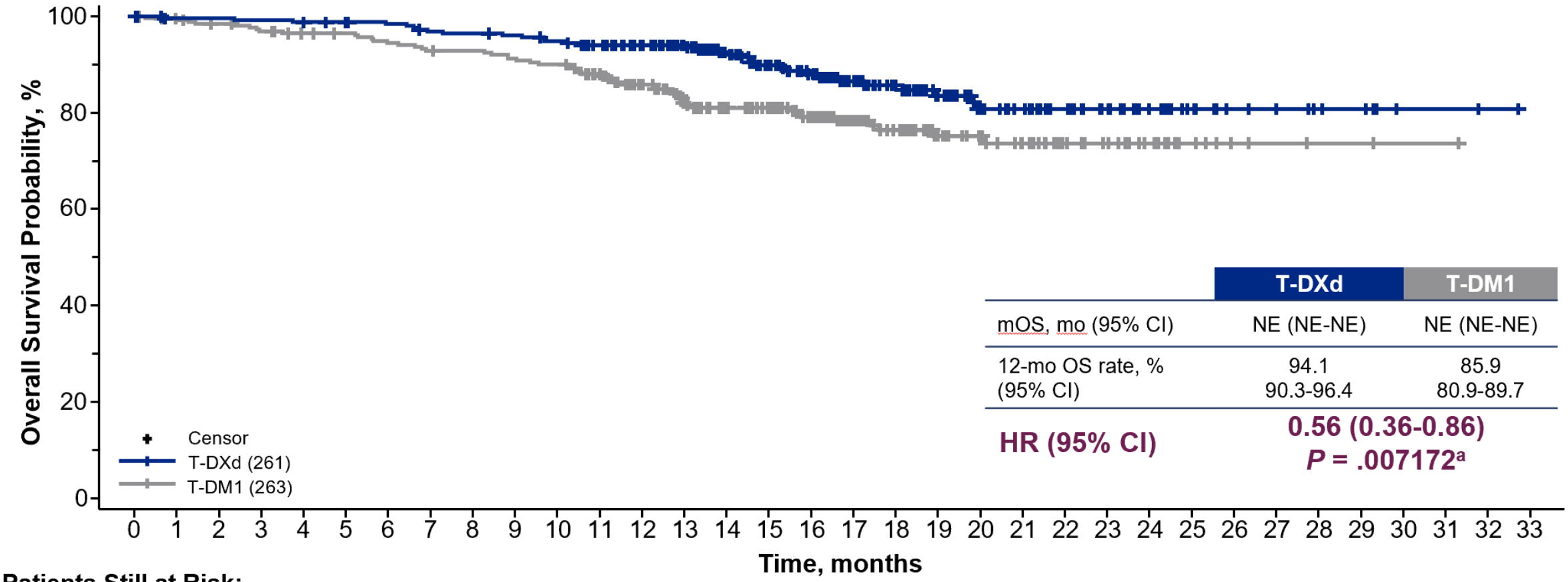
PFS in Key Subgroups

		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone Receptor Status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior Pertuzumab Treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral Disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior Lines of Therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Brain Metastases	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)



[a]Rapid progressors on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 (90.3-96.4)	85.9 (80.9-89.7)
HR (95% CI)	**0.56 (0.36-0.86)**	
	***P* = .007172[a]**	

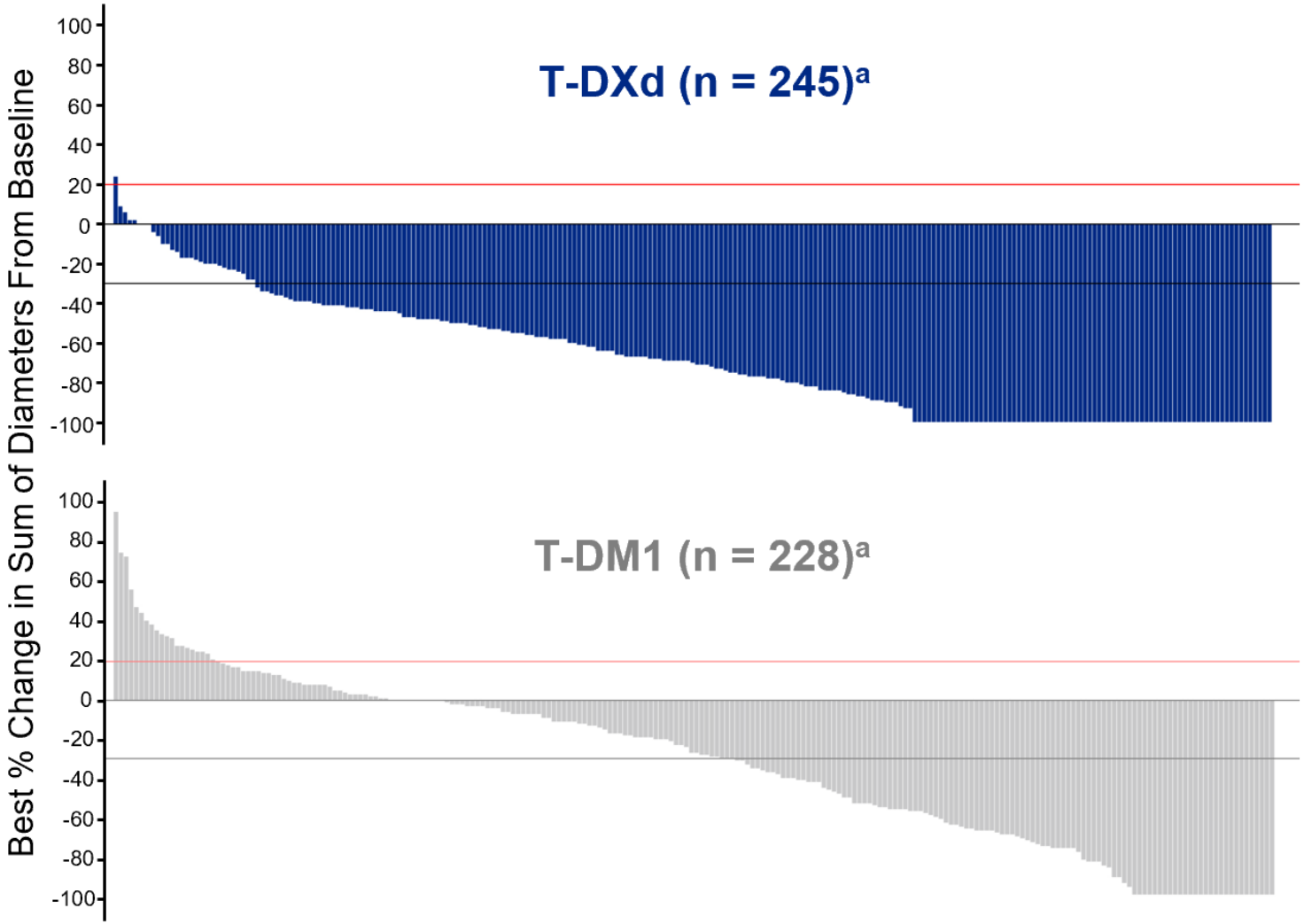
Patients Still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]*P* = .007172, but does not cross pre-specified boundary of *P* < .000265

Confirmed ORR and Best Overall Response



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Only subjects with measurable disease at baseline and at least one postbaseline target lesion assessment are included. [b]Based on BICR.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.

Overall Safety Summary

n (%)	T-DXd (n = 257)	T-DM1 (n = 261)
Any drug-related TEAE	252 (98.1)	226 (86.6)
Drug-related TEAE Grade ≥3	116 (45.1)	104 (39.8)
Serious drug-related TEAE	28 (10.9)	16 (6.1)
Drug-related TEAE associated with discontinuation	33 (12.8)	13 (5.0)
Drug-related TEAE associated with dose reduction	55 (21.4)	33 (12.6)
Drug-related TEAE associated with an outcome of death	0 (0.0)	0 (0.0)

- **Median treatment duration was 14.3 months (range, 0.7-29.8) for T-DXd and 6.9 months (range, 0.7-25.1) for T-DM1**
- The most common TEAE associated with treatment discontinuation for T-DXd was ILD/pneumonitis[a] (8.2%) and for T-DM1 was thrombocytopenia[b] (2.7%)
- The most common TEAEs associated with dose reduction for T-DXd were nausea (6.2%) and neutropenia[c] (3.5%) and for T-DM1 were thrombocytopenia[b] (4.2%) and ALT and AST increased (2.7% each)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; TEAE, treatment-related adverse event.
Relationship to study drug was determined by the treating investigator.
[a]Interstitial lung disease includes events that were adjudicated as ILD and related to use of T-DXd or T-DM1 (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). [b]This category includes the preferred terms platelet count decreased and thrombocytopenia. [c]This category includes the preferred terms neutrophil count decreased and neutropenia.

Drug-Related TEAEs in ≥20% of Patients

System Organ Class Preferred term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia[b]	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia[c]	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia[d]	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue[e]	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia[f]	93 (36.2)	1 (0.4)	6 (2.3)	0

Most drug-related TEAEs were gastrointestinal or hematological in nature

Adverse events were managed according to the protocol.
[a]This category includes the preferred terms neutrophil count decreased and neutropenia. [b]This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [c]This category includes the preferred terms white blood cell count decreased and leukopenia. [d]This category includes platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms fatigue, asthenia, and malaise. [f]Grade 1 alopecia: T-DXd = 26.5%, T-DM1 = 2.3%; grade 2, T-DXd = 9.3%.

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF decrease, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

LVEF, left-ventricular ejection fraction.
[a]Patients with prior history of ILD/pneumonitis requiring steroids were excluded. [b]Left ventricular dysfunction. [c]Decreased ejection fraction.

Conclusions

Daiichi-Sankyo

In the first randomized phase 3 trial in breast cancer, T-DXd demonstrated:

Highly clinically meaningful and statistically significant improvement in PFS compared with T-DM1 in patients with HER2-positive mBC

- PFS HR of 0.28 ($P = 7.8 \times 10^{-22}$)
- Consistent benefit seen across key subgroups and efficacy endpoints, with a confirmed ORR for T-DXd of 79.7% vs 34.2% for T-DM1 (CR, 16.1% vs 8.7%)

Encouraging OS trend at the time of first interim analysis

- 12-month OS rate for T-DXd was 94.1% vs 85.9% for T-DM1

A safety profile that is comparable between the 2 arms

- Similar rates of all grade and grade ≥3 drug-related TEAEs between arms
- There were no grade 4 or 5 ILD/pneumonitis events in either arm

These data support T-DXd becoming the standard of care for 2L HER2-positive mBC

次のステップ

◆ 規制当局への申請を2021年度第3四半期に予定

- 8月にFDA より
  リアルタイムオンコロジーレビュー* (RTOR) の対象に指定

◆ HER2陽性乳がんの早期治療ラインの開発に自信を得た

- DESTINY-Breast09 （1次治療, フェーズ3）及び DESTINY-Breast05 (ネオアジュバント治療後の残存浸潤性乳がん, フェーズ3) での臨床試験が進行中

*RTORは、患者さんが安全かつ効果的な治療をできるだけ早期に受けられるよう、より効率的な審査プロセスの探求を目指しています。RTORにより、申請者が正式に完全な申請書を提出する前に、 FDAが多くのデータを早期に審査することが可能となります。

Primary Data from DESTINY-Lung01: A Phase 2 Trial of Trastuzumab Deruxtecan (T-DXd) in Patients With *HER2*-Mutated (*HER2*m) Metastatic Non–Small Cell Lung Cancer (NSCLC)

Bob T. Li, MD, PhD, MPH[a], Egbert F. Smit, Yasushi Goto, Kazuhiko Nakagawa, Hibiki Udagawa, Julien Mazières, Misako Nagasaka, Lyudmila Bazhenova, Andreas N. Saltos, Enriqueta Felip, Jose M. Pacheco, Maurice Pérol, Luis Paz-Ares, Kapil Saxena, Ryota Shiga, Yingkai Cheng, Suddhasatta Acharyya, Javad Shahidi, David Planchard, Pasi A. Jänne

On behalf of the DESTINY-Lung01 investigators

[a]Memorial Sloan Kettering Cancer Center, New York, NY, USA

High Unmet Medical Need in Patients with *HER2*m NSCLC

- *HER2* mutations drive ~3% of nonsquamous NSCLC and are associated with slightly younger age, female sex, never-smoking history, a poor prognosis, and an increased incidence of brain metastasis[1-5]
- There are no approved HER2-targeted therapies for patients with NSCLC[6]
  - *HER2*m status is not routinely assessed[7], and this population is treated with standard chemotherapy and/or immunotherapy[8-14]
  - Efficacy in second- or later-line settings is limited (ORR, 7%-27%) [8-14]
- T-DXd is a HER2 antibody-drug conjugate[15,16] approved in various countries worldwide for the treatment of metastatic HER2-positive breast and gastric cancers

DESTINY-Lung01 assessed the efficacy and safety of T-DXd in patients with *HER2*m NSCLC who had relapsed on or were refractory to standard treatment

In an interim analysis (data cutoff November 25, 2019), results showed promising T-DXd activity[17]

Results from the primary analysis of the fully enrolled cohort of patients with a *HER2* mutation are presented

HER2, human epidermal growth factor 2; *HER2*m, *HER2*-mutated; NSCLC, non–small cell lung cancer; ORR, objective response rate; T-Dxd, trastuzumab deruxtecan.

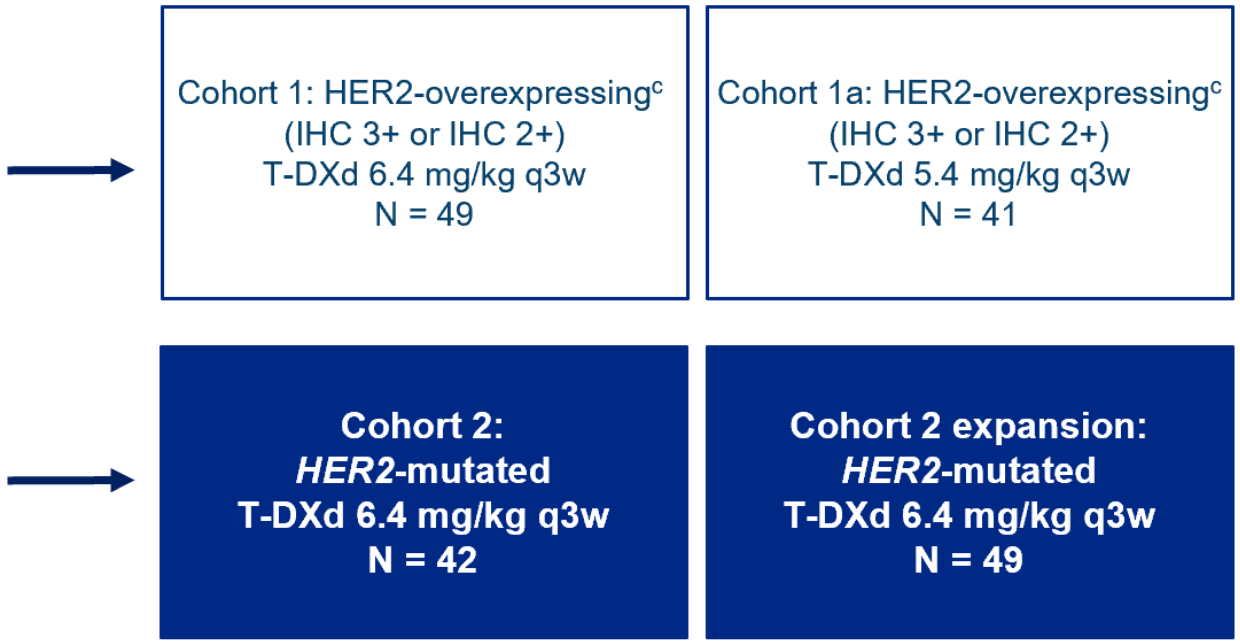
1. Stephens P et al. *Nature*. 2004;431:525-526; 2. Mazières J et al. *J Clin Oncol*. 2013;31:1997-2003; 3. Arcila ME et al. *Clin Cancer Res*. 2012;18:4910-4918; 4. Pillai RN et al. *Cancer*. 2017;123:4099-4105; 5. Offin M et al. *Cancer*. 2019;4380-4387; 6. Planchard D et al. *Ann Oncol*. 2018; iv192-iv237; 7. Pennell NA et al. *Am Soc Clin Oncol Educ Book*. 2019;(39):531-542. 8. Wu YL et al. *Ann Oncol* 2019;30:171-210; 9. Kim SY et al. *Lung Cancer Manag*. 2020;9:LMT36; 10. Akamatsu H et al. *Int J Clin Oncol*. 2019;24:731-70; 11. Mazières J et al. *Ann Oncol*. 2016;27:281-286; 12. Mazières J et al. *Ann Oncol*. 2019;30:1321-1328; 13. Garon EB et al. *Lancet*. 2014;384:665-673; 14. Guisier F et al. *J Thorac Oncol*. 2020;15:628-636; 15. Nakada T et al. *Chem Pharm Bull* (Tokyo). 2019;67:173-185; 16. Ogitani Y et al. *Clin Cancer Res*. 2016;22:5097-5108; 17. Smit et al. *World Congress of Lung Cancer*. 2020.

DESTINY-Lung01 Study Design

Multicenter, international, 2-cohort phase 2 trial (NCT03505710)

Key eligibility criteria

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



Primary end point

- Confirmed ORR by ICR[d]

Secondary end points

- DOR
- PFS
- OS
- DCR
- Safety

Exploratory end point

- Biomarkers of response

Data cutoff: May 3, 2021

- 91 patients with *HER2*m NSCLC were enrolled and treated with T-DXd
- 15 patients (16.5%) remain on treatment to date
- 76 patients (83.5%) discontinued, primarily for progressive disease (37.4%) and adverse events (29.7%)

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

DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Demographics and Baseline Characteristics

	T-DXd (N = 91)
Age, median (range), years	60.0 (29.0-88.0)
Female, %	65.9
Race, %	
Asian	34.1
White	44.0
Black	1.1
Other	20.9
Region, %	
Asia	25.3
Europe	36.3
North America	38.5
ECOG PS, %	
0 | 1	25.3 | 74.7
***HER2* mutation, %**	
Kinase domain	93.4
Extracellular domain	6.6
Asymptomatic CNS metastases at baseline, %	36.3
Smoking status, %	
Never | Former | Current	57.1 | 40.7 | 2.2
History of prior lung resection, %	22.0

CNS, central nervous system.

Prior Therapies

	Patients (N = 91)
History of any prior systemic cancer therapy, n (%)	**90 (98.9)**
Prior lines of treatment, median (range)	2 (0-7)[a]
Prior treatment, n (%)	
Platinum-based therapy	86 (94.5)
Anti–PD-(L)1 therapy	60 (65.9)
Platinum-based and anti–PD-(L)1 therapy[b]	57 (62.6)
Docetaxel	18 (19.8)
HER2 TKI[c]	13 (14.3)

[a]One patient was enrolled without receiving prior cancer therapy
[b]Given separately or in combination
[c]Patients previously treated with a HER2 antibody or an antibody-drug conjugate were ineligible, but those who previously received a HER2 TKI such as afatinib, pyrotinib, or poziotinib were allowed

PD-(L)1, programmed cell death (ligand) 1; TKI, tyrosine kinase inhibitor.

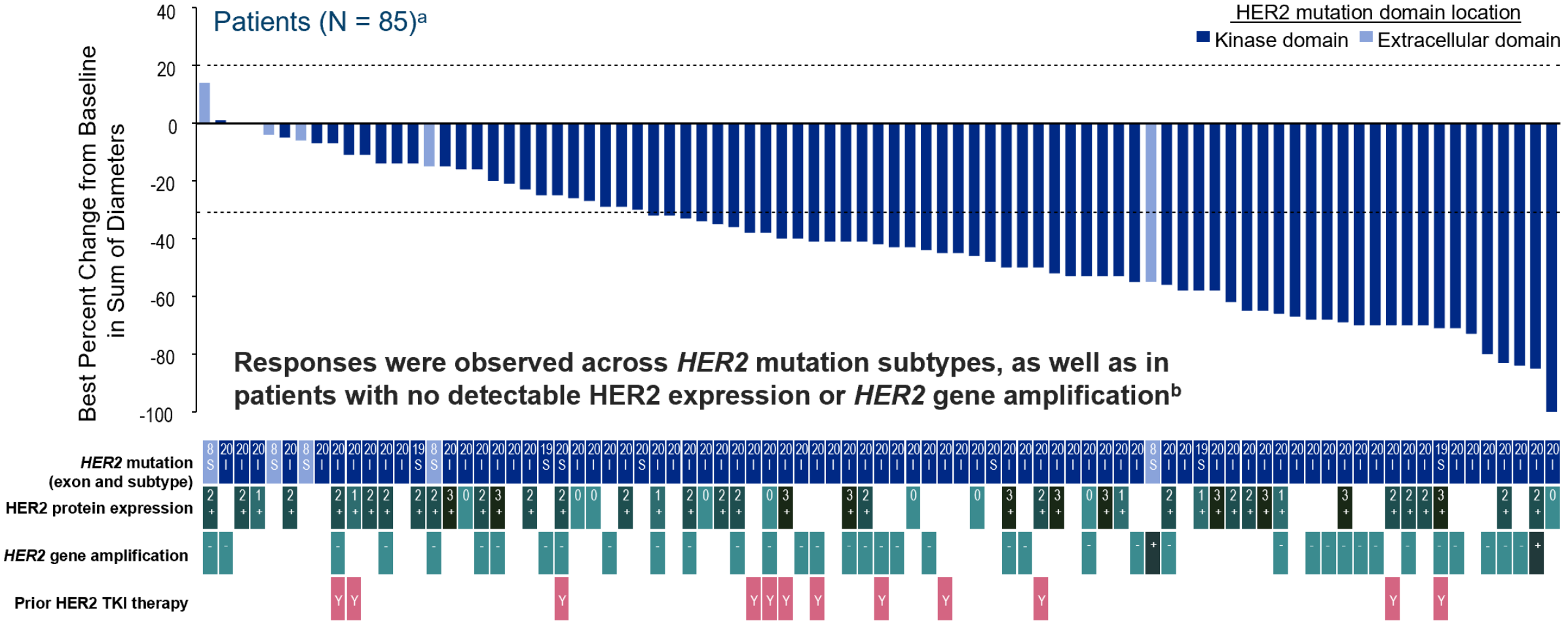
Confirmed ORR, Best Overall Response, and DoR

	Patients (N = 91)
Confirmed ORR[a], n (%)	**50 (54.9)** (95% CI, 44.2-65.4)
Best overall response, n (%)	
CR	**1 (1.1)**
PR	**49 (53.8)**
SD	**34 (37.4)**
PD	**3 (3.3)**
Not evaluable	**4 (4.4)**
DCR, n (%)	84 (92.3) (95% CI, 84.8-96.9)
Median DoR, months	9.3 (95% CI, 5.7-14.7)
Median follow up, months	13.1 (range, 0.7-29.1)

[a]Primary endpoint

CR, complete response; DoR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

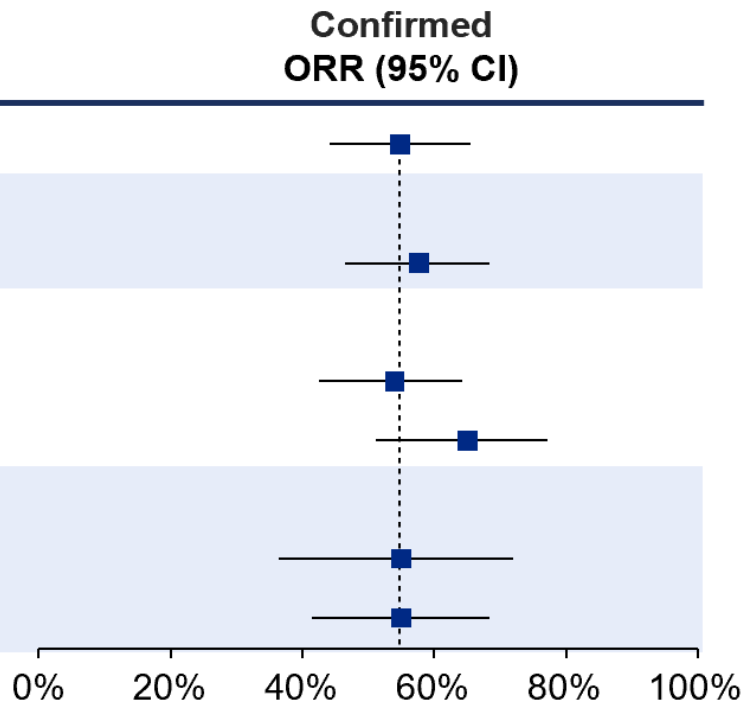
Best Percentage Change of Tumor Size From Baseline



[a]Best change in tumor size by ICR for 85 of 91 patients for whom baseline and postbaseline data were available. Baseline is last measurement taken before enrollment. [b]The Oncomine™ Dx Target Test (Thermo Fisher Scientific) was used to confirm local HER2 mutation status and to determine HER2 amplification status. HER2 protein expression status was determined by immunohistochemistry using a modified PATHWAY anti-HER2 (4B5) (Ventana Medical Systems, Inc.) assay. Shown is best (minimum) percentage change from baseline in the sum of diameters for all target lesions; (-), negative; (+), positive; I, insertion; N, no; S, substitution; Y, yes. Blank cells (except for the prior HER2 TKI therapy row) indicate patients whose tumor samples were not evaluable or assessed. The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression and the lower dashed line indicates a 30% decrease in tumor size (partial response).

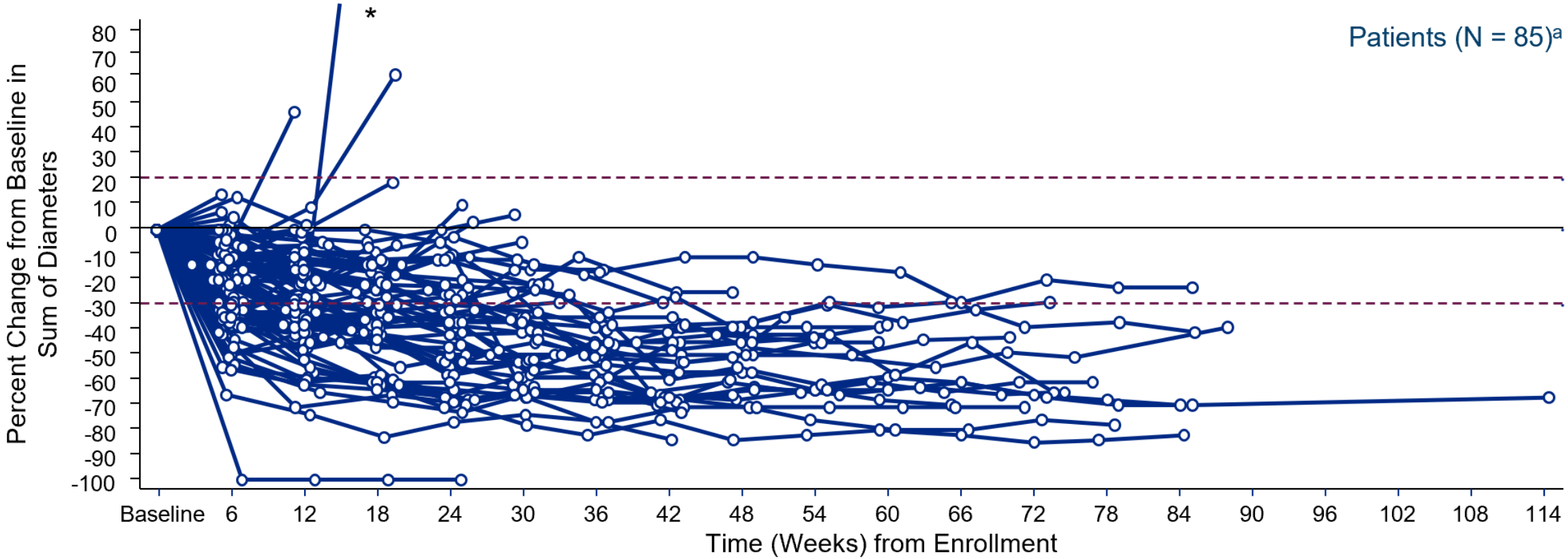
Response to T-DXd in Subgroups

	No. of Responders	Confirmed ORR (95% CI)
All patients	50/91	54.9 (44.2-65.4)
***HER2* mutation domain**		
Kinase domain	49/85	57.6 (46.5-68.3)
Prior treatment received		
Platinum-based therapy	46/86	53.5 (42.4-64.3)
Platinum-based therapy and anti-PD-(L)1 therapy[a]	37/57	64.9 (51.1-77.1)
Asymptomatic CNS metastasis at baseline[b]		
Yes	18/33	54.5 (36.4-71.9)
No	32/58	55.2 (41.5-68.3)



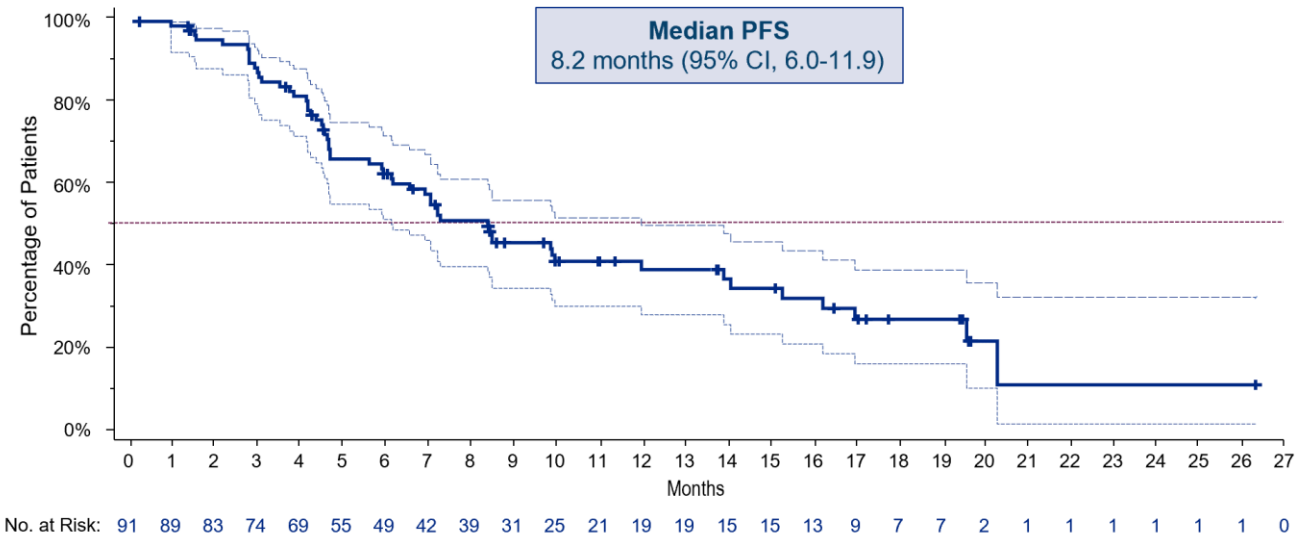
[a]Given separately or in combination
[b]Patients had asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy

Percentage Change of Tumor Size Over Time

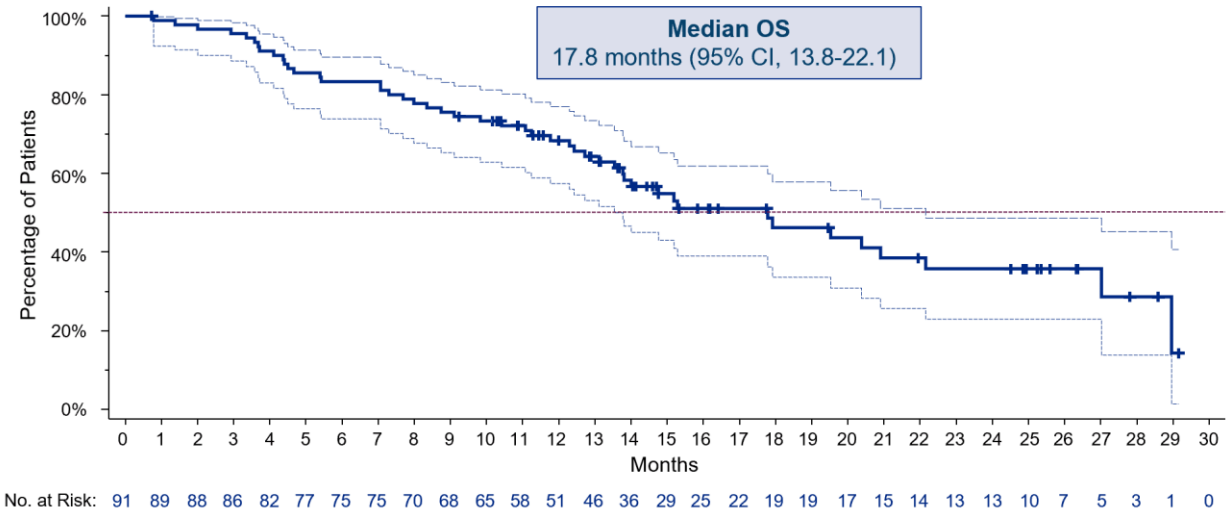


Median follow-up was 13.1 months (range, 0.7-29.1 months)
[a]Includes patients for whom baseline and postbaseline data were available.
*Patient outlier with a tumor increase of 236% from baseline at Week 18.

Progression-free Survival and Overall Survival



Median follow-up was 13.1 months (range, 0.7-29.1)
PFS assessed by ICR using RECIST v1.1., the median was based on Kaplan-Meier estimate, and 95% CI for median was computed using the Brookmeyer-Crowley method, and dashed lines indicate the 95% CI. Of 91 patients, 41 had progressive disease and 15 had died by the data cutoff date. Data for 35 patients were censored as indicated by tick marks; patients were censored if they discontinued treatment.



Median follow-up was 13.1 months (range, 0.7-29.1 months)
Dashed lines indicate the 95% CI. Of 91 patients, 47 had died by the data cutoff date. Data for 44 patients were censored as indicated by tick marks; patients were censored if they discontinued treatment.

Overall Safety Summary

n (%)	Patients (N = 91)
Any drug-related TEAE	88 (96.7)
Drug-related TEAE Grade ≥3	42 (46.2)
Serious drug-related TEAE	18 (19.8)
Drug-related TEAE associated with discontinuation[a]	23 (25.3)
Drug-related TEAE associated with dose reduction	31 (34.1)
Drug-related TEAE associated with an outcome of death	2 (2.2)[c]

- Median treatment duration was 6.9 months (range, 0.7-26.4 months)
- The most common drug-related TEAEs associated with treatment discontinuation were investigator-reported pneumonitis (13.2%) and ILD (5.5%)
- The most common drug-related TEAEs associated with dose reduction were nausea (11.0%) and fatigue (8.8%)

Relationship to study drug was determined by the treating investigator. [a]Pneumonitis (n = 12) and interstitial lung disease (n = 5) were among the drug-related TEAEs associated with discontinuation. [b]1 patient experienced grade 3 ILD as reported by investigator and died. The reported ILD was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee.
ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.

Drug-related TEAEs Reported by Investigator

n (%)	Patients (N = 91)	
	Any grade	Grade ≥3
Patients with ≥1 drug-related TEAEs	88 (96.7)	42 (46.2)
Drug-related TEAEs with ≥20% incidence in all patients		
Nausea	66 (72.5)	8 (8.8)
Fatigue[a]	48 (52.7)	6 (6.6)
Alopecia	42 (46.2)	0
Vomiting	36 (39.6)	3 (3.3)
Neutropenia[b]	32 (35.2)	17 (18.7)
Anemia[c]	30 (33.0)	9 (9.9)
Diarrhea	29 (31.9)	3 (3.3)
Decreased appetite	27 (29.7)	0
Leukopenia[d]	21 (23.1)	4 (4.4)
Constipation	20 (22.0)	0

[a]This category includes the preferred terms fatigue, asthenia, and malaise.
[b]This category includes the preferred terms neutrophil count decreased and neutropenia.
[c]This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased.
[d]This category includes the preferred terms white blood cell count decreased and leukopenia.

Adjudicated Drug-Related ILD

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
n (%)	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)	24 (26.4)

- The median time to onset of first reported drug-related ILD/pneumonitis was 141 days (range, 14-462 days), with a median duration of 43 days (95% CI, 24-94 days)
- 75% of adjudicated drug-related ILD/pneumonitis[a] cases were of low grade (Grade 1/2)
- 21 of 24 patients with adjudicated drug-related ILD/pneumonitis received ≥1 dose of glucocorticoids.
  However, not all glucocorticoid treatment was administered per the ILD/pneumonitis management guidelines[b]
- At the time of data cutoff, 54% (13/24) of investigator-reported cases had fully resolved

[a]Drug-related ILD/pneumonitis was determined by the Independent Adjudication Committee based on the current MedDRA version for the narrow ILD standard MedDRA query (SMQ), selected terms from the broad ILD SMQ, and respiratory failure and acute respiratory failure. [b]Events of ILD/pneumonitis in the present study were actively managed based on the protocol-defined ILD/pneumonitis management guidelines.

Conclusions

- T-DXd demonstrated **robust and durable anticancer activity** in patients with previously-treated *HER2*m NSCLC
  - Efficacy was consistently observed across subgroups, including in those patients with stable CNS metastases
  - Exploratory analyses demonstrated anticancer activity across different *HER2* mutation subtypes, as well as in patients with no detectable HER2 expression or *HER2* gene amplification
- Overall, the **safety profile** was **consistent** with previously reported studies
  - Most adjudicated drug-related ILD/pneumonitis cases were of low grade
  - ILD/pneumonitis remains an important identified risk. Effective early detection and management are critical in preventing high-grade ILD/pneumonitis
- The 5.4 mg/kg dose is being explored in future studies to evaluate the optimal dosing regimen in patients with *HER2*m NSCLC (DESTINY-Lung02; NCT04644237)
- DESTINY-Lung01 provides **compelling evidence of positive benefit/risk balance** with T-DXd in the 2L+ setting and supports its establishment as a **potential new treatment standard**

次のステップ

- **HER2変異 非小細胞肺がんにおける2次治療以降の申請戦略について、当局と協議を進めている**

- **DESTINY-Lung04 を2021年度 第3四半期に開始予定**
  - HER2エクソン19または20の変異を有する治癒切除不能な局所進行性または転移性の非小細胞肺がん患者を対象とした1次治療でのフェーズ3試験

NSCLC: non small cell lung cancer

ENHERTU®: Clinical Development Plan | Breast cancer

As of Sep 2021			FY2020	FY2021	FY2022	Planning
HER2 Positive		Metastatic 3L~	DESTINY-Breast01 completed			
			DESTINY-Breast02 monotherapy vs PC			
		Metastatic 2L	DESTINY-Breast03 monotherapy vs T-DM1			
			DESTINY-Breast07 combination (2L/1L) Ph1b/2			
		Metastatic 1L				
			DESTINY-Breast09 T-DXd ± pertuzumab vs THP			
		Post-neoadjuvant	DESTINY-Breast05 monotherapy vs T-DM1			
		Neoadjuvant				Phase 3
		Adjuvant				Phase 3
HER2 Low	HR+ HR-	Metastatic Post Chemo	DESTINY-Breast04 monotherapy vs PC			
			DESTINY-Breast08 combination			
		Post-neoadjuvant				Phase 3
	HR+	Metastatic Chemo Naive	DESTINY-Breast06 monotherapy vs PC			
		Metastatic Endocrine Therapy				Phase 3
	HR-	Metastatic 1L	BEGONIA durvalumab combination Ph1b/2 (Arm 6)			
		Neoadjuvant				Phase 3

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

PC: physician's choice

ENHERTU®: Clinical Development Plan | Gastric cancer & NSCLC

As of Sep 2021			FY2020	FY2021	FY2022	Planning
Gastric	HER2 Positive	Advanced/ Metastatic 3L~	DESTINY-Gastric01	DESTINY-Gastric06 China Ph2		
		Advanced/ Metastatic 2L	DESTINY-Gastric02 monotherapy - West			
				DESTINY-Gastric04 mono vs ramucirumab+paclitaxel		
			DESTINY-Gastric03 combination (2L/1L) Ph1b/2			
		Advanced/ Metastatic 1L				Phase 3
NSCLC	HER2 Expressing	Advanced/ Metastatic 2L~	DESTINY-Lung01 monotherapy			
			HUDSON durvalumab combination			
		Advanced/ Metastatic 2L				Phase 3
		Advanced/ Metastatic 1L		DESTINY-Lung03 combination		
						Phase 3
	HER2 Mutated	Advanced/ Metastatic 2L~	DESTINY-Lung01 monotherapy			
				DESTINY-Lung02 monotherapy		
		Advanced/ Metastatic 1L		DESTINY-Lung04 Ph3 vs SOC		
	Expressing /Mutated	Early disease				Phase 3

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

NSCLC: non small cell lung cancer

ENHERTU®: Clinical Development Plan | CRC & other tumors

As of June 2021			FY2020	FY2021	FY2022	Planning
CRC	HER2 Expressing	Metastatic 3L	DESTINY-CRC01 monotherapy	DESTINY-CRC02 monotherapy		
		Metastatic 2L				Phase 3
		Metastatic 1L				Phase 3
Other Tumors/ multiple tumors	HER2 Expressing	Metastatic 2L	Nivolumab combination (breast, bladder)			
			Pembrolizumab combination (breast, NSCLC)			
			DESTINY-PanTumor02			
		Ovarian				Phase 2
	HER2 Mutated	Metastatic 2L	DESTINY-PanTumor01			

Ph 1 ongoing | Ph 2 ongoing | Ph 3 ongoing | New | Completed

Study initiation & end points are all shown as either beginning of 1H or 2H

CRC: colorectal cancer, NSCLC: non small cell lung cancer

A Phase 1/2 Multicenter, First-in-Human Study of DS-7300 (B7-H3 DXd-ADC) in Patients (pts) With Advanced Solid Tumors

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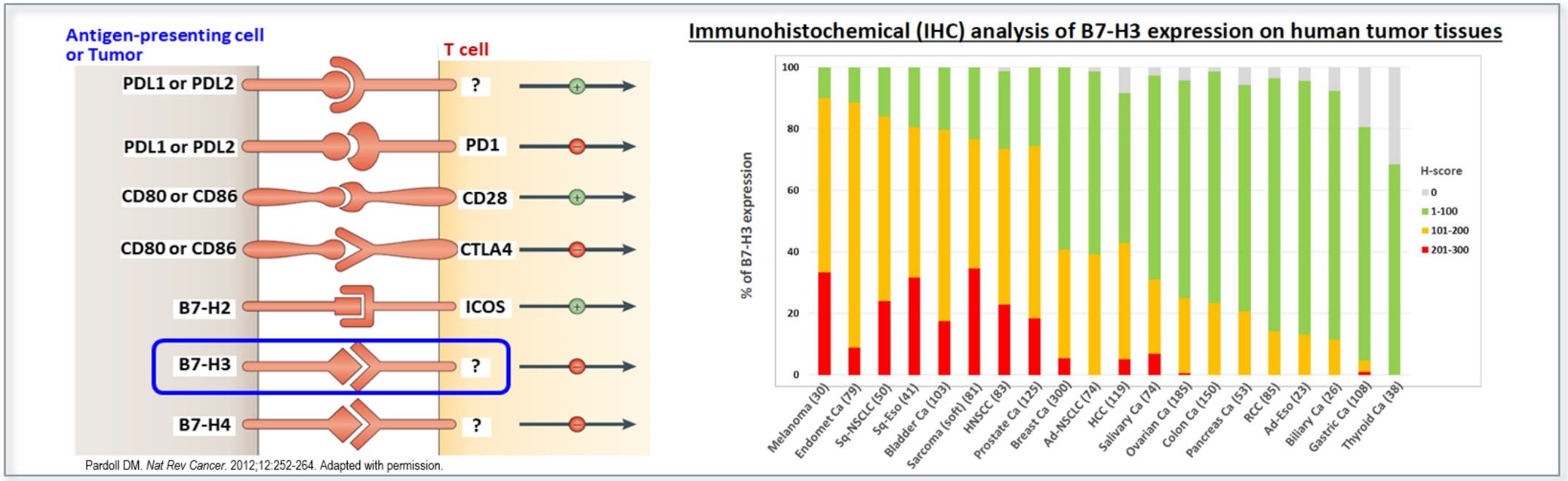
Background and Rationale

- B7 homologue 3 (B7-H3, CD276) is a transmembrane protein overexpressed in various cancers, including lung, prostate, esophageal, and breast cancers, and head and neck squamous cell carcinoma (HNSCC)[1-4]
  - B7-H3 overexpression is associated with poor prognosis[1,2,4]

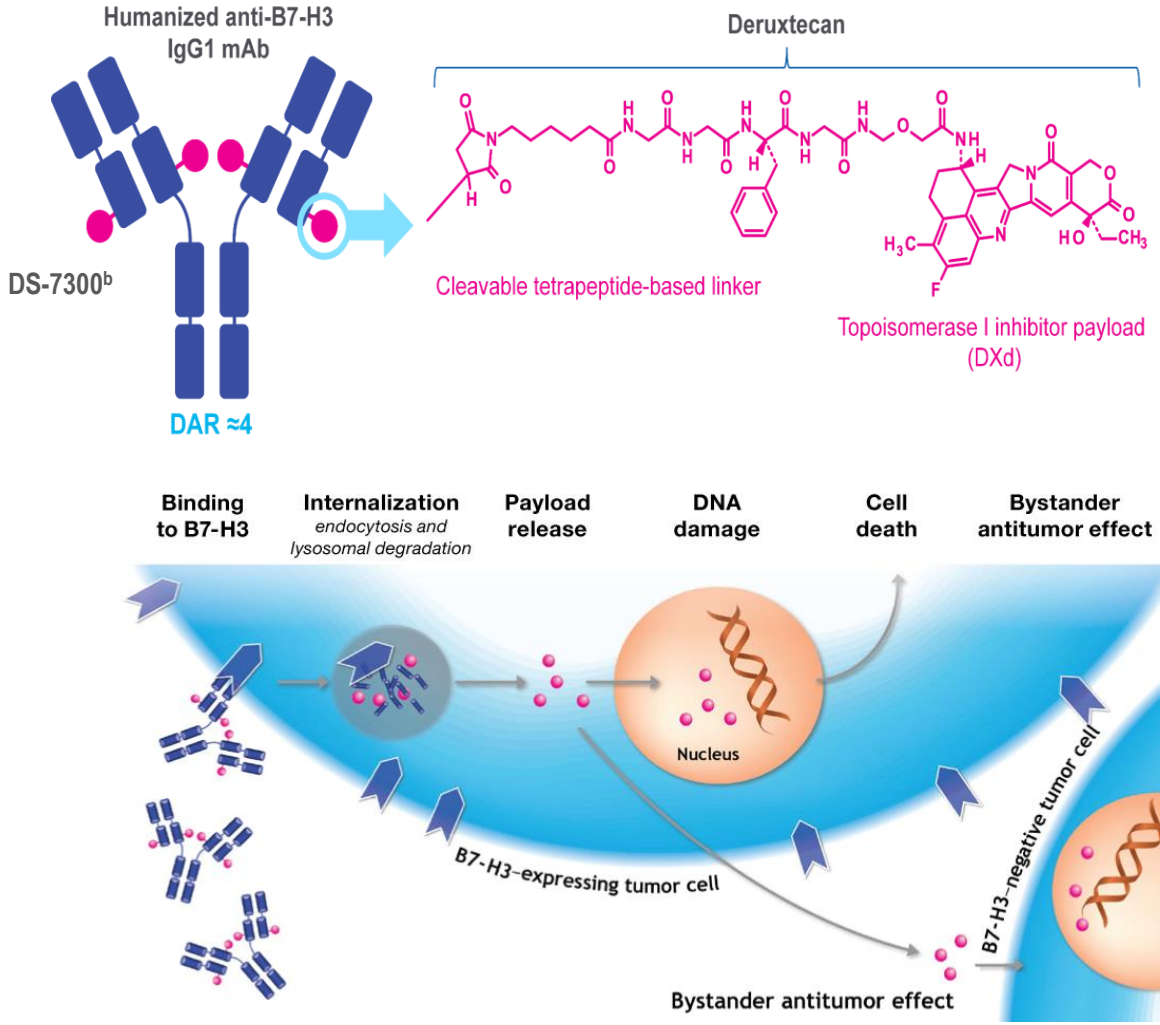


Ad, adenocarcinoma; Eso, esophageal cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; Sq, squamous cell carcinoma

1. Yamoto M, et al. EORTC-NCI-AACR 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 2020.

Background and Rationale: DS-7300

- Payload mechanism of action: topoisomerase I inhibitor [a,1-5]
- High potency of payload [a,2-5]
- Optimized drug-to-antibody ratio [a,c,1-4]
- Payload with short systemic half-life [a,c,2,3]
- Stable linker-payload [a,2,3,5]
- Tumor-selective cleavable linker [a,2-6]
- Bystander antitumor effect [a,2,7]



[a] The clinical relevance of these features is under investigation. [b] Image is for illustrative purposes only; actual drug-to-antibody ratio and drug positions may vary. [c] Based on animal data.

1. Okajima D, et al. Poster presented at: AACR-NCI-EORTC International Conference; October 26-30, 2019; Boston, MA. Abstract C026. **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.** Hashimoto Y, et al. *Clin Cancer Res.* 2019;25(23):7151-7161. **5.** Koganemaru S, et al. *Mol Cancer Ther.* 2019;18(11):2043-2050. **6.** Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. **7.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

A Multicenter, Open-Label, 2-Part, Multiple-Dose, First-in-Human, Phase 1/2 Study of DS-7300

Daiichi-Sankyo

NCT04145622

Part 1: Dose escalation

- DS-7300 IV Q3W monotherapy in advanced solid tumors
- Advanced/unresectable or metastatic solid tumors (unselected for B7-H3 expression)
- ECOG PS 0-1
- ≥1 measurable lesion according to RECIST version 1.1
- Key inclusion criteria
  - HNSCC, ESCC, squamous and adeno NSCLC, SCLC, bladder cancer, sarcoma, endometrial cancer, melanoma, CRPC, or BC that is refractory to or intolerant of standard treatment or for which no standard treatment is available

0.8 mg/kg → 1.6 mg/kg → 3.2 mg/kg → 4.8 mg/kg → 6.4 mg/kg → 8.0 mg/kg → 12.0 mg/kg → 16.0 mg/kg

MTD/RDE

Part 2: Dose expansion

- DS-7300 IV Q3W monotherapy in selected advanced solid tumors

Cohort 1: ESCC (up to n=25)

Cohort 2: mCRPC (up to n=40)

Cohort 3: SCLC (up to n≈40)

Key primary endpoints (Dose escalation):

- DLTs, SAEs, TEAEs, AESIs
- Here, we report initial results from the dose-escalation portion of the trial

AESI, adverse event of special interest; BC, breast cancer; CRPC, castration-resistant prostate cancer; DLT, dose-limiting toxicity; ECOG PS, Easter Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RDE, recommended dose for expansion; SAE, serious adverse event; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event

Results: Baseline Demographics and Disease Characteristics

	DS-7300 Dose Level								Total (N=70)
	0.8 mg/kg (n=5)	1.6 mg/kg (n=5)	3.2 mg/kg (n=7)	4.8 mg/kg (n=5)	6.4 mg/kg (n=8)	8.0 mg/kg (n=12)	12.0 mg/kg (n=21)	16.0 mg/kg (n=7)	
Male, n (%)	3 (60)	4 (80)	5 (71.4)	3 (60)	7 (87.5)	11 (91.7)	17 (81)	5 (71.4)	55 (78.6)
Age, median (range), years	64 (46-67)	69 (35-73)	66 (41-77)	59 (56-60)	59.5 (44-74)	68 (56-77)	69 (43-82)	57 (53-70)	65 (35-82)
≥65 years, n (%)	2 (40)	3 (60)	5 (71.4)	0	3 (37.5)	9 (75)	14 (66.7)	1 (14.3)	37 (52.9)
ECOG PS, n (%)									
0	4 (80)	3 (60)	4 (57.1)	3 (60)	4 (50)	2 (16.7)	6 (28.6)	3 (42.9)	29 (41.4)
1	1 (20)	2 (40)	3 (42.9)	2 (40)	4 (50)	10 (83.3)	15 (71.4)	4 (57.1)	41 (58.6)
Cancer type, n (%)									
CRPC	0	1 (20)	1 (14.3)	0	4 (50)	5 (41.7)	12 (57.1)	1 (14.3)	24 (34.3)
HNSCC	1 (20)	1 (20)	3 (42.9)	0	1 (12.5)	1 (8.3)	3 (14.3)	2 (28.6)	12 (17.1)
Sarcoma	2 (40)	1 (20)	1 (14.3)	0	1 (12.5)	1 (8.3)	1 (4.8)	1 (14.3)	8 (11.4)
SCLC	0	0	1 (14.3)	0	1 (12.5)	2 (16.7)	3 (14.3)	1 (14.3)	8 (11.4)
Endometrial cancer	0	1 (20)	0	1 (20)	0	0	1 (4.8)	1 (14.3)	4 (5.7)
ESCC	1 (20)	0	0	1 (20)	0	2 (16.7)	0	0	4 (5.7)
Squamous NSCLC	0	0	1 (14.3)	1 (20)	0	0	1 (4.8)	1 (14.3)	4 (5.7)
Breast cancer	1 (20)	0	0	1 (20)	0	0	0	0	2 (2.9)
Melanoma	0	1 (20)	0	1 (20)	0	0	0	0	2 (2.9)
Bladder cancer	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
Prior lines of therapy, median (range)	4 (2-6)	3 (2-10)	3 (1-7)	5 (3-6)	5 (2-7)	4 (2-9)	5 (1-8)	4 (2-8)	4 (1-10)

Data cutoff July 21, 2021
ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

Results: Summary of Overall Safety

- No DLTs[a] were observed in dose escalation
- All-grade AESIs of ILD/pneumonitis or IRRs occurred in 2 (2.9%) and 28 patients (40%), respectively; no hepatotoxicity occurred
- One case of grade 5 ILD (adjudicated as treatment related) occurred at 16 mg/kg and 1 case of grade 1 ILD (pending adjudication) occurred at 12 mg/kg

Patients, n (%)	DS-7300								Total (N=70)
	0.8 mg/kg (n=5)	1.6 mg/kg (n=5)	3.2 mg/kg (n=7)	4.8 mg/kg (n=5)	6.4 mg/kg (n=8)	8.0 mg/kg (n=12)	12.0 mg/kg (n=21)	16.0 mg/kg (n=7)	
Tx duration, median (range), weeks	13 (6-33)	12 (9-47.9)	12 (6-18)	12.1 (6-18)	17.1 (6-37)	21.1 (5.9-44)	14.9 (3-36)	6 (3-21.9)	13.1 (3-47.9)
TEAEs[b]	4 (80)	5 (100)	7 (100)	5 (100)	8 (100)	12 (100)	21 (100)	7 (100)	69 (98.6)
Grade ≥3 TEAEs[b]	0	0	1 (14.3)	1 (20)	1 (12.5)	5 (41.7)	9 (42.9)	5 (71.4)	22 (31.4)
Serious TEAEs[b]	1 (20)	0	2 (28.6)	1 (20)	1 (12.5)	3 (25)	4 (19.0)	3 (42.9)	15 (21.4)
TEAEs leading to death[b]	0	0	0	0	0	1 (8.3)	0	1 (14.3)	2 (2.9)
TEAEs leading to Tx discontinuation	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
AESIs[b]									
Infusion-related reactions	1 (20)	0	1 (14.3)	3 (60)	4 (50)	4 (33.3)	11 (52.4)	4 (57.1)	28 (40)
Interstitial lung disease	0	0	0	0	0	0	1 (4.8)	1 (14.3)	2 (2.9)

Data cutoff July 21, 2021

AESI, adverse event of special interest; ILD, interstitial lung disease; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event; Tx, treatment.

[a] A DLT is defined as any TEAE that occurs during the DLT evaluation period excluding toxicities clearly related to disease progression or intercurrent illness and is grade ≥3 according to NCI-CTCAE Version 5.0. [b] Regardless of causality.

Results: Most Common TEAEs (Any Grade)

- The most common TEAEs of any grade included nausea, IRRs, vomiting, and decreased appetite
  - All IRRs were grade ≤2

Most Common (Occurring in ≥10% of All Patients) Treatment-Emergent Adverse Events (Any Grade), Regardless of Causality

TEAEs, n (%)	0.8 mg/kg (n=5)	1.6 mg/kg (n=5)	3.2 mg/kg (n=7)	4.8 mg/kg (n=5)	6.4 mg/kg (n=8)	8.0 mg/kg (n=12)	12.0 mg/kg (n=21)	16.0 mg/kg (n=7)	Total N=70
Any TEAE	4 (80)	5 (100)	7 (100)	5 (100)	8 (100)	12 (100)	21 (100)	7 (100)	69 (98.6)
Nausea	3 (60)	1 (20)	3 (42.9)	2 (40)	3 (37.5)	6 (50)	16 (76.2)	5 (71.4)	39 (55.7)
IRR	1 (20)	0	1 (14.3)	3 (60)	4 (50)	4 (33.3)	11 (52.4)	4 (57.1)	28 (40)
Vomiting	2 (40)	1 (20)	2 (28.6)	0	1 (12.5)	5 (41.7)	7 (33.3)	1 (14.3)	19 (27.1)
Decreased appetite	1 (20)	1 (20)	3 (42.9)	1 (20)	3 (37.5)	3 (25)	6 (28.6)	2 (28.6)	20 (28.6)
Dehydration	0	1 (20)	1 (14.3)	0	1 (12.5)	2 (16.7)	3 (14.3)	0	8 (11.4)
Diarrhea	0	0	1 (14.3)	0	0	2 (16.7)	5 (23.8)	0	8 (11.4)
Chills	0	0	1 (14.3)	0	0	3 (25)	5 (23.8)	0	9 (12.9)
Fatigue	1 (20)	1 (20)	2 (28.6)	0	2 (25)	1 (8.3)	8 (38.1)	0	15 (21.4)
Pyrexia	1 (20)	2 (40)	2 (28.6)	0	0	3 (25)	1 (4.8)	0	9 (12.9)

Data cutoff July 21, 2021

Results: Grade ≥3 TEAEs

- The most common grade ≥3 TEAEs were anemia and lymphocyte count decreased
- The only Grade ≥3 treatment-related AEs were anemia (n=6), lymphocyte count decreased (n=2), neutropenia, asthenia, neutrophil count decreased, and ILD (n=1 each)

Grade ≥3 Treatment-Emergent Adverse Events, Regardless of Causality

Grade ≥3 TEAEs, n (%)	0.8 mg/kg (n=5)	1.6 mg/kg (n=5)	3.2 mg/kg (n=7)	4.8 mg/kg (n=5)	6.4 mg/kg (n=8)	8.0 mg/kg (n=12)	12.0 mg/kg (n=21)	16.0 mg/kg (n=7)	Total N=70
Anemia	0	0	0	0	1 (12.5)	3 (25)	5 (23.8)	2 (28.6)	11 (15.7)
Lymphocyte count decreased	0	0	0	0	0	0	2 (9.6)	0	2 (2.8)
Interstitial lung disease	0	0	0	0	0	0	1 (14.3)	0	1 (1.4)
Febrile neutropenia	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
Asthenia	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Blood creatinine increased	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
QT prolonged	0	0	1 (14.3)	0	0	0	0	0	1 (1.4)
Neutropenia[a]	0	0	0	0	0	0	2 (9.6)	0	2 (2.8)
Dehydration	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Hypercalcemia	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
Osteoarthritis	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
Dyspnea	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Hypoxia	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Pleural effusion	0	0	0	1 (20)	0	0	0	0	1 (1.4)
Arterial thrombosis	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
Myelosuppression	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
COVID-19	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
Sepsis	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Urinary tract infection	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Wound infection	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
Cancer pain	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
Encephalopathy	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
Ureteric obstruction	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
Embolism arterial	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)

Data cutoff July 21, 2021. [a]Includes neutrophil count decreased.

Results: Initial Efficacy (Dose Escalation)

- Among 70 patients enrolled, 15 partial responses were observed[a]
- 32 patients had stable disease, including 24 patients ongoing on study treatment

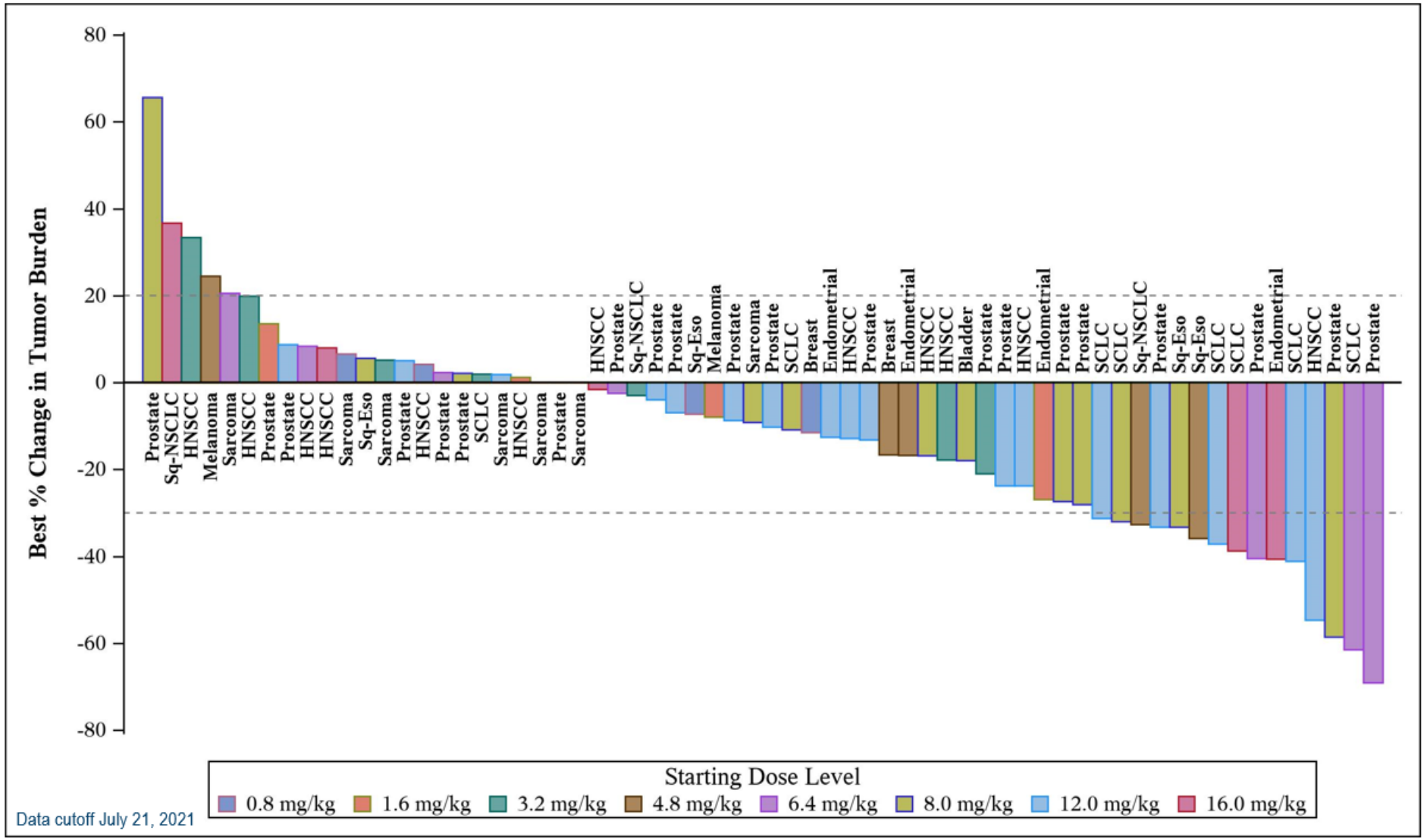
Summary of Efficacy in Dose Escalation (per RECIST v1.1)

Patients, n	DS-7300								
	0.8 mg/kg (n=5)	1.6 mg/kg (n=5)	3.2 mg/kg (n=7)	4.8 mg/kg (n=5)	6.4 mg/kg (n=8)	8.0 mg/kg (n=12)	12.0 mg/kg (n=21)	16.0 mg/kg (n=7)	Total (N=70)
Best response									
CR	0	0	0	0	0	0	0	0	0
PR[a]	0	0	0	2	3	3	5	2	15
SD	4	4	3	1	2	5	12	1	32
PD	1	1	4	2	2	4	1	2	17
NE[b]	0	0	0	0	1	0	3	2	6

Data cutoff July 21, 2021

[a] Total confirmed and unconfirmed PRs was 10 and 5, respectively; unconfirmed partial responses are still ongoing. [b] Not evaluable per RECIST v 1.1.
CR, complete response; PD, progressive disease; NE, not evaluable; PR, partial response; SD, stable disease

Results: Initial Efficacy (Dose Escalation Cohorts)

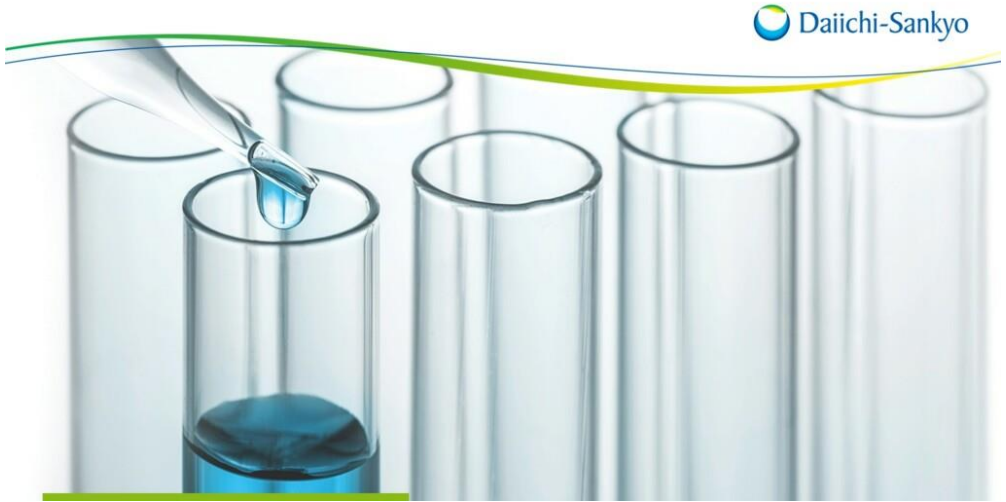


Conclusions

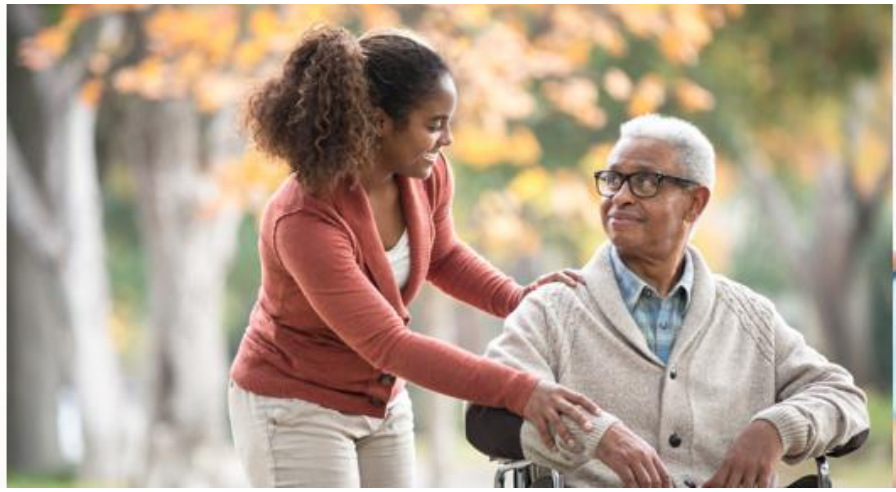
- In this first-in-human trial of single-agent DS-7300, a novel B7-H3 ADC, no DLTs were observed, and DS-7300 was generally well tolerated across all doses investigated to date in heavily pretreated patients with advanced solid tumors
- 15 PRs, including 10 confirmed and 5 unconfirmed, were observed in RECIST-evaluable patients at various doses during dose escalation
- Dose expansion of the study (part 2) is open and currently enrolling patients with select solid tumor types, including SCLC, ESCC, and mCRPC, to further evaluate DS-7300 efficacy, safety, and tolerability

結び

- 本日発表のデータは、がん患者さんの治療を変革する医薬品の創出において当社のリーダーシップが強まっていることを示すと共に、複数のがんに対する当社独自のADC技術の強みを実証し続けている。
- 研究開発ポートフォリオ全体のアップデートを、R&D day（12月14日開催）で予定しています。



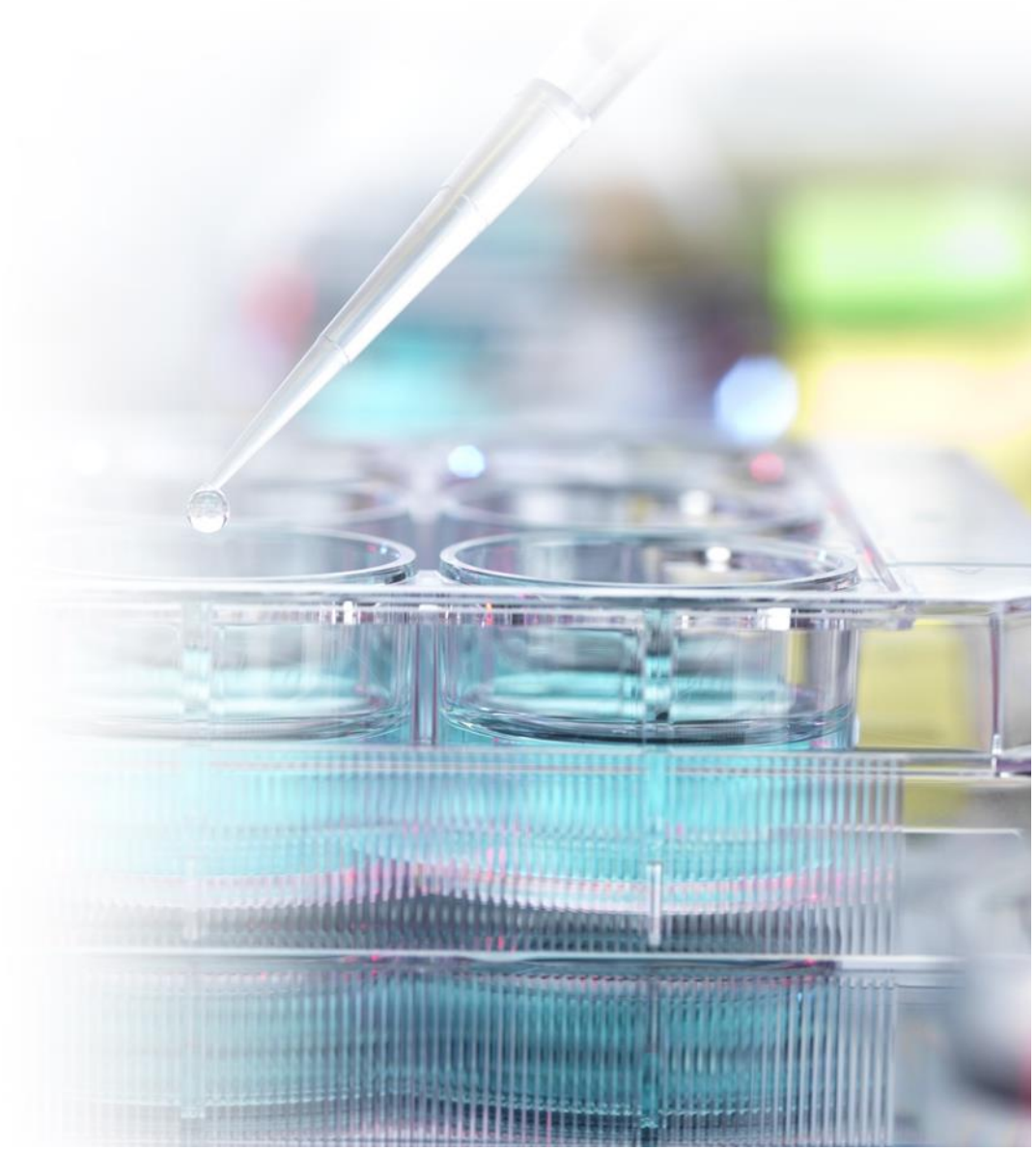
第一三共グループは世界中の人々の
健康で豊かな生活に貢献してまいります



❹ 添付資料

ESMO/WCLC 発表

- DESTINY-Breast03
- DESTINY-Breast01
- DESTINY-Lung01
- DESTINY-Gastric02
- TROPION-PanTumor01
  非小細胞肺がん コホート
- TROPION-PanTumor01
  アクショナブル遺伝子変異を有する
  非小細胞肺がんサブ解析
- DS-7300 フェーズ1/2



Trastuzumab Deruxtecan (T-DXd) vs Trastuzumab Emtansine (T-DM1) in Patients With HER2+ Metastatic Breast Cancer: Results of the Randomized, Phase 3 Study DESTINY-Breast03

Javier Cortés, MD[a], Sung-Bae Kim, Wei-Pang Chung,
Seock-Ah Im, Yeon Hee Park, Roberto Hegg, Min-Hwan Kim, Ling-Ming Tseng, Vanessa Petry, Chi-Feng Chung,
Hiroji Iwata, Erika Hamilton, Giuseppe Curigliano, Binghe Xu, Caleb Lee,
Yali Liu, Jillian Cathcart, Emarjola Bako, Sunil Verma, Sara Hurvitz
On behalf of the DESTINY-Breast03 investigators

[a]Medical Oncology, International Breast Cancer Center (IBCC), Quironsalud Group, and Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain; Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Department of Medicine, Madrid, Spain.

Progress Has Been Made in HER2+ mBC, yet Unmet Need Persists

Standard of Care[a]

1L Trastuzumab + pertuzumab + taxane, **CLEOPATRA:** mPFS = 18.7 months[1]

- mBC 1L standard-of-care was established in the CLEOPATRA trial[1,2]

2L+ T-DM1, **EMILIA:** mPFS = 9.6 mo[3]

- EMILIA trial established T-DM1 as 2L+ standard-of-care
- In the changing treatment landscape, more recent clinical trials and real-world studies have demonstrated mPFS outcomes with T-DM1 in the range of 6-7 months[2,4-7]
  - mPFS for T-DM1 in the randomized KATE2 was 6.8 months (2020)[4]

3L+ T-DXd **DESTINY-Breast01:** mPFS = 19.4 months[8]

- T-DXd demonstrated robust activity in a 3L+ phase 2 single arm study, leading to regulatory approvals globally[2,8]

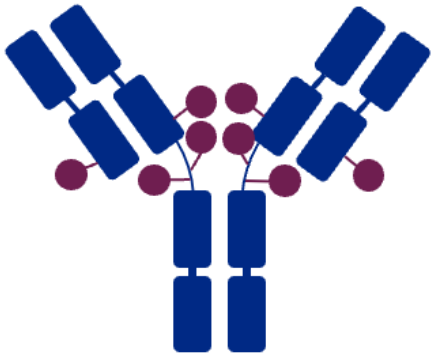
Given these data, T-DXd was evaluated in a head-to-head trial versus T-DM1 in previously treated HER2+ mBC

1L, first line; 2L, second line; 3L, third line; HER2, human epidermal growth factor receptor 2; mBC, metastatic breast cancer; mPFS, median progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Not intended for cross-trial comparison.

1. Swain SM et al. *N Engl J Med.* 2015;372:724-34. 2. Perez J et al. *Expert Opin Biol Ther*. 2021;21:811-24. 3. Verma S et al. *N Engl J Med*. 2012;367:1783-91. 4. Emens LA et al. *Lancet Oncol*. 2020;21:1283-95. 5. Daniels et al. *Breast*. 2021;58:106-12. 6. Lupichuk S et al. *Breast Cancer (Auckl).* 2019;13:1178223419879429. 7. Vici P et al. *Oncotarget.* 2017;8:56921-56931. 8. Modi S et al. Presented at San Antonio Breast Cancer Symposium. 2020. Poster PD3-06.

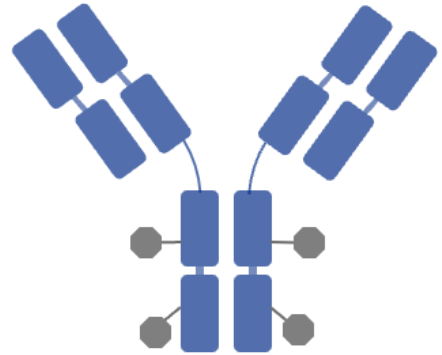
ADC Characteristic Differences Between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



ADC, antibody-drug conjugate; MoA, mechanism of action.
[a]The clinical relevance of these features is under investigation.

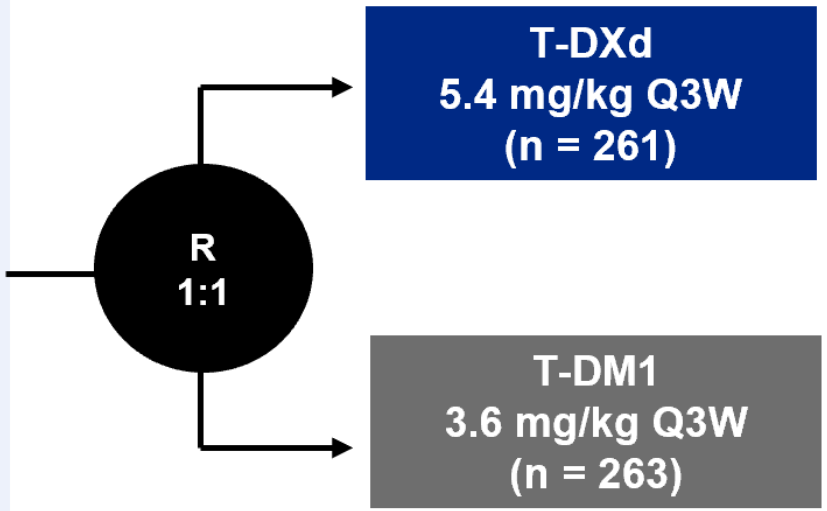
1. Nakada T et al. *Chem Pharm Bull (Tokyo).* 2019;67:173-85. 2. Ogitani Y et al. *Clin Cancer Res.* 2016;22:5097-108. 3. Trail PA et al. *Pharmacol Ther.* 2018;181:126-42.
4. Ogitani Y et al. *Cancer Sci.* 2016;107:1039-46. 5. LoRusso PM et al. *Clin Cancer Res*. 2011;17:6437-47.

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

An open-label, multicenter study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease



Primary endpoint
- PFS (BICR)

Key secondary endpoint
- OS

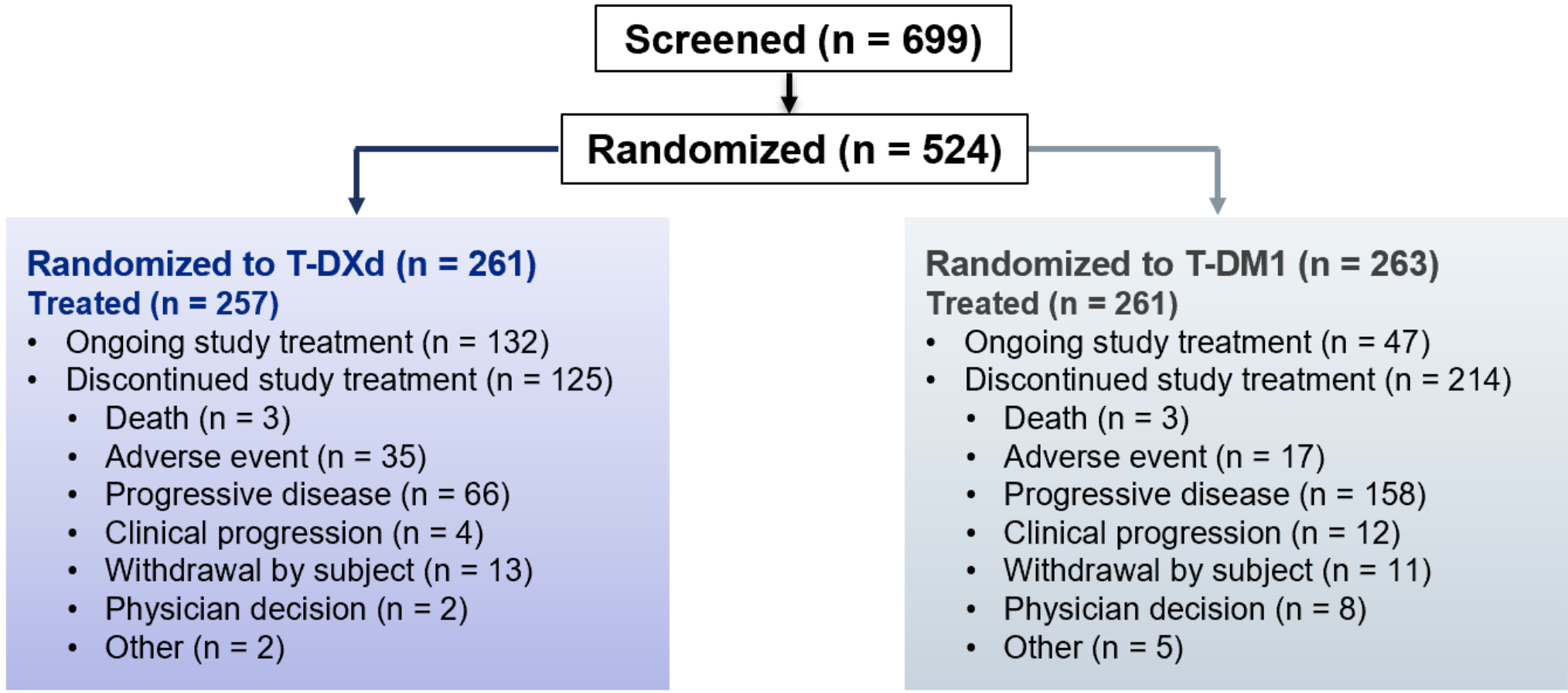
Secondary endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

BICR, blinded independent central review; DOR, duration of response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; Ph3, phase 3; Q3W, every 3 weeks.
[a]HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b]Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane

Patient Disposition



Median follow up for T-DXd was 16.2 months and for T-DM1 was 15.3 months

Baseline Characteristics

	T-DXd (n = 261)	T-DM1 (n = 263)
Age, median (range), years	54.3 (27.9-83.1)	54.2 (20.2-83.0)
Female, %	99.6	99.6
Region, %		
Europe	20.7	19.0
Asia	57.1	60.8
North America	6.5	6.5
Rest of world	15.7	13.7
HER2 status (IHC[a], %)		
3+	89.7	88.2
2+ (ISH amplified)	9.6	11.4
1+ | Not Evaluable | Not Examined	0.4 | 0.4 | 0	0 | 0.4 | 0
ECOG PS, %		
0 | 1 | Missing	59.0 | 40.6 | 0.4	66.5 | 33.1 | 0.4
Hormone receptor, %		
Positive | Negative	50.2 | 49.8	51.0 | 49.0
Brain metastases, %		
Yes | No	23.8 | 76.2	19.8 | 80.2
Visceral disease, %		
Yes | No	70.5 | 29.5	70.3 | 29.7

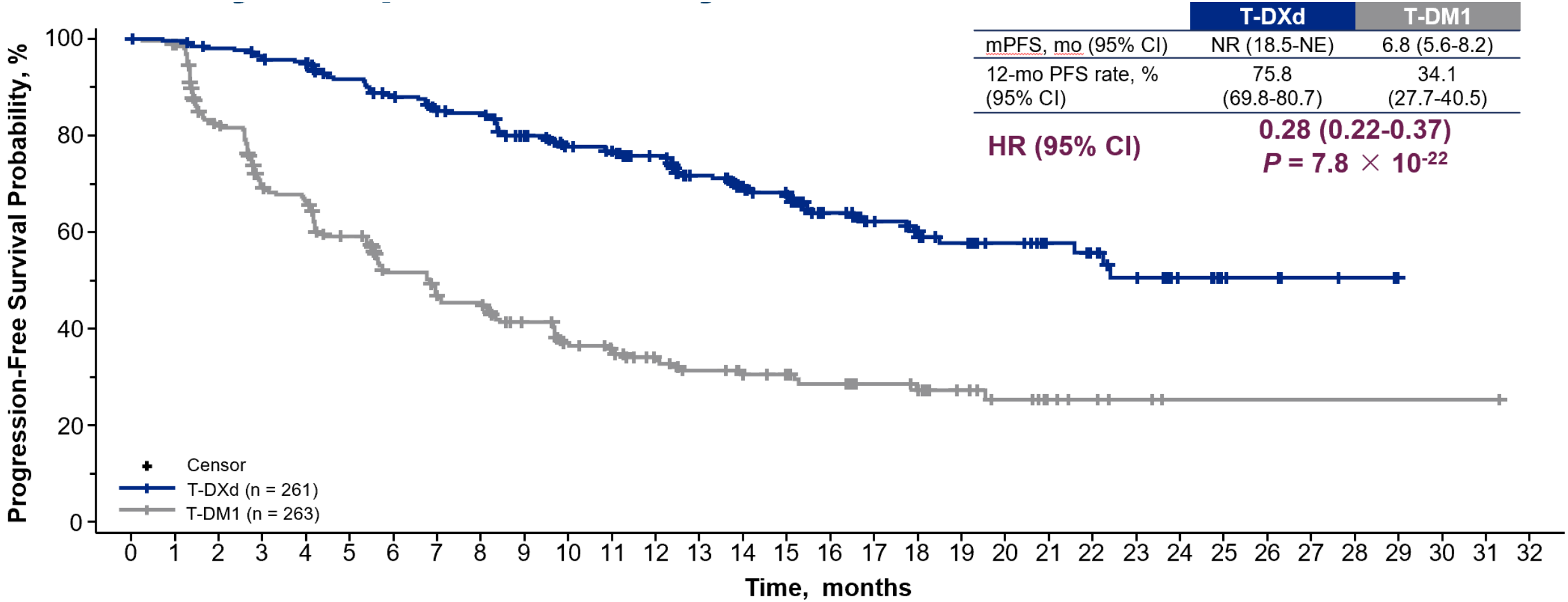
ECOG PS, Eastern Cooperative Oncology Group performance status; IHC, immunohistochemistry; ISH, in situ hybridization.
[a]HER2-status as evaluated by central lab.

Prior Therapies

	T-DXd (n = 261)	T-DM1 (n = 263)
Prior Treatment for mBC, n (%)		
No	21 (8.0)	29 (11.0)
Yes	240 (92.0)	234 (89.0)
Prior lines of therapy in the metastatic setting (includes rapid progressors as one line of treatment)[a], n (%)		
0	2 (0.8)	3 (1.1)
1	130 (49.8)	123 (46.8)
2	56 (21.5)	65 (24.7)
3	35 (13.4)	35 (13.3)
4	15 (5.7)	19 (7.2)
≥5	23 (8.8)	18 (6.8)
Prior cancer therapy[b], %		
Trastuzumab	99.6	99.6
Pertuzumab	62.1	60.1
Other anti-HER2		
Anti-HER2 TKI	16.1	13.7
Other anti-HER2 antibody or ADC	0.8	1.1

TKI, tyrosine-kinase inhibitor.
[a]Rapid progressors defined as progression within 6 mo of (neo)adjuvant therapy) or 12 mo if regimen contained pertuzumab. Line of therapy does not include endocrine therapy.
[b]All patients received at least 1 prior cancer therapy. One patient with prior T-DM1 treatment was enrolled in error in the T-DXd arm.

Primary Endpoint: PFS by BICR



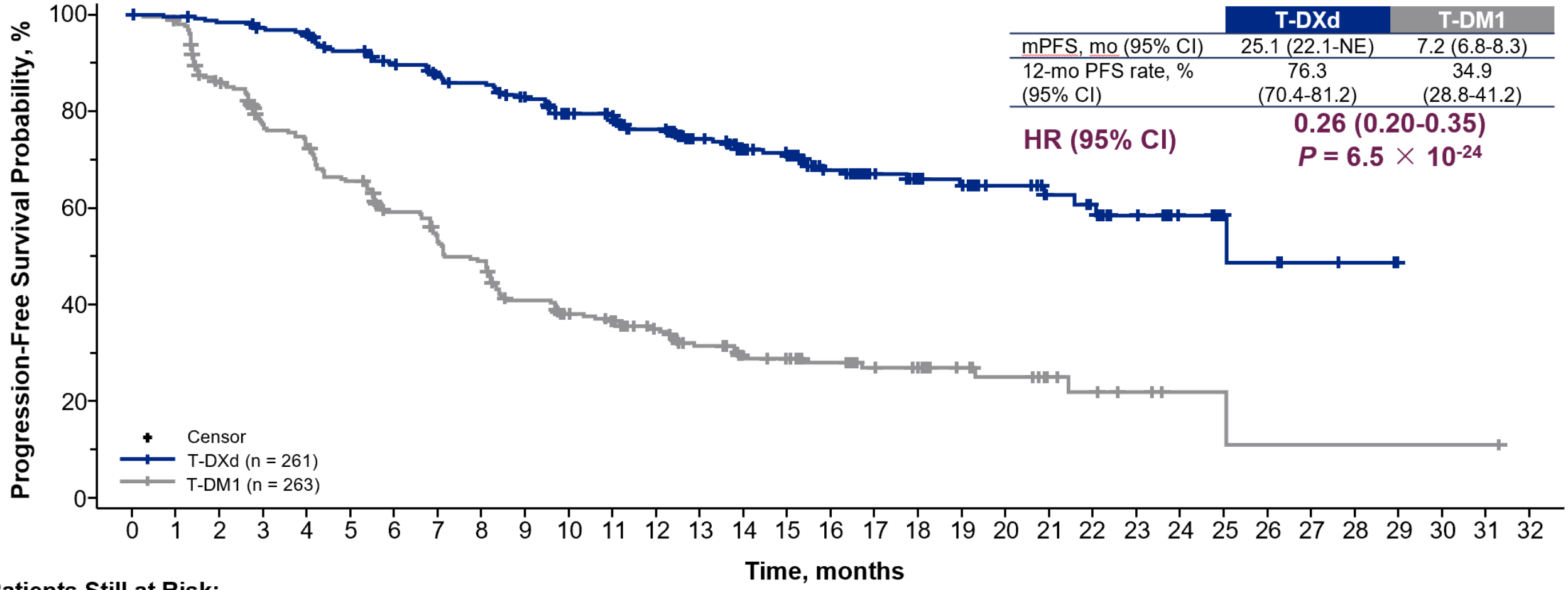
	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37)	
	$P = 7.8 \times 10^{-22}$	

Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0			
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	1	0

Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and for T-DM1 was 13.9 months (range, 11.8-15.1)
HR, hazard ratio; INV, investigator; mo, month; NE, not estimable; NR, not reached.

Secondary Endpoint: PFS by Investigator Assessment



	T-DXd	T-DM1
mPFS, mo (95% CI)	25.1 (22.1-NE)	7.2 (6.8-8.3)
12-mo PFS rate, % (95% CI)	76.3 (70.4-81.2)	34.9 (28.8-41.2)

HR (95% CI) **0.26 (0.20-0.35)**

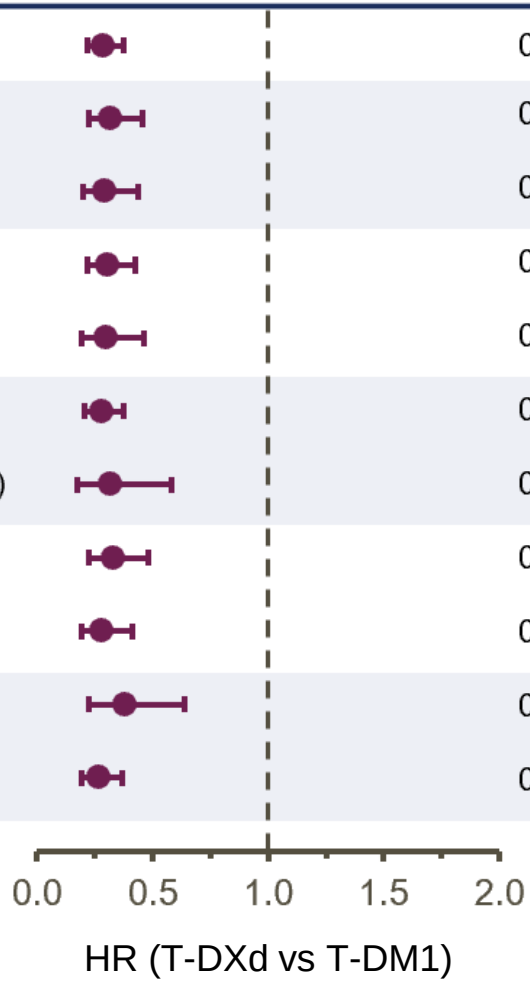
$P = 6.5 \times 10^{-24}$

Patients Still at Risk:

T-DXd (261)	261	256	252	247	244	230	221	209	205	195	179	176	158	140	120	113	85	64	53	48	37	31	27	20	11	7	5	3	2	0	
T-DM1 (263)	263	253	216	185	175	156	136	119	110	88	78	72	61	51	43	39	34	25	23	16	13	9	7	5	2	2	1	1	1	1	1	1	0

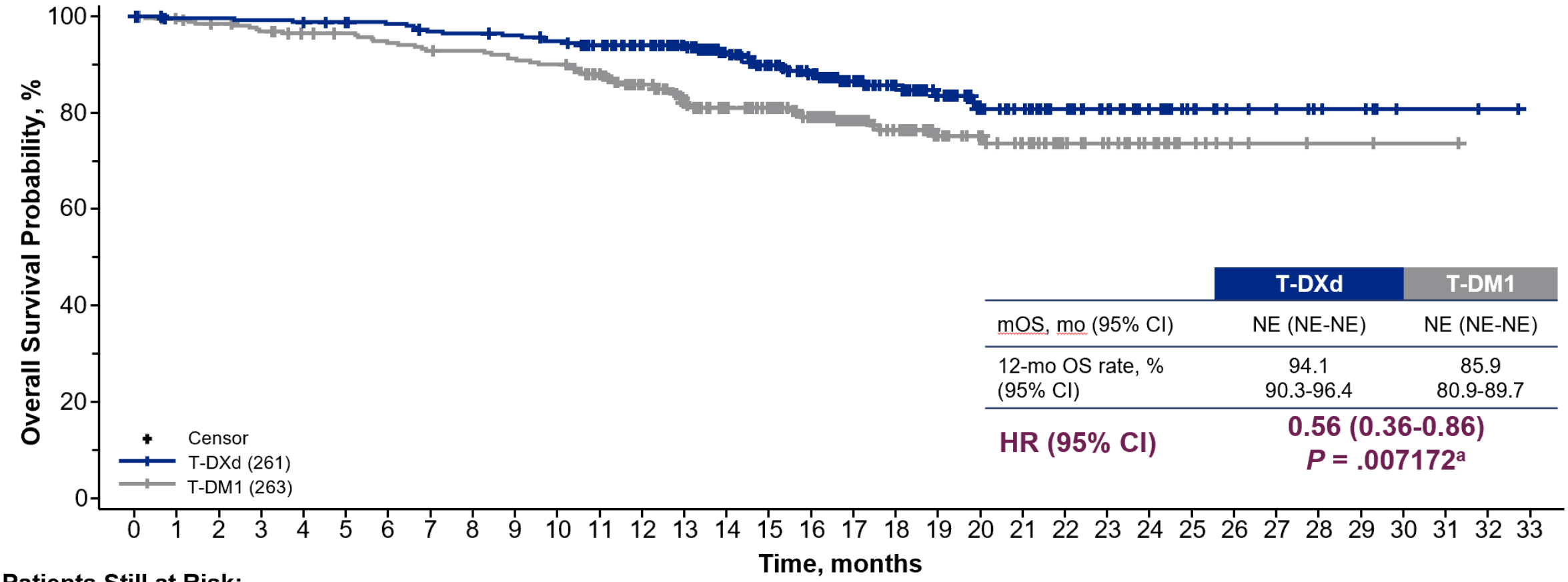
PFS in Key Subgroups

		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone Receptor Status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior Pertuzumab Treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral Disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior Lines of Therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Brain Metastases	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)



[a]Rapid progressors on (neo)adjuvant therapy were included. Line of therapy does not include endocrine therapy.

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 90.3-96.4	85.9 80.9-89.7
HR (95% CI)	**0.56 (0.36-0.86)**	
	***P* = .007172[a]**	

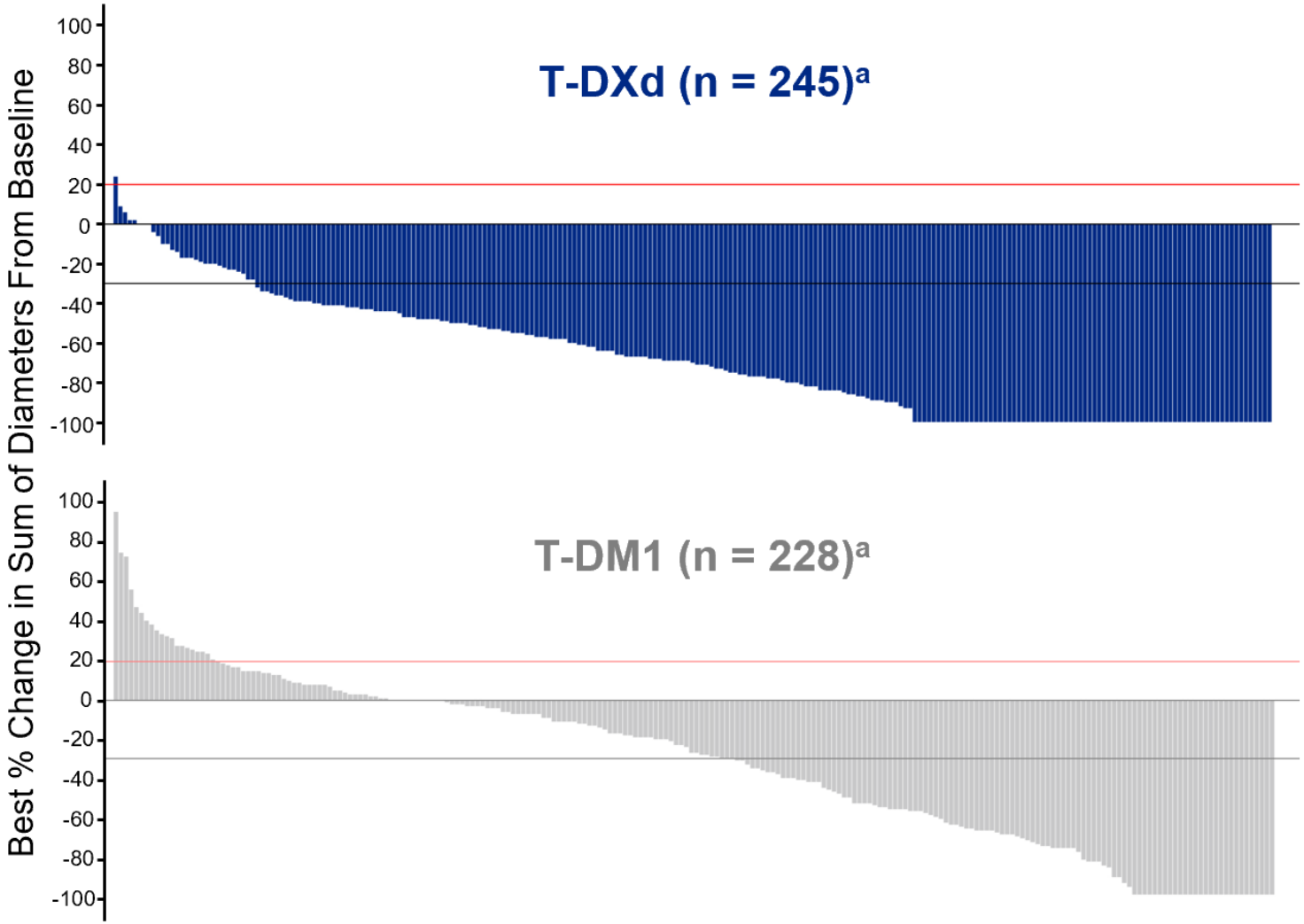
Patients Still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)

[a]*P* = .007172, but does not cross pre-specified boundary of *P* < .000265

Confirmed ORR and Best Overall Response



	T-DXd (n = 261)	T-DM1 (n = 263)
Confirmed ORR		
n (%)[b]	208 **(79.7)**	90 **(34.2)**
[95% CI]	[74.3-84.4]	[28.5-40.3]
	P < .0001	
CR	42 **(16.1)**	23 **(8.7)**
PR	166 **(63.6)**	67 **(25.5)**
SD	44 (16.9)	112 (42.6)
PD	3 (1.1)	46 (17.5)
Not evaluable	6 (2.3)	15 (5.7)
CR + PR + SD (DCR)	252 (96.6)	202 (76.8)

CR, complete response; DCR, disease control rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Only subjects with measurable disease at baseline and at least one postbaseline target lesion assessment are included. [b]Based on BICR.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.

Overall Safety Summary

n (%)	T-DXd (n = 257)	T-DM1 (n = 261)
Any drug-related TEAE	252 (98.1)	226 (86.6)
Drug-related TEAE Grade ≥3	116 (45.1)	104 (39.8)
Serious drug-related TEAE	28 (10.9)	16 (6.1)
Drug-related TEAE associated with discontinuation	33 (12.8)	13 (5.0)
Drug-related TEAE associated with dose reduction	55 (21.4)	33 (12.6)
Drug-related TEAE associated with an outcome of death	0 (0.0)	0 (0.0)

- **Median treatment duration was 14.3 months (range, 0.7-29.8) for T-DXd and 6.9 months (range, 0.7-25.1) for T-DM1**
- The most common TEAE associated with treatment discontinuation for T-DXd was ILD/pneumonitis[a] (8.2%) and for T-DM1 was thrombocytopenia[b] (2.7%)
- The most common TEAEs associated with dose reduction for T-DXd were nausea (6.2%) and neutropenia[c] (3.5%) and for T-DM1 were thrombocytopenia[b] (4.2%) and ALT and AST increased (2.7% each)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ILD, interstitial lung disease; TEAE, treatment-related adverse event.
Relationship to study drug was determined by the treating investigator.
[a]Interstitial lung disease includes events that were adjudicated as ILD and related to use of T-DXd or T-DM1 (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). [b]This category includes the preferred terms platelet count decreased and thrombocytopenia. [c]This category includes the preferred terms neutrophil count decreased and neutropenia.

Drug-Related TEAEs in ≥20% of Patients

System Organ Class Preferred term, n (%)	T-DXd (n = 257)		T-DM1 (n = 261)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Blood and lymphatic system disorders				
Neutropenia[a]	110 (42.8)	49 (19.1)	29 (11.1)	8 (3.1)
Anemia[b]	78 (30.4)	15 (5.8)	37 (14.2)	11 (4.2)
Leukopenia[c]	77 (30.0)	17 (6.6)	20 (7.7)	1 (0.4)
Thrombocytopenia[d]	64 (24.9)	18 (7.0)	135 (51.7)	65 (24.9)
Gastrointestinal disorders				
Nausea	187 (72.8)	17 (6.6)	72 (27.6)	1 (0.4)
Vomiting	113 (44.0)	4 (1.6)	15 (5.7)	1 (0.4)
Diarrhea	61 (23.7)	1 (0.4)	10 (3.8)	1 (0.4)
Constipation	58 (22.6)	0	25 (9.6)	0
General disorders				
Fatigue[e]	115 (44.7)	13 (5.1)	77 (29.5)	2 (0.8)
Investigations				
AST increased	60 (23.3)	2 (0.8)	97 (37.2)	13 (5.0)
ALT increased	50 (19.5)	4 (1.6)	71 (27.2)	12 (4.6)
Metabolism and nutrition disorders				
Decreased appetite	67 (26.1)	3 (1.2)	33 (12.6)	0
Skin and subcutaneous tissue disorders				
Alopecia[f]	93 (36.2)	1 (0.4)	6 (2.3)	0

Most drug-related TEAEs were gastrointestinal or hematological in nature

Adverse events were managed according to the protocol.
[a]This category includes the preferred terms neutrophil count decreased and neutropenia. [b]This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased. [c]This category includes the preferred terms white blood cell count decreased and leukopenia. [d]This category includes platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms fatigue, asthenia, and malaise. [f]Grade 1 alopecia: T-DXd = 26.5%, T-DM1 = 2.3%; grade 2, T-DXd = 9.3%.

Adverse Events of Special Interest

Adjudicated as drug-related ILD/pneumonitis[a], n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	7 (2.7)	18 (7.0)	2 (0.8)	0	0	27 (10.5)
T-DM1 (n = 261)	4 (1.5)	1 (0.4)	0	0	0	5 (1.9)

- There were no grade 4 or 5 adjudicated drug-related ILD/pneumonitis events observed with T-DXd

LVEF decrease, n (%)						
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 257)	1 (0.4)[b]	6 (2.3)[c]	0	0	0	7 (2.7)
T-DM1 (n = 261)	0	1 (0.4)[c]	0	0	0	1 (0.4)

- In the T-DXd arm, all reported adverse events of LVEF decrease were asymptomatic and no cases of cardiac failure occurred

LVEF, left-ventricular ejection fraction.
[a]Patients with prior history of ILD/pneumonitis requiring steroids were excluded. [b]Left ventricular dysfunction. [c]Decreased ejection fraction.

Conclusions

Daiichi-Sankyo

In the first randomized phase 3 trial in breast cancer, T-DXd demonstrated:

Highly clinically meaningful and statistically significant improvement in PFS compared with T-DM1 in patients with HER2-positive mBC

- PFS HR of 0.28 ($P = 7.8 \times 10^{-22}$)
- Consistent benefit seen across key subgroups and efficacy endpoints, with a confirmed ORR for T-DXd of 79.7% vs 34.2% for T-DM1 (CR, 16.1% vs 8.7%)

Encouraging OS trend at the time of first interim analysis

- 12-month OS rate for T-DXd was 94.1% vs 85.9% for T-DM1

A safety profile that is comparable between the 2 arms

- Similar rates of all grade and grade ≥3 drug-related TEAEs between arms
- There were no grade 4 or 5 ILD/pneumonitis events in either arm

These data support T-DXd becoming the standard of care for 2L HER2-positive mBC

279P

Trastuzumab Deruxtecan (T-DXd) in Patients with HER2-Positive Metastatic Breast Cancer: Updated Survival Results from a Phase 2 Trial (DESTINY-Breast01)

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Background

- Approximately 20% of breast cancers overexpress human epidermal growth factor receptor 2 (HER2)[1]
- T-DXd is approved for the treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens in the metastatic setting[2]
- DESTINY-Breast01 (NCT03248492) is an international, multicenter, open-label phase 2 study of T-DXd in patients with HER2-positive metastatic breast cancer (MBC); the results from this study supported global regulatory approval[3,4]
- Data from prior data cutoffs (primary: August 1, 2019[3]; initial update: June 8, 2020[4]) showed that patients receiving T-DXd had durable responses
  - At the initial update (June 8, 2020) presented at the 2020 San Antonio Breast Cancer Symposium, confirmed overall response rate (ORR) was 61.4%, duration of response (DOR) was 20.8 months, median progression-free survival (PFS) was 19.4 months, and median overall survival (OS) was 24.6 months[4]
  - Safety results were also consistent with previously reported data on T-DXd[3,4]
- Previous reports of median OS were limited by high percentages of censored patients; updated, mature survival results at the most recent data cutoff (March 26, 2021) are reported here

Conclusions

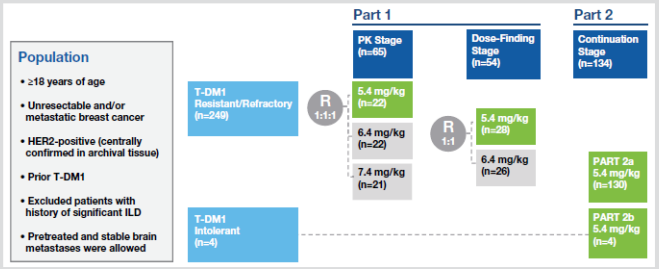
- With 6 months of additional follow-up, and more than half of the patients now with OS events, T-DXd demonstrated an estimated median OS of 29.1 months and a high landmark survival at 12, 18, and 24 months (85%, 75%, and 58%, respectively)
- These updated results continue to demonstrate a significant and sustained survival benefit of T-DXd in heavily previously treated patients with HER2-positive MBC (median prior lines of treatments, 6)
- Safety results were consistent with the known safety profile of T-DXd[3,4]
- T-DXd is currently undergoing further investigation in randomized controlled clinical trials assessing patients with:
  - HER2-positive BC (DESTINY-Breast02, DESTINY-Breast03, DESTINY-Breast05, DESTINY-Breast07, and DESTINY-Breast09)
  - HER2-low BC (DESTINY-Breast04 and DESTINY-Breast06)

Poster presented at the European Society for Medical Oncology (ESMO) 2021 Annual Meeting; September 16-21, 2021.

Methods

- DESTINY-Breast01 evaluated T-DXd in adult patients with HER2-positive (centrally confirmed; immunohistochemistry [IHC] 3+ or in-situ hybridization [ISH]+), metastatic or unresectable BC (**Figure 1**)
  - Patients whose disease progressed on or after trastuzumab emtansine were included in the study
  - Of the 253 patients who enrolled, 184 received T-DXd 5.4 mg/kg (primary analysis set)
- The primary endpoint was ORR, and additional endpoints included DOR, PFS, and OS

Figure 1. DESTINY-Breast01 Study Design



BC, breast cancer; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; PK, pharmacokinetic; R, randomization; T-DM1, trastuzumab emtansine.

Results

Patients

- A total of 184 patients were assessed; ages ranged from 28 to 96 years and the median number of prior lines of therapy in the metastatic setting was 6 (range, 2-27)
- Baseline demographic and clinical characteristics are shown in **Table 1**
- As of March 26, 2021, the median duration of follow-up was 26.5 months (range, 0.7-39.1), 6 months longer than that of the previous most recent analysis (**Table 2**)
- In total, 15% (n = 28) of patients remained on treatment and 85% (n = 156) discontinued
  - Discontinuations were due to progressive disease (46%, n = 85), adverse events (19%, n = 35), patient withdrawal (6%, n = 11), physician decision (4%, n = 8), death (4%, n = 7), or other (5%, n = 10)

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	T-DXd 5.4 mg/kg (N = 184)[a]
Age, years, median (range)	55.0 (28-96)
Female, %	100
Region, %	
Asia/North America/Europe	34.2/28.8/37.0
ECOG performance status 0/1/2, %	55.4/44.0/0.5
Hormone receptor positive/negative/unknown, %	52.7/45.1/2.2
HER2 expression, %[b]	
IHC 3+	83.7
IHC 2+; ISH+/IHC 1+; ISH+	15.2
Missing	1.1
Presence of visceral disease, %	91.8
Prior treatment for metastatic disease	
Median (range)	6 (2-27)
Trastuzumab/T-DM1, %	100/100
Pertuzumab, %	65.8
Other anti-HER2, %	54.3
Hormone therapy, %	48.9
Other systemic therapy, %	99.5

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]All 184 patients received ≥1 dose of T-DXd.
[b]HER2 status was centrally assessed in archival tissue according to guidelines of the American Society of Clinical Oncology/College of American Pathologists.

Table 2. Summary of Efficacy

Intent-to-Treat Analysis	August 2019 DCO T-DXd 5.4 mg/kg (N = 184)	June 2020 DCO T-DXd 5.4 mg/kg (N = 184)	March 2021 DCO T-DXd 5.4 mg/kg (N = 184)
Median duration of follow up (range), months	11.1 (0.7-19.9)	20.5 (0.7-31.4)	26.5 (0.7-39.1)
Patients remaining on treatment, n (%)	79 (42.9)	37 (20.1)	28 (15.2)
Confirmed ORR[a] by ICR, n (%) 95% CI	112 (60.9) 53.4-68.0	113[b] (61.4) 54.0-68.5	114 (62.0) 54.5-69.0
CR	11 (6.0)	12 (6.5)	13 (7.1)
PR	101 (54.9)	101 (54.9)	101 (54.9)
SD	67 (36.4)	66 (35.9)	65 (35.3)
PD	3 (1.6)	3 (1.6)	3 (1.6)
Not evaluable	2 (1.1)	2 (1.1)	2 (1.1)
Median DOR (95% CI), months	14.8 (13.8-16.9)	20.8[b] (15.0-NE)	18.2 (15.0-NE)
Median TTR (95% CI), months	1.6 (1.4-2.7)		
Median PFS (95% CI), months	16.4 (12.7-NE)	19.4 (14.1-NE)	19.4 (14.1-25.0)
Median OS (95% CI), months	NE (NE-NE)	24.6 (23.1-NE)	29.1 (24.6-36.1)

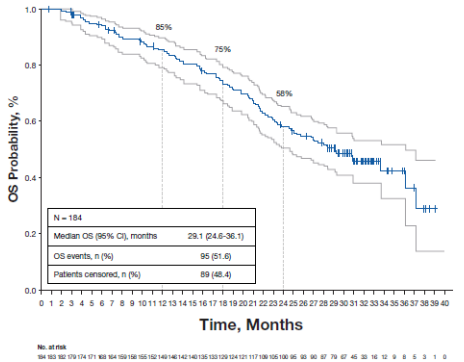
CR, complete response; DCO, data cutoff; DOR, duration of response; ICR, independent central review; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTR, time to response.
[a]ORR = CR + PR.
[b]One patient had a PR prior to the June 8, 2020 cutoff date that was confirmed after the cutoff date. The patient had a confirmed best overall response of PR on the first PR date in the central data but was not included in the analysis of DOR.

Results (continued)

Efficacy

- As of March 26, 2021, median duration of OS follow-up was 31.1 months (95% CI, 30.7-32.0)
- The updated median OS was 29.1 months (95% CI, 24.6-36.1), and with greater data maturity, more than half of the patients had OS events (95/184, 51.6%) (**Figure 2**)
  - Estimated 12-month OS was 85% (95% CI, 79-90)
  - Estimated 18-month OS was 75% (95% CI, 67-80)
  - Estimated 24-month OS was 58% (95% CI, 51-65)

Figure 2. Kaplan-Meier Analysis of Overall Survival (OS)



- A summary of efficacy results is shown in **Table 2**
- Best percent change from baseline in target lesions is shown in **Figure 3**
- At data cutoff, median PFS was 19.4 months (95% CI, 14-25), which was unchanged from the prior June 2020 data cutoff, with 76 (41%) PFS events (**Figure 4**)
- Median DOR was 18.2 months (95% CI, 15-NE) at the updated data cutoff (March 2021) (**Figure 5**)

Figure 3. Best Percent Change From Baseline in Target Lesions

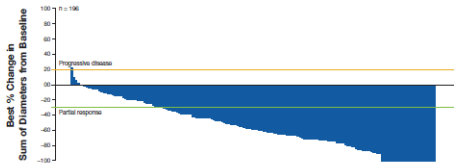


Figure 4. Kaplan-Meier Analysis of Progression-Free Survival (PFS)

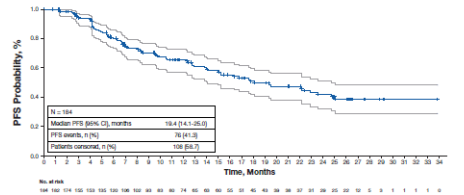
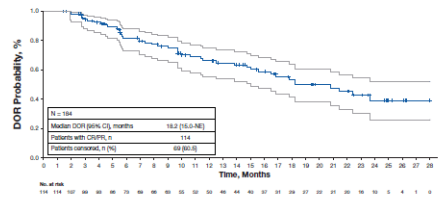


Figure 5. Kaplan-Meier Analysis of Duration of Response (DOR)



Safety Summary

- As most patients had previously discontinued treatment, the overall safety profile of T-DXd was consistent with prior results[3,4]
- These results continue to demonstrate a generally tolerable safety profile in patients treated with T-DXd (**Table 3**)
- One new case of grade 1 T-DXd–related interstitial lung disease (ILD) as determined by independent adjudication committee was reported since the last data cutoff (**Table 4**)
  - With ongoing follow-up, there were no additional reported cases of grade ≥3 ILD/pneumonitis events

Table 3. Overall Safety Summary

Type of Adverse Event,[a] n (%)	August 2019 DCO T-DXd 5.4 mg/kg (N = 184)	June 2020 DCO T-DXd 5.4 mg/kg (N = 184)	March 2021 DCO T-DXd 5.4 mg/kg (N = 184)
Any TEAE	183 (99.5)	183 (99.5)	183 (99.5)
Drug-related	183 (99.5)	183 (99.5)	183 (99.5)
TEAE grade ≥3	105 (57.1)	113 (61.4)	116 (63.0)
Drug-related	89 (48.4)	97 (52.7)	99 (53.8)
Dose adjustments			
TEAE associated with discontinuation	28 (15.2)	34 (18.5)	35 (19.0)
Drug-related	27 (14.7)	33 (17.9)	33 (17.9)
TEAE associated with dose reduction	43 (23.4)	44 (23.9)	46 (25.0)
Drug-related	40 (21.7)	39 (21.2)[b]	43 (23.4)
TEAE associated with dose interruption	65 (35.3)	75 (40.8)	77 (41.8)
Drug-related	53 (28.8)	60 (32.6)	60 (32.6)
Death			
TEAE associated with death[c]	9 (4.9)	10 (5.4)	10 (5.4)
Drug-related	2 (1.1)	3 (1.6)	3 (1.6)

DCO, data cutoff; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]Relationship to study drug was determined by the treating investigator.
[b]Based on updated investigator assessment.
[c]Each of the following TEAEs was associated with a fatal outcome: respiratory failure, acute respiratory failure, disease progression, general physical health deterioration, lymphangitis, pneumonia, pneumonitis, shock hemorrhagic; 1 patient had 2 TEAEs associated with death: acute kidney injury and acute hepatic failure.

Table 4. Drug-related Interstitial Lung Disease/Pneumonitis[a]

Interstitial Lung Disease, n (%)	August 2019 DCO T-DXd 5.4 mg/kg (N = 184)	June 2020 DCO T-DXd 5.4 mg/kg (N = 184)	March 2021 DCO T-DXd 5.4 mg/kg (N = 184)
Grade 1	5 (2.7)	6 (3.3)	7 (3.8)
Grade 2	15 (8.2)	16 (8.7)	16 (8.7)
Grade 3	1 (0.5)	1 (0.5)	1 (0.5)
Grade 4	0	0	0
Grade 5	4 (2.2)	5 (2.7)	5 (2.7)
Any grade/total	25 (13.6)	28 (15.2)	29 (15.8)

DCO, data cutoff; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]As determined by an independent interstitial lung disease adjudication committee. At data cutoff, 1 grade 1 event and 1 grade 3 event were pending adjudication.

Acknowledgments

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Disclosures

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4. Modi S et al. *Amer Assoc Cancer Research*. 2021;81(4):PD3-06.

Primary Data from DESTINY-Lung01: A Phase 2 Trial of Trastuzumab Deruxtecan (T-DXd) in Patients With *HER2*-Mutated (*HER2*m) Metastatic Non–Small Cell Lung Cancer (NSCLC)

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On behalf of the DESTINY-Lung01 investigators

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High Unmet Medical Need in Patients with *HER2*m NSCLC

- *HER2* mutations drive ~3% of nonsquamous NSCLC and are associated with slightly younger age, female sex, never-smoking history, a poor prognosis, and an increased incidence of brain metastasis[1-5]
- There are no approved HER2-targeted therapies for patients with NSCLC[6]
  - *HER2*m status is not routinely assessed[7], and this population is treated with standard chemotherapy and/or immunotherapy[8-14]
  - Efficacy in second- or later-line settings is limited (ORR, 7%-27%) [8-14]
- T-DXd is a HER2 antibody-drug conjugate[15,16] approved in various countries worldwide for the treatment of metastatic HER2-positive breast and gastric cancers

DESTINY-Lung01 assessed the efficacy and safety of T-DXd in patients with *HER2*m NSCLC who had relapsed on or were refractory to standard treatment

In an interim analysis (data cutoff November 25, 2019), results showed promising T-DXd activity[17]

Results from the primary analysis of the fully enrolled cohort of patients with a *HER2* mutation are presented

HER2, human epidermal growth factor 2; *HER2*m, *HER2*-mutated; NSCLC, non–small cell lung cancer; ORR, objective response rate; T-Dxd, trastuzumab deruxtecan.

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DESTINY-Lung01 Study Design

Multicenter, international, 2-cohort phase 2 trial (NCT03505710)

Key eligibility criteria

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

Cohort 1: HER2-overexpressing[c] (IHC 3+ or IHC 2+)
T-DXd 6.4 mg/kg q3w
N = 49

Cohort 1a: HER2-overexpressing[c] (IHC 3+ or IHC 2+)
T-DXd 5.4 mg/kg q3w
N = 41

Cohort 2: *HER2*-mutated T-DXd 6.4 mg/kg q3w N = 42

Cohort 2 expansion: *HER2*-mutated T-DXd 6.4 mg/kg q3w N = 49

Primary end point

- Confirmed ORR by ICR[d]

Secondary end points

- DOR
- PFS
- OS
- DCR
- Safety

Exploratory end point

- Biomarkers of response

Data cutoff: May 3, 2021

- 91 patients with *HER2*m NSCLC were enrolled and treated with T-DXd
- 15 patients (16.5%) remain on treatment to date
- 76 patients (83.5%) discontinued, primarily for progressive disease (37.4%) and adverse events (29.7%)

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

DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; q3w, every 3 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Demographics and Baseline Characteristics

	T-DXd (N = 91)
Age, median (range), years	60.0 (29.0-88.0)
Female, %	65.9
Race, %	
Asian	34.1
White	44.0
Black	1.1
Other	20.9
Region, %	
Asia	25.3
Europe	36.3
North America	38.5
ECOG PS, %	
0 | 1	25.3 | 74.7
***HER2* mutation, %**	
Kinase domain	93.4
Extracellular domain	6.6
Asymptomatic CNS metastases at baseline, %	36.3
Smoking status, %	
Never | Former | Current	57.1 | 40.7 | 2.2
History of prior lung resection, %	22.0

CNS, central nervous system.

Prior Therapies

	Patients (N = 91)
History of any prior systemic cancer therapy, n (%)	**90 (98.9)**
Prior lines of treatment, median (range)	2 (0-7)[a]
Prior treatment, n (%)	
Platinum-based therapy	86 (94.5)
Anti–PD-(L)1 therapy	60 (65.9)
Platinum-based and anti–PD-(L)1 therapy[b]	57 (62.6)
Docetaxel	18 (19.8)
HER2 TKI[c]	13 (14.3)

[a]One patient was enrolled without receiving prior cancer therapy
[b]Given separately or in combination
[c]Patients previously treated with a HER2 antibody or an antibody-drug conjugate were ineligible, but those who previously received a HER2 TKI such as afatinib, pyrotinib, or poziotinib were allowed

PD-(L)1, programmed cell death (ligand) 1; TKI, tyrosine kinase inhibitor.

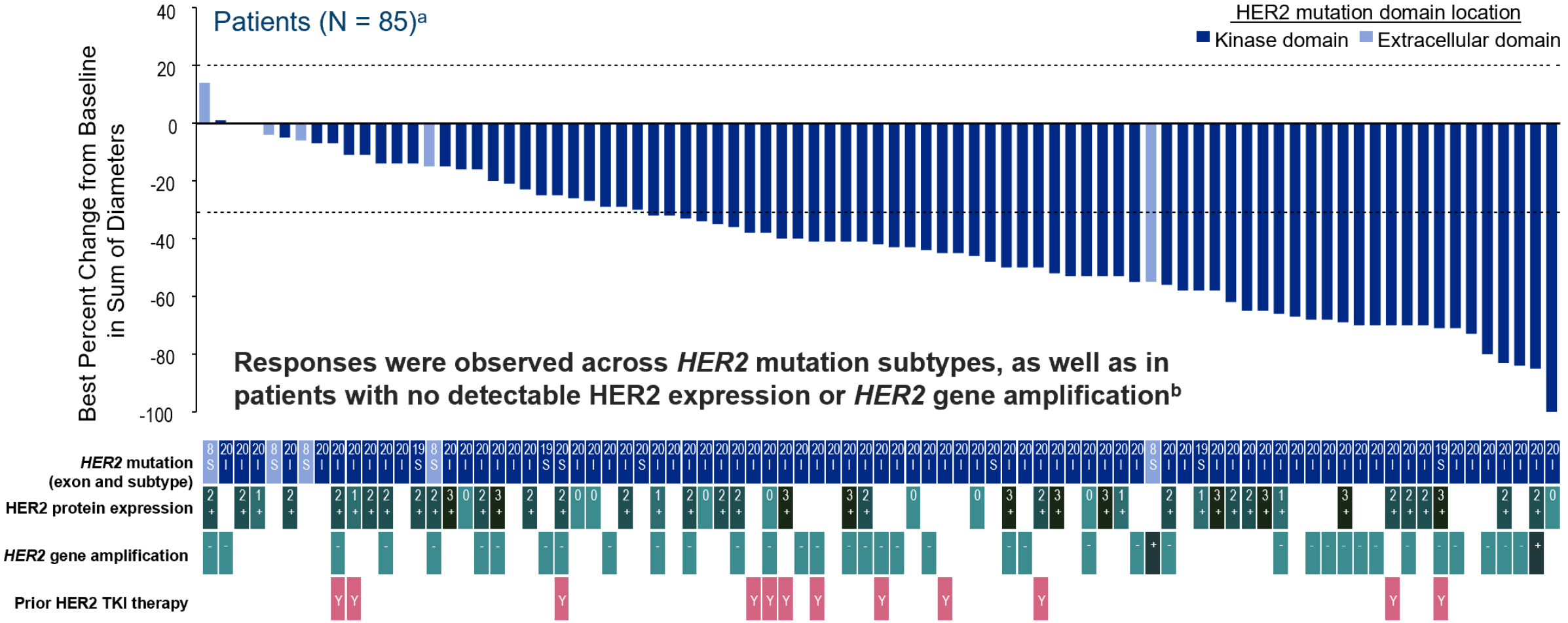
Confirmed ORR, Best Overall Response, and DoR

	Patients (N = 91)
Confirmed ORR[a], n (%)	**50 (54.9)** (95% CI, 44.2-65.4)
Best overall response, n (%)	
CR	**1 (1.1)**
PR	**49 (53.8)**
SD	**34 (37.4)**
PD	**3 (3.3)**
Not evaluable	**4 (4.4)**
DCR, n (%)	84 (92.3) (95% CI, 84.8-96.9)
Median DoR, months	9.3 (95% CI, 5.7-14.7)
Median follow up, months	13.1 (range, 0.7-29.1)

[a]Primary endpoint

CR, complete response; DoR, duration of response; PD, progressive disease; PR, partial response; SD, stable disease.

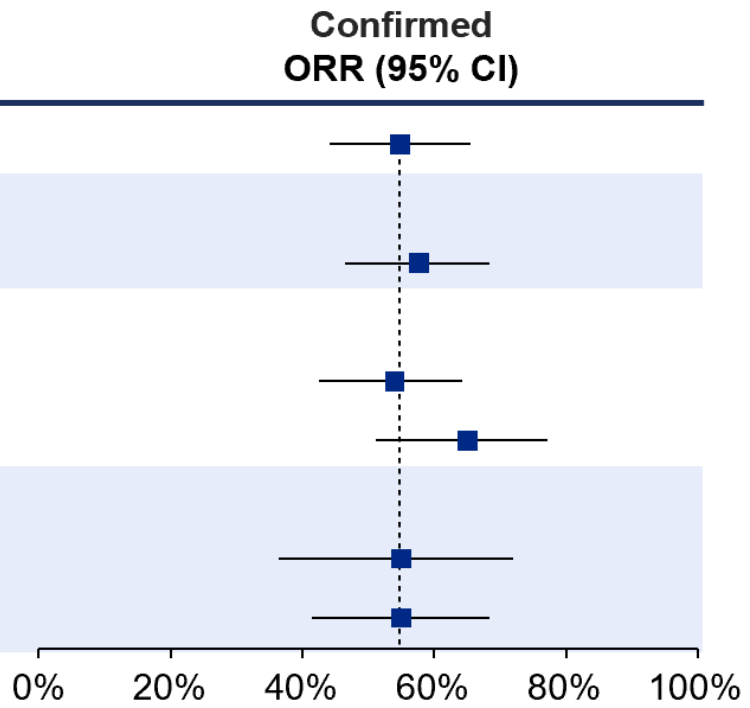
Best Percentage Change of Tumor Size From Baseline



[a]Best change in tumor size by ICR for 85 of 91 patients for whom baseline and postbaseline data were available. Baseline is last measurement taken before enrollment. [b]The Oncomine™ Dx Target Test (Thermo Fisher Scientific) was used to confirm local HER2 mutation status and to determine HER2 amplification status. HER2 protein expression status was determined by immunohistochemistry using a modified PATHWAY anti-HER2 (4B5) (Ventana Medical Systems, Inc.) assay. Shown is best (minimum) percentage change from baseline in the sum of diameters for all target lesions; (-), negative; (+), positive; I, insertion; N, no; S, substitution; Y, yes. Blank cells (except for the prior HER2 TKI therapy row) indicate patients whose tumor samples were not evaluable or assessed. The upper dashed horizontal line indicates a 20% increase in tumor size in the patients who had disease progression and the lower dashed line indicates a 30% decrease in tumor size (partial response).

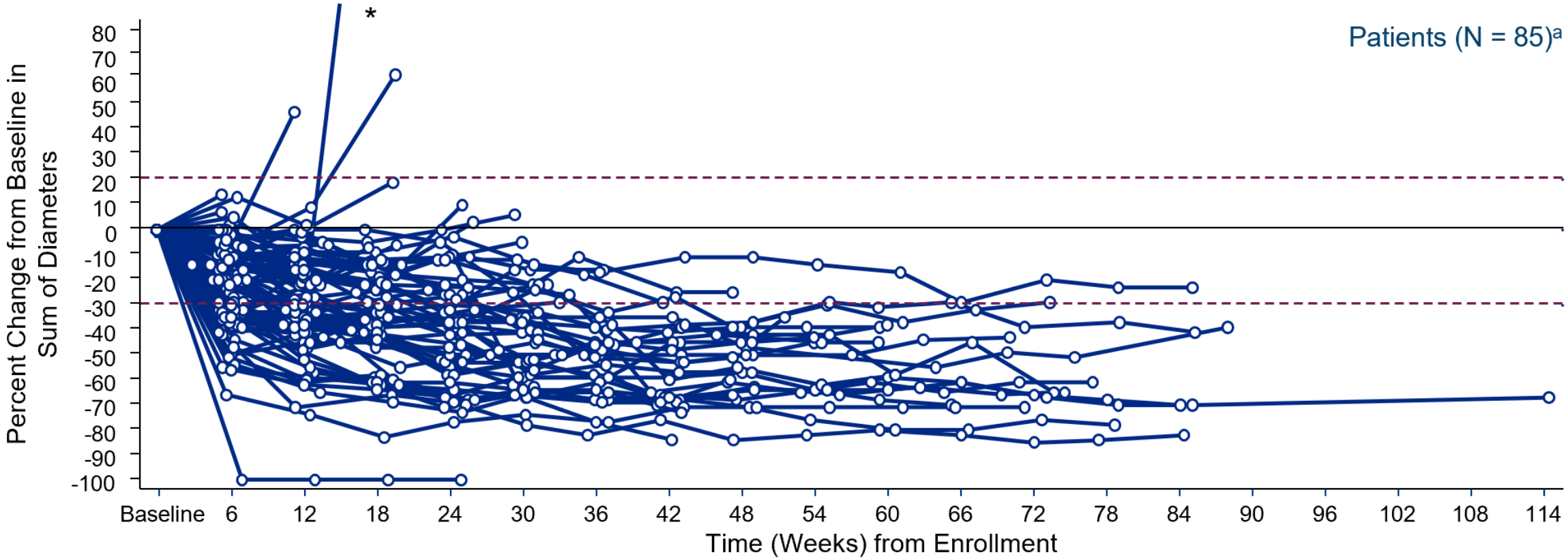
Response to T-DXd in Subgroups

	No. of Responders	Confirmed ORR (95% CI)
All patients	50/91	54.9 (44.2-65.4)
***HER2* mutation domain**		
Kinase domain	49/85	57.6 (46.5-68.3)
Prior treatment received		
Platinum-based therapy	46/86	53.5 (42.4-64.3)
Platinum-based therapy and anti-PD-(L)1 therapy[a]	37/57	64.9 (51.1-77.1)
Asymptomatic CNS metastasis at baseline[b]		
Yes	18/33	54.5 (36.4-71.9)
No	32/58	55.2 (41.5-68.3)



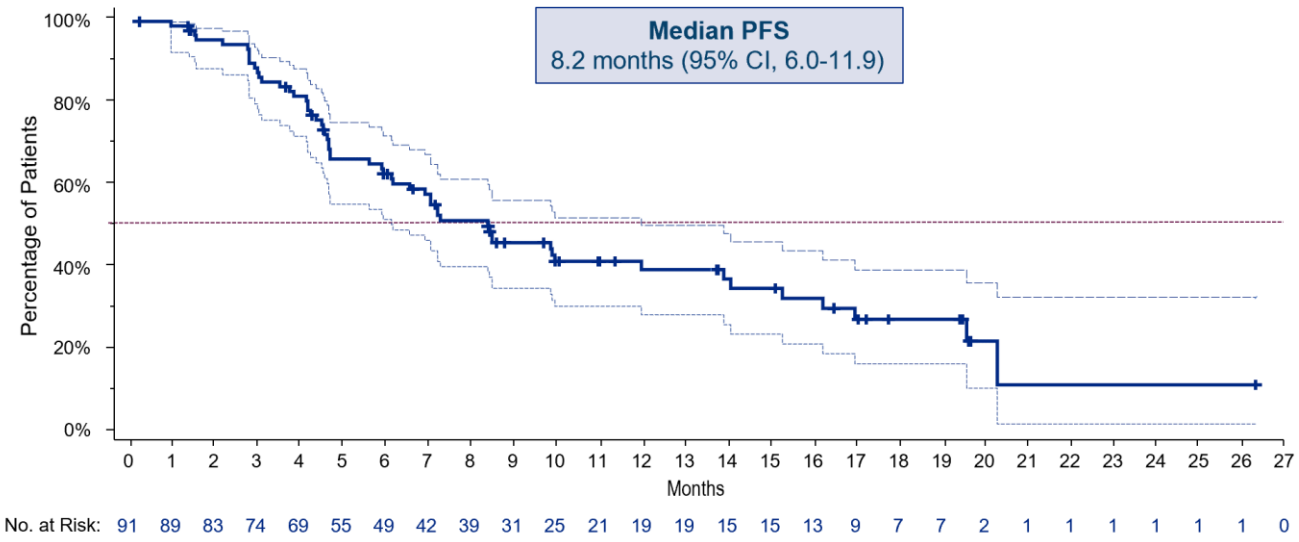
[a]Given separately or in combination
[b]Patients had asymptomatic brain metastases not requiring ongoing steroid or anticonvulsant therapy

Percentage Change of Tumor Size Over Time

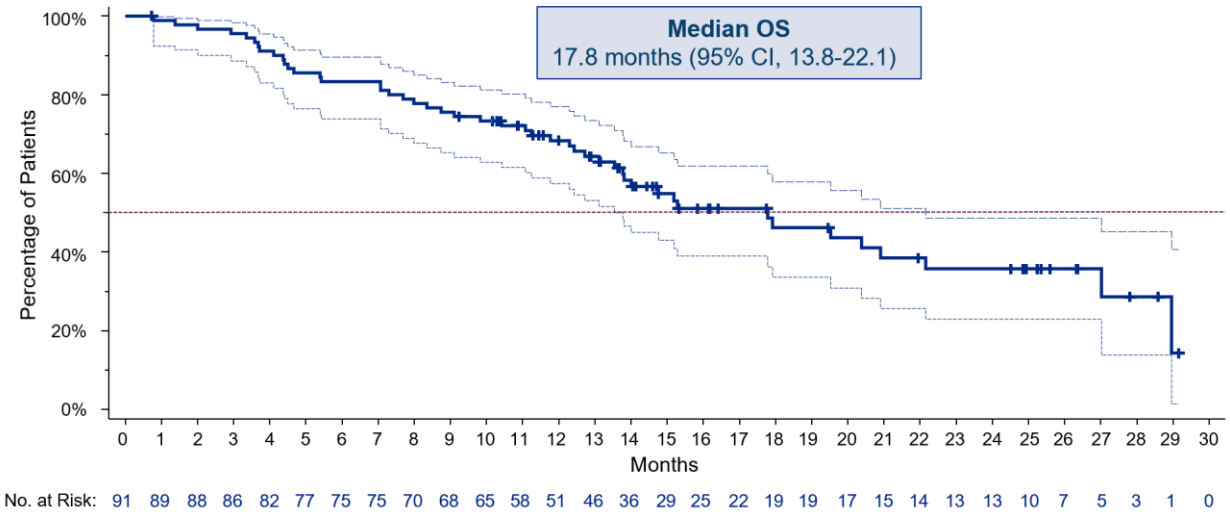


Median follow-up was 13.1 months (range, 0.7-29.1 months)
[a]Includes patients for whom baseline and postbaseline data were available.
*Patient outlier with a tumor increase of 236% from baseline at Week 18.

Progression-free Survival and Overall Survival



Median follow-up was 13.1 months (range, 0.7-29.1)
PFS assessed by ICR using RECIST v1.1., the median was based on Kaplan-Meier estimate, and 95% CI for median was computed using the Brookmeyer-Crowley method, and dashed lines indicate the 95% CI. Of 91 patients, 41 had progressive disease and 15 had died by the data cutoff date. Data for 35 patients were censored as indicated by tick marks; patients were censored if they discontinued treatment.



Median follow-up was 13.1 months (range, 0.7-29.1 months)
Dashed lines indicate the 95% CI. Of 91 patients, 47 had died by the data cutoff date. Data for 44 patients were censored as indicated by tick marks; patients were censored if they discontinued treatment.

Overall Safety Summary

n (%)	Patients (N = 91)
Any drug-related TEAE	88 (96.7)
Drug-related TEAE Grade ≥3	42 (46.2)
Serious drug-related TEAE	18 (19.8)
Drug-related TEAE associated with discontinuation[a]	23 (25.3)
Drug-related TEAE associated with dose reduction	31 (34.1)
Drug-related TEAE associated with an outcome of death	2 (2.2)[c]

- Median treatment duration was 6.9 months (range, 0.7-26.4 months)
- The most common drug-related TEAEs associated with treatment discontinuation were investigator-reported pneumonitis (13.2%) and ILD (5.5%)
- The most common drug-related TEAEs associated with dose reduction were nausea (11.0%) and fatigue (8.8%)

Relationship to study drug was determined by the treating investigator. [a]Pneumonitis (n = 12) and interstitial lung disease (n = 5) were among the drug-related TEAEs associated with discontinuation. [b]1 patient experienced grade 3 ILD as reported by investigator and died. The reported ILD was subsequently adjudicated as grade 5 by the interstitial lung disease adjudication committee.
ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.

Drug-related TEAEs Reported by Investigator

n (%)	Patients (N = 91)	
	Any grade	Grade ≥3
Patients with ≥1 drug-related TEAEs	88 (96.7)	42 (46.2)
Drug-related TEAEs with ≥20% incidence in all patients		
Nausea	66 (72.5)	8 (8.8)
Fatigue[a]	48 (52.7)	6 (6.6)
Alopecia	42 (46.2)	0
Vomiting	36 (39.6)	3 (3.3)
Neutropenia[b]	32 (35.2)	17 (18.7)
Anemia[c]	30 (33.0)	9 (9.9)
Diarrhea	29 (31.9)	3 (3.3)
Decreased appetite	27 (29.7)	0
Leukopenia[d]	21 (23.1)	4 (4.4)
Constipation	20 (22.0)	0

[a]This category includes the preferred terms fatigue, asthenia, and malaise.
[b]This category includes the preferred terms neutrophil count decreased and neutropenia.
[c]This category includes the preferred terms hemoglobin decreased, red blood cell count decreased, anemia, and hematocrit decreased.
[d]This category includes the preferred terms white blood cell count decreased and leukopenia.

Adjudicated Drug-Related ILD

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
n (%)	3 (3.3)	15 (16.5)	4 (4.4)	0	2 (2.2)	24 (26.4)

- The median time to onset of first reported drug-related ILD/pneumonitis was 141 days (range, 14-462 days), with a median duration of 43 days (95% CI, 24-94 days)
- 75% of adjudicated drug-related ILD/pneumonitis[a] cases were of low grade (Grade 1/2)
- 21 of 24 patients with adjudicated drug-related ILD/pneumonitis received ≥1 dose of glucocorticoids.
  However, not all glucocorticoid treatment was administered per the ILD/pneumonitis management guidelines[b]
- At the time of data cutoff, 54% (13/24) of investigator-reported cases had fully resolved

[a]Drug-related ILD/pneumonitis was determined by the Independent Adjudication Committee based on the current MedDRA version for the narrow ILD standard MedDRA query (SMQ), selected terms from the broad ILD SMQ, and respiratory failure and acute respiratory failure. [b]Events of ILD/pneumonitis in the present study were actively managed based on the protocol-defined ILD/pneumonitis management guidelines.

Conclusions

- T-DXd demonstrated **robust and durable anticancer activity** in patients with previously-treated *HER2*m NSCLC
  - Efficacy was consistently observed across subgroups, including in those patients with stable CNS metastases
  - Exploratory analyses demonstrated anticancer activity across different *HER2* mutation subtypes, as well as in patients with no detectable HER2 expression or *HER2* gene amplification
- Overall, the **safety profile** was **consistent** with previously reported studies
  - Most adjudicated drug-related ILD/pneumonitis cases were of low grade
  - ILD/pneumonitis remains an important identified risk. Effective early detection and management are critical in preventing high-grade ILD/pneumonitis
- The 5.4 mg/kg dose is being explored in future studies to evaluate the optimal dosing regimen in patients with *HER2*m NSCLC (DESTINY-Lung02; NCT04644237)
- DESTINY-Lung01 provides **compelling evidence of positive benefit/risk balance** with T-DXd in the 2L+ setting and supports its establishment as a **potential new treatment standard**

Publication in The New England Journal of Medicine

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in *HER2*-Mutant Non–Small-Cell Lung Cancer

Bob T. Li, M.D., Ph.D., M.P.H., Egbert F. Smit, M.D., Ph.D., Yasushi Goto, M.D., Ph.D., Kazuhiko Nakagawa, M.D., Hibiki Udagawa, M.D., Julien Mazières, M.D., Misako Nagasaka, M.D., Ph.D., Lyudmila Bazhenova, M.D., Andreas N. Saltos, M.D., Enriqueta Felip, M.D., Ph.D., Jose M. Pacheco, M.D., Maurice Pérol, M.D., Luis Paz-Ares, M.D., Kapil Saxena, M.D., Ryota Shiga, B.Sc., Yingkai Cheng, M.D., Ph.D., Suddhasatta Acharyya, Ph.D., Patrik Vitazka, M.D., Ph.D., Javad Shahidi, M.D., David Planchard, M.D., Ph.D., and Pasi A. Jänne, M.D., Ph.D., for the DESTINY-Lung01 Trial Investigators*

Primary Analysis of a Phase 2 Single-Arm Trial of Trastuzumab Deruxtecan (T-DXd) in Western Patients With HER2-Positive (HER2+) Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Cancer Who Progressed on or After a Trastuzumab-containing Regimen

Eric Van Cutsem, MD[a], Maria di Bartolomeo, Elizabeth Smyth, Ian Chau, Haeseong Park, Salvatore Siena, Sara Lonardi, Zev A. Wainberg, Jaffer Ajani, Joseph Chao, Jabed Seraj, Yoshinori Kawaguchi, Amy Qin, Jasmeet Singh, Gerold Meinhardt, Geoffrey Ku
On behalf of the DESTINY-Gastric02 investigators

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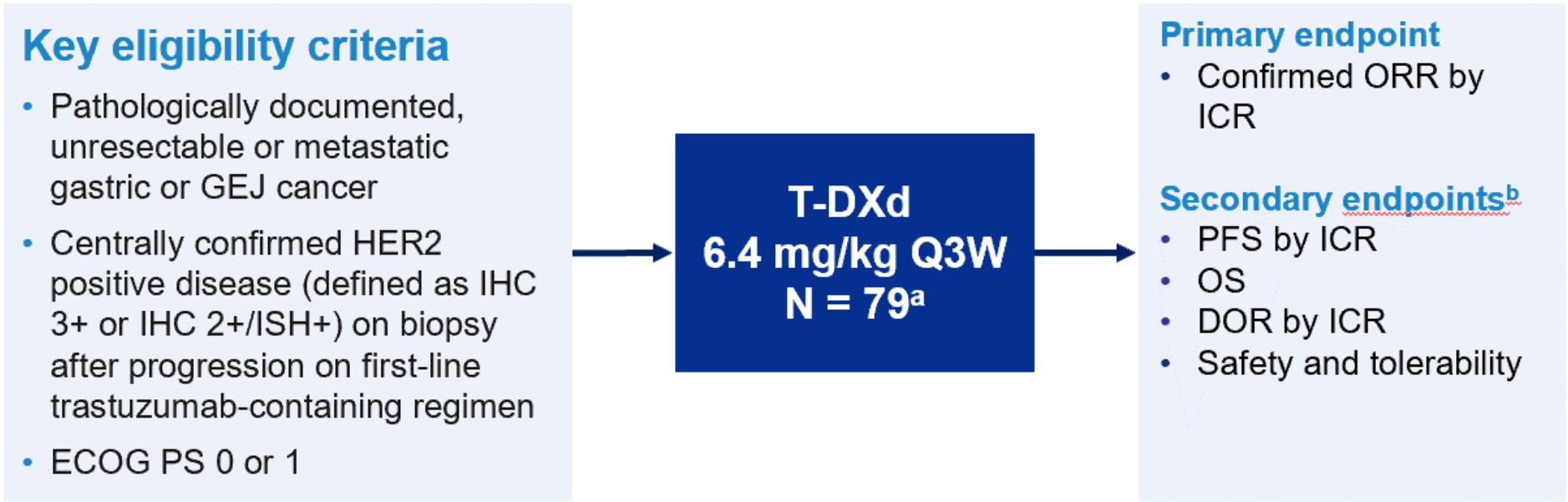
DESTINY-Gastric02 Study Design

An open-label, multicenter phase 2 study in Western patients with HER2+ gastric or GEJ cancer (NCT04014075)



- DESTINY-Gastric02 is the first study focused only on second-line T-DXd monotherapy in Western patients with HER2+ gastric/GEJ cancer who have progressed on a trastuzumab-containing regimen
  - It is the follow-on study to DESTINY-Gastric01, which evaluated T-DXd third-line or later in Asian patients[1]
- Patients were enrolled in Europe (Belgium, Great Britain, Italy, Spain) and the United States (data cutoff: April 9, 2021)

[a]Enrollment of 80 patients was planned; actual enrollment was 79 patients.
[b]Other secondary endpoints were ORR, PFS, and DOR by investigator assessment, pharmacokinetics, anti-drug antibodies, and patient-reported outcomes.
1. Shitara K et al. *N Engl J Med*. 2020;382:2419-30.
DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; Q3W, every 3 weeks.

Patient Demographics and Disease Characteristics

Demographics	Patients N = 79
Age	
Median (range), years	60.7 (20.3 – 77.8)
<65, %	58.2
≥65, %	41.8
Male, %	72.2
Race, %	
White	87.3
Black or African American	1.3
Asian	5.1
American Indian or Alaskan native	0
Native Hawaiian or Pacific Islander	1.3
Other	3.8
Missing	1.3

Disease characteristics	Patients N = 79
ECOG PS, %	
0	36.7
1	63.3
HER2 expression, %	
IHC 3+	86.1
IHC 2+/ISH+	12.7
Not evaluable	1.3[a]
Adenocarcinoma, %	98.7
Intestinal	24.1
Diffuse	1.3
Mixed	1.3
Unknown	72.2[b]
Cancer type, %	
Gastric	34.2
GEJ	65.8
Number of metastatic sites, %	
<2	6.3
≥2	93.7
Liver metastasis at baseline, %	63.3
Time from diagnosis, median (range), mo	14.2 (3.6 – 88.5)

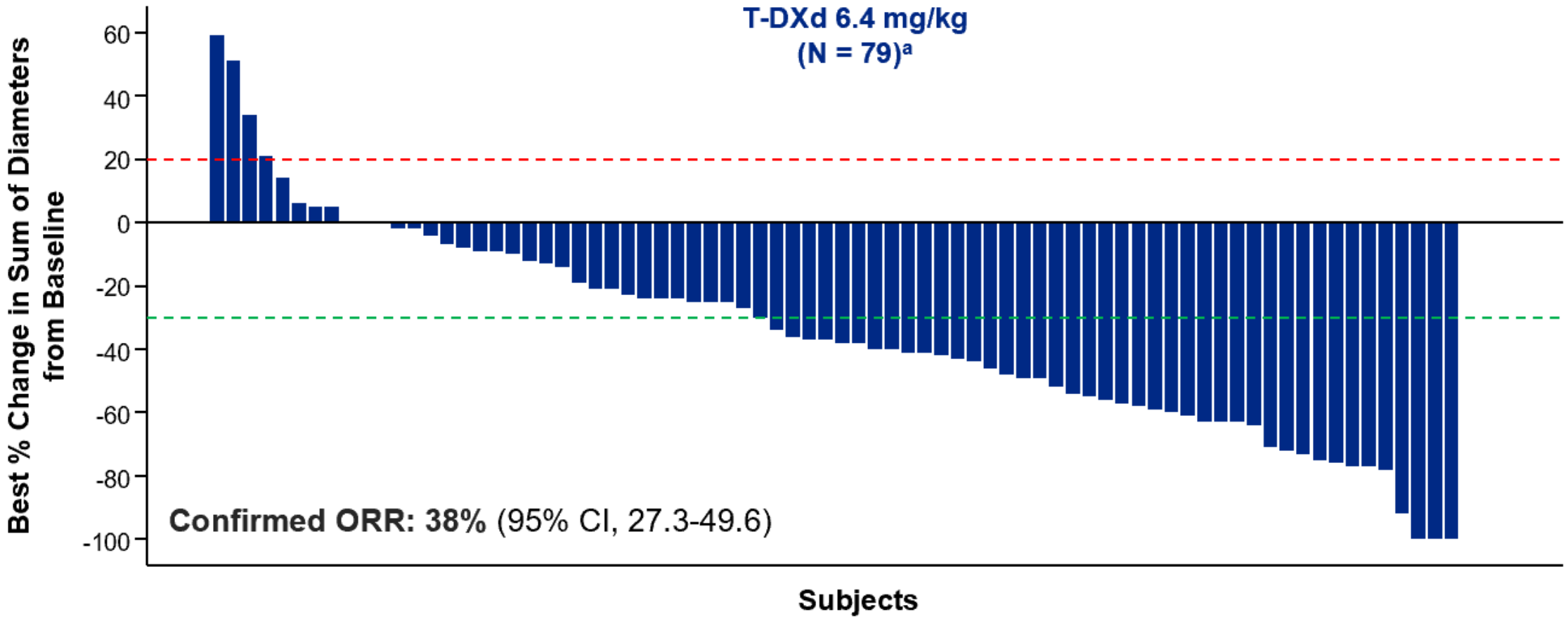
[a]Patient's enrollment was based on local laboratory testing.
[b]One patient had non-adenocarcinoma histological subtype.

Efficacy Endpoints

	Patients (N = 79)
Confirmed ORR[a], n (%)	**30 (38)** (95% CI, 27.3-49.6)
Confirmed best overall response, n (%)	
CR	**3 (3.8)**
PR	**27 (34.2)**
SD	**34 (43.0)**
PD	**13 (16.5)**
Not evaluable	**2 (2.5)**
Median DOR,[b] months	8.1 (95% CI, 4.1-NE)
Confirmed DCR[c], n (%)	64 (81.0) (95% CI, 70.6-89.0)
Median TTR, months	1.4 (95% CI, 1.4-2.6)
Median PFS,[d] months	5.5 (95% CI, 4.2-7.3)
Median follow up, months	5.7 (range, 0.7-15.2)

Cutoff date: April 9, 2021.
[a]Primary endpoint. [b]Secondary endpoint analysis based on responders (n=30); 21 patients were censored (reasons: initiating new anticancer therapy, adequate tumor assessment no longer available, and ongoing without occurrence of progressive disease or death). [c]Exploratory endpoint. [d]Secondary endpoint analysis in the full analysis set based on 42 events (36 PD, 6 deaths).
BOR, best overall response; CR, complete response; DCR, disease control rate; mo, months; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease; TTR, time to response.

Best Percentage Change of Tumor Size from Baseline



[a]3 patients were missing baseline or post-baseline target lesion assessment.
Red line at 20% indicates progressive disease; green line at -30% indicates partial response.
Analysis conducted in the full analysis set.

Overall Safety Summary

n (%)	Patients (N = 79)
Any drug-related TEAE	74 (93.7)
Drug-related TEAE Grade ≥3	21 (26.6)
Serious drug-related TEAE	8 (10.1)
Drug-related TEAE associated with discontinuation	7 (8.9)
Drug-related TEAE associated with dose reduction	15 (19.0)
Drug-related TEAE associated with an outcome of death	1 (1.3)

- Median treatment duration was 4.3 months (range, 0.7-15.9 months)
- The most common drug-related TEAEs associated with treatment discontinuation were investigator-reported pneumonitis (3.8%) and ILD (2.5%)
- The most common drug-related TEAEs associated with dose reduction were nausea (7.6%) and decreased neutrophil count (5.1%)

Data are shown as number (%) of patients unless stated otherwise.
ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.

Drug-related TEAEs in ≥15% of Patients

n (%)	Patients (N = 79) Any Grade	Grade ≥3
Patients with ≥1 drug-related TEAEs	74 (93.7)	21 (26.6)
Drug-related TEAEs with ≥15% incidence in all patients		
Nausea	46 (58.2)	3 (3.8)
Fatigue	29 (36.7)	3 (3.8)
Vomiting	26 (32.9)	1 (1.3)
Diarrhea	22 (27.8)	1 (1.3)
Decreased appetite	18 (22.8)	1 (1.3)
Alopecia	17 (21.5)	0
Anemia	15 (19.0)	6 (7.6)
Decreased platelet count	13 (16.5)	1 (1.3)
Decreased neutrophil count	12 (15.2)	6 (7.6)

Adjudicated Drug-Related ILD/Pneumonitis

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
n (%)	2 (2.5)	3 (3.8)	0	0	1 (1.3)	6 (7.6)

- Median time to onset of adjudicated drug-related ILD/pneumonitis was 80.5 days (range, 53-85 days), with a median duration of 38.0 days (range, 15-142 days)
- 83% of adjudicated drug-related ILD/pneumonitis cases were low grade (Grade 1-2)

Conclusions

- DESTINY-Gastric02 is the first study focused only on 2L T-DXd monotherapy in Western HER2+ patients with gastric/GEJ cancer who progressed on a trastuzumab-containing regimen
- Efficacy results demonstrate clinically meaningful and durable responses
- Safety profile was generally consistent with the established safety profile of T-DXd
- DESTINY-Gastric02 provides clinical evidence for T-DXd as a valuable 2L HER2-targeted treatment option and supports the ongoing randomized phase 3 trial, DESTINY-Gastric04 (NCT04704934)

TROPION-PanTumor01: Updated Results From the NSCLC Cohort of the Phase 1 Study of Datopotamab Deruxtecan in Solid Tumors

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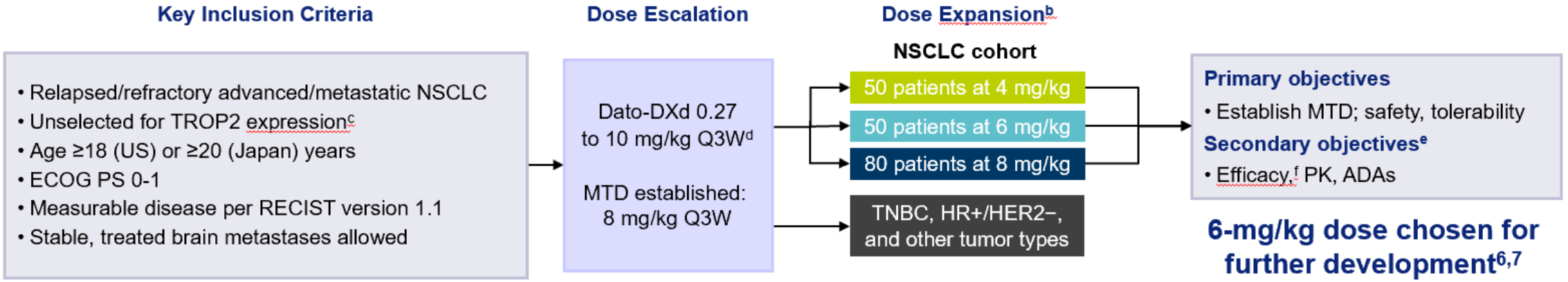
Introduction and Methods

- Patients with advanced or metastatic NSCLC represent a high unmet need[1]
- TROP2 is highly expressed in NSCLC and has been associated with poor prognosis[2-4]
- Datopotamab deruxtecan (Dato-DXd) is an antibody drug conjugate composed of a humanized anti-TROP2 monoclonal antibody conjugated to a potent topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker; this enables a bystander tumor effect resulting in elimination of both target tumor cells and surrounding cells[5,6]
- Previous results from the TROPION-PanTumor01 first-in-human study of Dato-DXd (NCT03401385) demonstrated highly encouraging antitumor activity with a manageable safety profile in patients with NSCLC.[6,7] Here we present updated results from the NSCLC cohort, with a data cutoff of April 6, 2021[a]

TROPION-PanTumor01 Study Design



ADA, antidrug antibody; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer; TROP2, trophoblast cell-surface antigen 2.

[a] This analysis in the NSCLC cohort was performed 6 months after the last patient received their first dose of study drug on October 6, 2020. [b] Includes patients treated in the dose-escalation and dose-expansion portions. [c] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [d] The 4-, 6-, and 8-mg/kg dose levels are being further evaluated for safety and efficacy. [e] Additional exploratory objectives include analyses of biomarkers associated with response. [f] Response assessments are based on RECIST v1.1.

1. Simeone JC, et al. *Future Oncol.* 2019;15(30):3491-3502. 2. Mito R, et al. *Pathol Int.* 2020;70(5):287-294. 3. Inamura K, et al. *Oncotarget.* 2017;8(17):28725-28735. 4. Jiang A, et al. *Oncol Lett*. 2013;6(2):375-380. 5. Okajima D, et al. AACR-NCI-EORTC 2019. Abstract C026. 6. Meric-Bernstam F, et al. ASCO 2021. Abstract 9058. 7. Spira A, et al. WCLC 2020. Abstract 3407.

Baseline Characteristics and Patient Disposition

Characteristic	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
Age, median (range), years	61 (35-82)	63 (38-76)	64 (31-84)
Age ≥65 years, %	36	40	46
Weight, median (range), kg	72 (38-156)	66 (39-104)	70 (38-115)
Male, %	54	56	51
Country, %			
United States	58	76	79
Japan	42	24	21
Histology, %			
Nonsquamous	82	90	88
Squamous	18	10	13
≥3 Prior lines of therapy, %	54	62	64
Previous systemic treatment, %			
Immunotherapy	88	74	88
Platinum-based chemotherapy	96	96	98
Tyrosine kinase inhibitor	20	18	19
***EGFR* mutations, %**	14	16	19
History of brain metastases, %	36	34	41

Treatment status	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
Ongoing study treatment, n (%)[a]	9 (18)	5 (10)	7 (9)
Discontinued from study treatment, n (%)	41 (82)	45 (90)	73 (91)
Progression[b]	31 (62)	34 (68)	43 (54)
Adverse events	8 (16)	6 (12)	20 (25)
Death	0	1 (2)	1 (1)
Other[c]	2 (4)	4 (8)	9 (11)
Duration on study, median (range), mo	12.1 (7-29)	9.5 (6-27)	16.8 (10-25)
Exposure, median (range), mo	4.1 (0.7-27.6)	3.5 (0.7-26.2)	3.3 (0.7-20.4)

- Patients were heavily pretreated, with 74%-88% having received prior immunotherapy and 96%-98% having received prior platinum-based chemotherapy across dose cohorts

Data cutoff: April 6, 2021.
EGFR, epidermal growth factor receptor.
[a] Due to a later time of enrollment, follow-up was shorter for patients treated with the 4- and 6-mg/kg doses than for those treated with the 8-mg/kg dose. [b] Includes progressive disease per RECIST v1.1 and clinical progression.
[c] Includes physician decision, withdrawal by subject, and other.

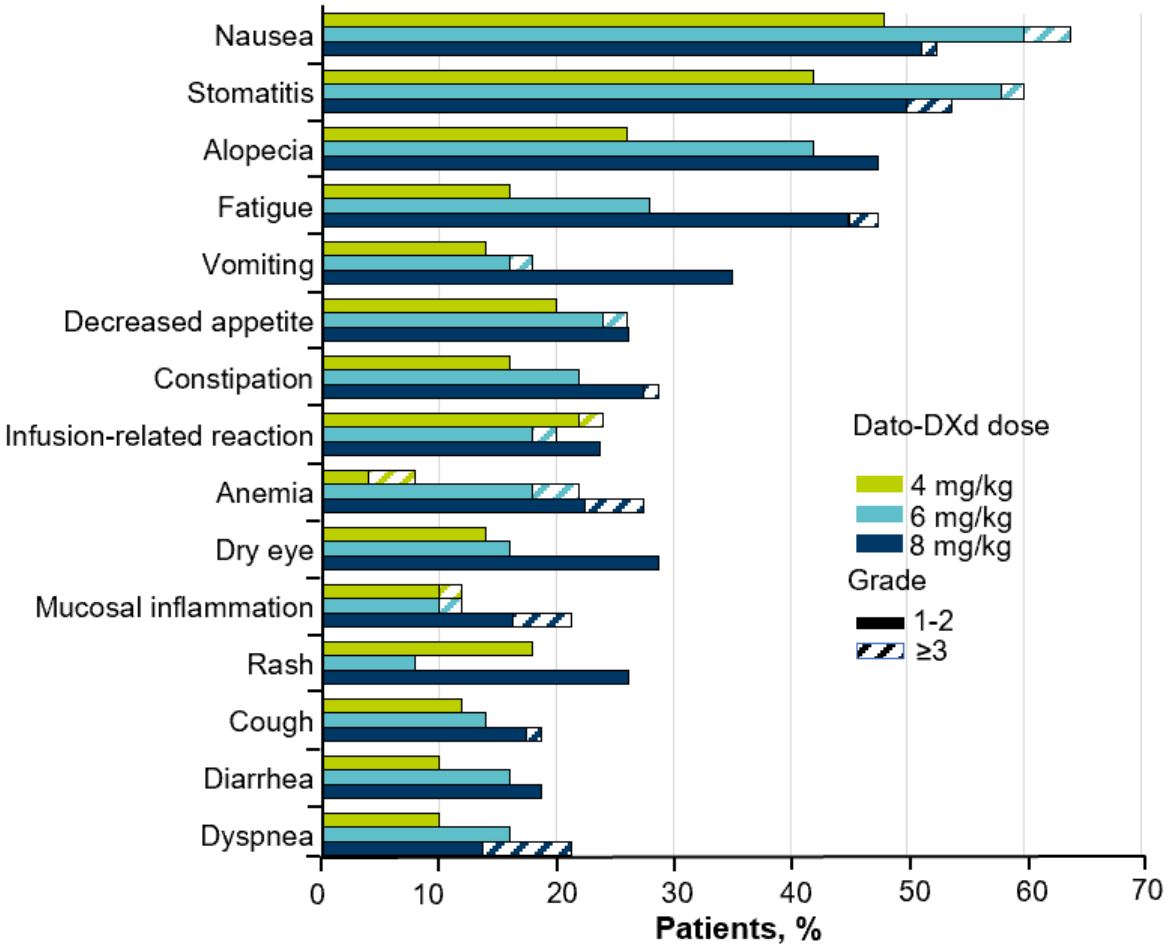
Safety

Overall Safety Summary

Patients, n (%)	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
TEAE	49 (98)	49 (98)	80 (100)
Grade ≥3	15 (30)	27 (54)	46 (58)
Drug-related TEAE	47 (94)	41 (82)	78 (98)
Grade ≥3	7 (14)	13 (26)	28 (35)
Serious TEAE	10 (20)	24 (48)	40 (50)
Grade ≥3	10 (20)	18 (36)	37 (46)
Dose adjustments			
TEAEs associated with discontinuation	8 (16)	7 (14)	19 (24)
TEAEs associated with dose interruption	4 (8)	15 (30)	29 (36)
TEAEs associated with dose reduction	1 (2)	5 (10)	23 (29)
ILD adjudicated as drug related[a]	5 (10)	3 (6)	11 (14)
Grade ≤2	4 (8)	2 (4)	7 (9)
Grades 3-4	1 (2)	1 (2)	1 (1)
Grade 5	0	0	3 (4)

- The safety profile was manageable with mainly mild/moderate toxicity; TEAEs were primarily nonhematologic

TEAEs in ≥15% of Patients[b]



Data cutoff: April 6, 2021.
ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] Cases of ILD adjudicated as drug related comprised 5 patients in the 4-mg/kg cohort (1 grade 1, 3 grade 2, 1 grade 3), 3 patients in the 6-mg/kg cohort (2 grade 2, 1 grade 4), and 11 patients in the 8-mg/kg cohort (2 grade 1, 5 grade 2, 1 grade 3, 3 grade 5). [b] Of 180 patients (4 mg/kg [n=50]; 6 mg/kg [n=50]; 8 mg/kg [n=80]).

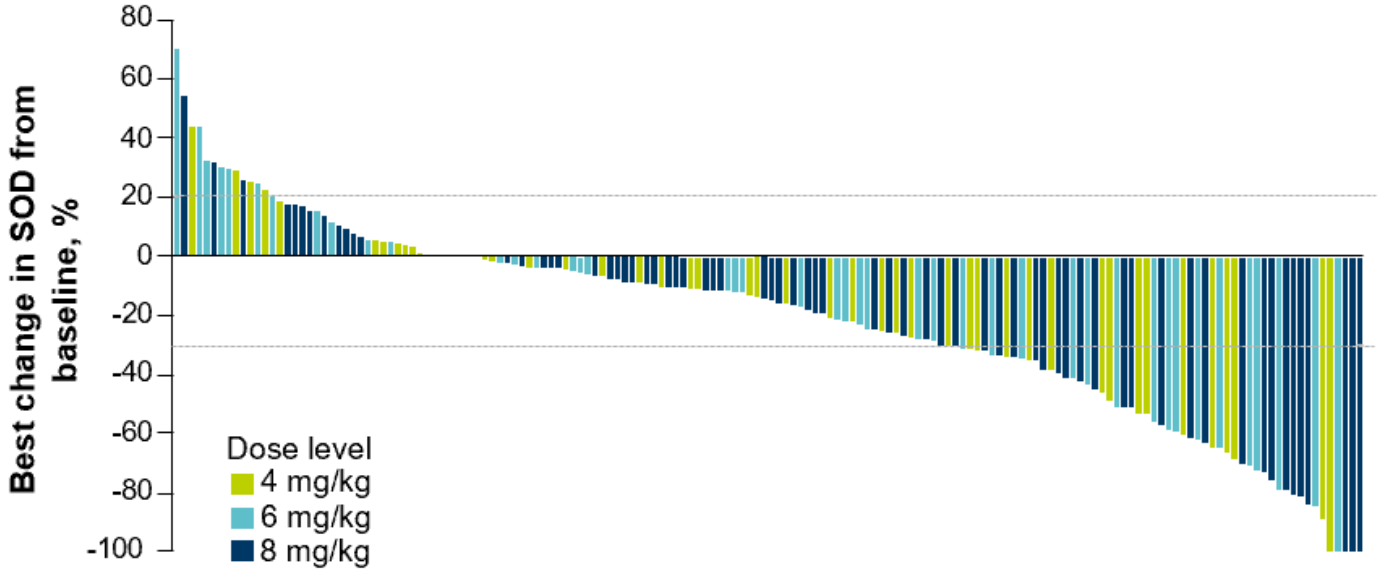
Antitumor Activity of Dato-DXd

Best Overall Response (BICR)

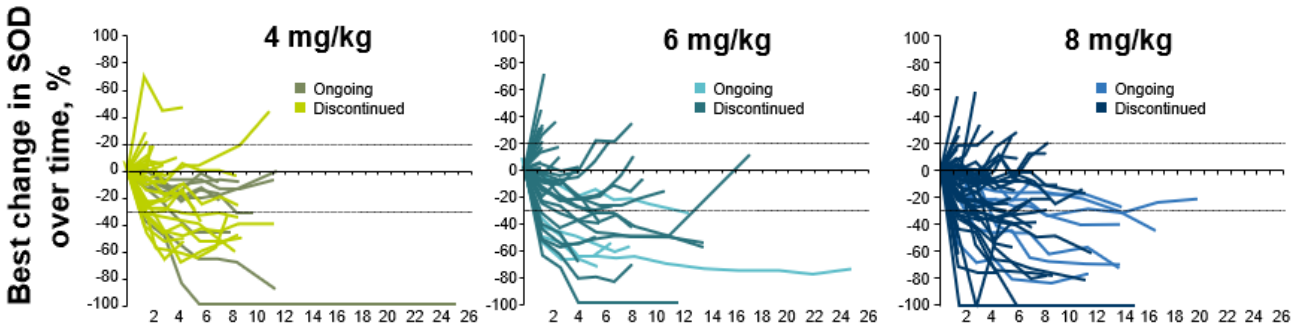
Patients[a]	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)[b]	12 (24)	14 (28)	19 (24)
CR, n (%)	0	0	1 (1)
PR, n (%)[b]	12 (24)	14 (28)	18 (23)
SD, n (%)	25 (50)	20 (40)	42 (53)
Non-CR/PD, n (%)	1 (2)	2 (4)	2 (3)
PD, n (%)	7 (14)	10 (20)	8 (10)
NE, n (%)	5 (10)	5 (10)	9 (11)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (5.6-NE)	9.4 (5.8-NE)

- Antitumor activity was observed at 4-, 6-, and 8-mg/kg doses of Dato-DXd
- Most responses were durable over time, including a median duration of response of 10.5 months in the 6-mg/kg cohort

Best Change in Sum of Diameters (per BICR)



Change in Sum of Diameters of Target Lesion (per BICR) Over Time



Data cutoff: April 6, 2021.

BICR, blinded independent central review; CR, complete response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SOD, sum of diameters; SD, stable disease.

[a] Includes response-evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b] ORR and CR/PR include 1 response in the 6-mg/kg cohort that is pending confirmation.

Summary

- In the updated data cutoff for the NSCLC cohort, Dato-DXd continued to demonstrate highly encouraging antitumor activity and a manageable safety profile at the 4-, 6-, and 8-mg/kg doses in this heavily pretreated population
- The 6-mg/kg dose has been selected for further development
  - The 6-mg/kg dose was better tolerated than the 8-mg/kg dose, with low rates of discontinuation due to adverse events
  - 28% of patients achieved an ORR, and the median DOR was 10.5 months
- TROPION-PanTumor01 is also investigating Dato-DXd in other tumor types. Promising antitumor activity and a similar safety profile have been observed in the TNBC cohort[1]
- Dato-DXd is currently being evaluated in the phase 3 TROPION-Lung01 trial (NCT04656652)[2] and additional phase 1 and 2 trials in NSCLC[3-5]

1. Bardia A, et al. ESMO Breast Cancer 2021. Abstract LBA4. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT04656652. 3. Levy B, et al. WCLC 2021. Abstract 564. 4. Borghaei H, et al. WCLC 2021. Abstract 588. 5. Johnson M, et al. WCLC 2021. Abstract 653.

Efficacy of Datopotamab Deruxtecan (Dato-DXd) in Patients With Advanced/Metastatic Non-Small Cell Lung Cancer (NSCLC) and Actionable Genomic Alterations (AGAs): Preliminary Results From the Phase 1 TROPION-PanTumor01 Study

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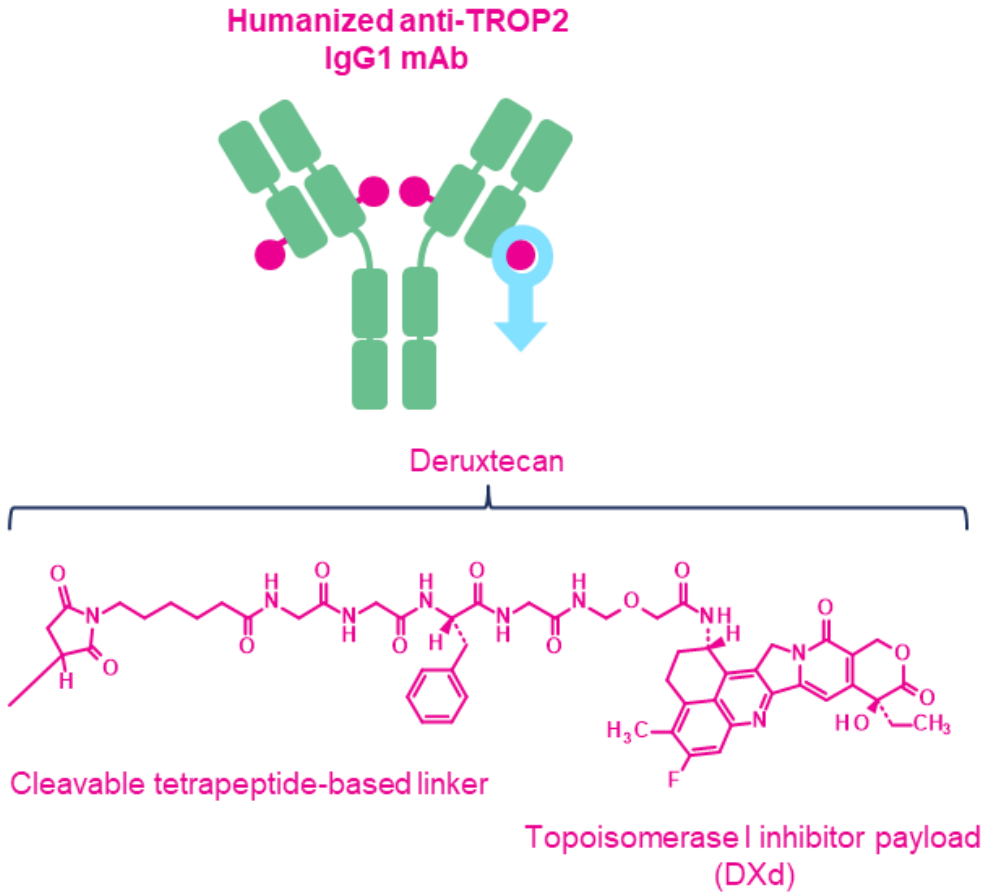
Introduction

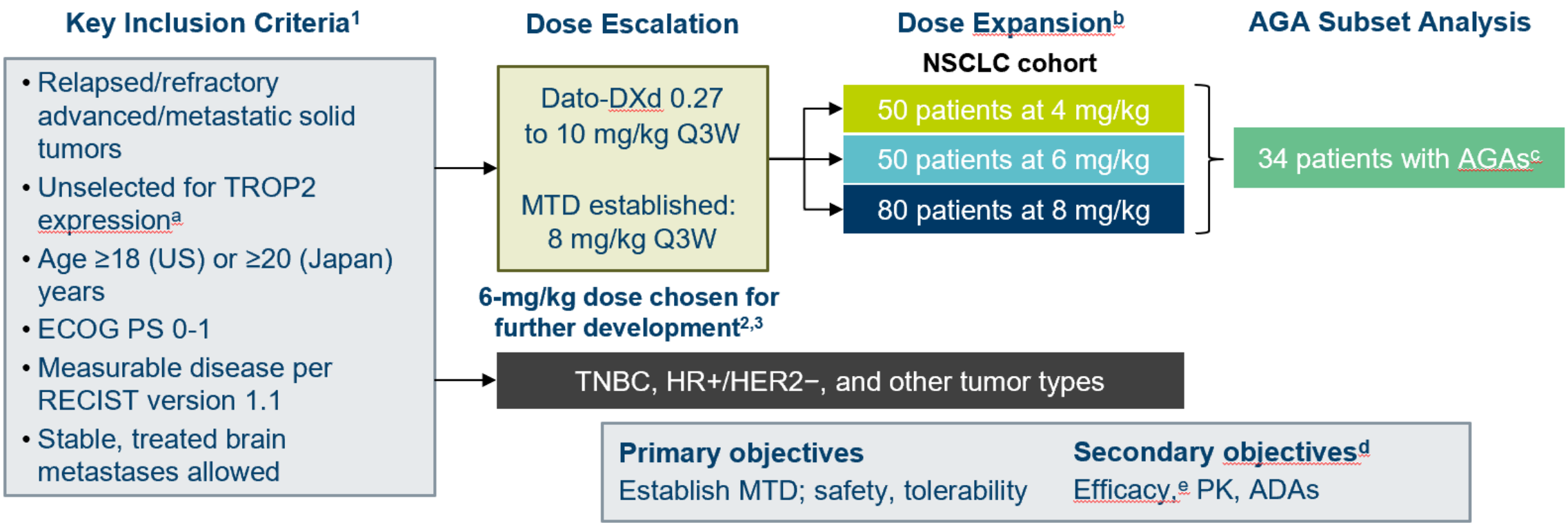
- Patients with advanced/metastatic NSCLC with AGAs, eg, *EGFR* or *ALK* mutations, derive limited benefit from existing treatments once TKIs and platinum chemotherapy fail[1,2]
- TROP2 is highly expressed in NSCLC, regardless of genomic mutation status, and has been associated with poor prognosis[3-5]
- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate composed of a humanized anti-TROP2 monoclonal antibody conjugated to a potent topoisomerase I inhibitor payload via a stable tetrapeptide-based cleavable linker[6,7]
- Previous results from the TROPION-PanTumor01 study (NCT03401385) demonstrated encouraging antitumor activity of Dato-DXd, with a manageable safety profile in heavily pretreated NSCLC.[7,8] Here we present results in the subset of patients with AGAs



ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; IgG1, immunoglobulin G1; mAb, monoclonal antibody; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; TROP2, trophoblast cell-surface antigen 2.

1. Scagliotti GV, et al. *Cancer Treat Rev*. 2015;41(6):465-475. 2. Maione P, et al. *Ther Adv Med Oncol*. 2015;7(5):263-273. 3. Mito R, et al. *Pathol Int.* 2020;70(5):287-294. 4. Inamura K, et al. *Oncotarget.* 2017;8(17):28725-28735. 5. Jiang A, et al. *Oncol Lett*. 2013;6(2):375-380. 6. Okajima D, et al. AACR-NCI-EORTC 2019. Abstract C026. 7. Meric-Bernstam F, et al. ASCO 2021. Abstract 9058. 8. Spira A, et al. WCLC 2020. Abstract 3407.

TROPION-PanTumor01 Study Design



ADA, antidrug antibody; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MTD, maximum tolerated dose; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer.

[a] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b] Includes patients treated in the dose-escalation and dose-expansion portions. [c] AGAs were investigator reported. [d] Additional exploratory objectives include analyses of biomarkers associated with response. [e] Response assessments are based on RECIST 1.1.

1. ClinicalTrials.gov. Accessed August 26, 2021. https://clinicaltrials.gov/ct2/show/NCT03401385. 2. Meric-Bernstam F, et al. ASCO 2021. Abstract 9058. 3. Spira A, et al. WCLC 2020. Abstract 3407.

NSCLC With AGAs: Baseline Characteristics and Disposition

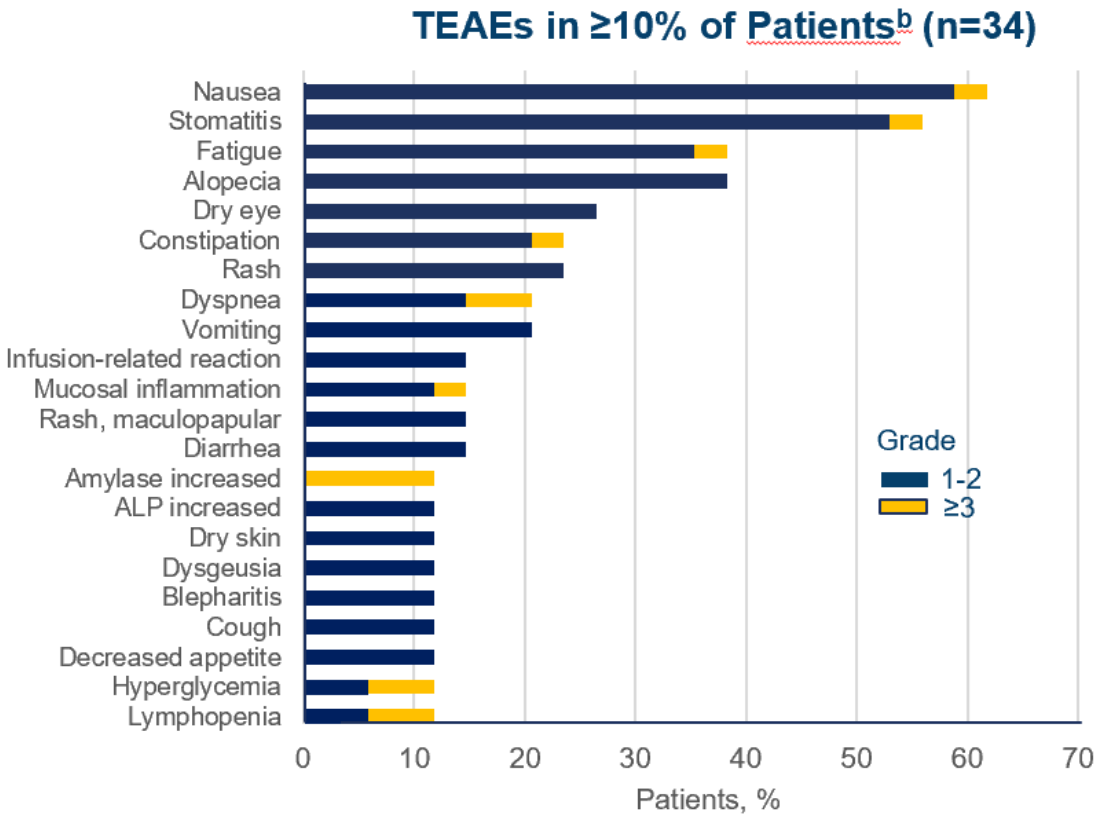
Characteristic	Dato-DXd n=34
Age, median (range), years	62 (42-80)
Weight, median (range), kg	60 (38-107)
Female, %	56
Nonsquamous histology, %	97
≥3 Prior lines of therapy, %	82
Previous systemic treatment, %	
Immunotherapy	41
Platinum-based chemotherapy	91
Tyrosine kinase inhibitor	85
Osimertinib	69[a]
Actionable genomic alterations, %	
EGFR mutation[b]	85
ALK fusion	9
ROS1 fusion	3
RET fusion	3

Treatment status	Dato-DXd n=34
Received study treatment, %	
4 mg/kg	24
6 mg/kg	29
8 mg/kg	47
Ongoing study treatment, %	12
Discontinued from study treatment, %	88
Progression[c]	65
Adverse event	15
Death	3
Other[d]	6
Duration on study, median (range), mo	13.4 (7-28)
Exposure, median (range), mo	5.8 (0.7-17.2)

Data cutoff: April 6, 2021.
RET, ret proto-oncogene ROS1, ROS proto-oncogene 1.
[a] Among patients with *EGFR* mutations. [b] Among those with *EGFR* mutations, 10% had exon 20 insertions. [c] Includes progressive disease per RECIST 1.1 and clinical progression. [d] Includes physician decision, withdrawal by patient, and other.

NSCLC With AGAs: Safety

Adverse events, n (%)	Dato-DXd n=34
TEAE, %	100
Grade ≥3	53
Drug-related TEAE, %	88
Grade ≥3	38
Serious TEAE, %	35
Grade ≥3	29
Dose adjustments, %	
TEAEs associated with discontinuation	15
TEAEs associated with dose interruption	27
TEAEs associated with dose reduction	15
ILD adjudicated as drug related, n[a]	1
Grade ≤2	0
Grade 3/4	0
Grade 5	1



Data cutoff: April 6, 2021.
ALP, alkaline phosphatase; ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] The case of adjudicated ILD occurred in a patient who received Dato-DXd 8 mg/kg. [b] Any grade TEAEs occurring in <10% of patients but with grade ≥3 occurring in ≥5% of patients included ulcerative keratitis.
Garon EB, et al. WCLC 2021. Abstract MA03.02.

- The safety profile of Dato-DXd was manageable and consistent with that observed in the overall NSCLC population in TROPION-PanTumor01; TEAEs were primarily nonhematologic

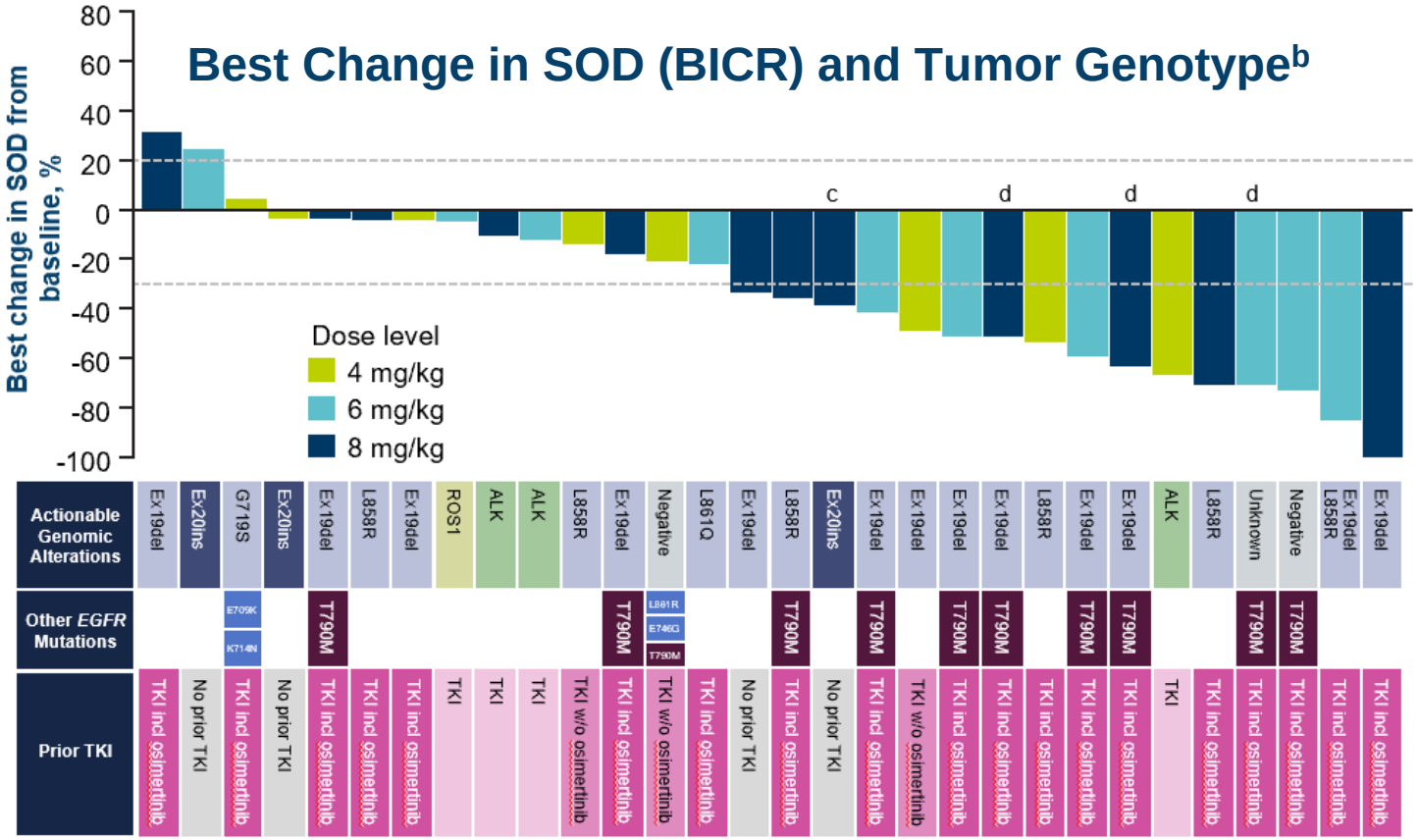
NSCLC With AGAs: Antitumor Activity

Best Overall Response (BICR)

Patients[a]	Dato-DXd n=34
ORR, n (%)	12 (35)
CR	0
PR	12 (35)
SD, n (%)	14 (41)
Non-CR/PD, n (%)	2 (6)
PD, n (%)	2 (6)
NE, n (%)	4 (12)
DOR, median (95% CI), mo	9.5 (3.3-NE)

- Clinical activity was observed in *EGFR* (Ex19del, L858R) including after osimertinib and across other AGAs

Best Change in SOD (BICR) and Tumor Genotype[b]



Data cutoff: April 6, 2021.
BICR, blinded independent central review; CR, complete response; DOR, duration of response; incl, including; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SOD, sum of diameters; SD, stable disease; w/o, without.
[a] Includes response-evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b] 4 patients were not included in the waterfall plot: 2 who did not have a target lesion per BICR and 2 who did not have on-study treatment images. [c] Patient NE. [d] Patients with unconfirmed PR.

Summary

- **Antitumor activity observed in heavily pretreated advanced NSCLC with AGAs is highly encouraging**
  - The ORR was 35% and median DOR was 9.5 months, which was consistent with those in the overall NSCLC population
- **The safety profile was manageable and consistent with that observed in the overall NSCLC study population[1]**
  - The most common AEs were nausea and stomatitis
  - AEs were generally grade 1/2
- **Dato-DXd is being further evaluated in NSCLC with AGAs after targeted therapy and platinum-based chemotherapy options have been exhausted (TROPION-Lung05; NCT04484142)[2]**
  - Eligible AGAs are *EGFR* (including exon 20 insertions), *ALK*, *ROS1*, *RET*, *BRAF*, *NTRK*, and *MET* exon 14 skipping

AE, adverse event; BRAF, B-Raf proto-oncogene; MET, MET proto-oncogene; NTRK, neurotrophic receptor tyrosine kinase.

1. Garon EB, et al. WCLC 2021. Abstract MA03.02. 2. Johnson ML, et al. WCLC 2021. Abstract P47.05.

A Phase 1/2 Multicenter, First-in-Human Study of DS-7300 (B7-H3 DXd-ADC) in Patients (pts) With Advanced Solid Tumors

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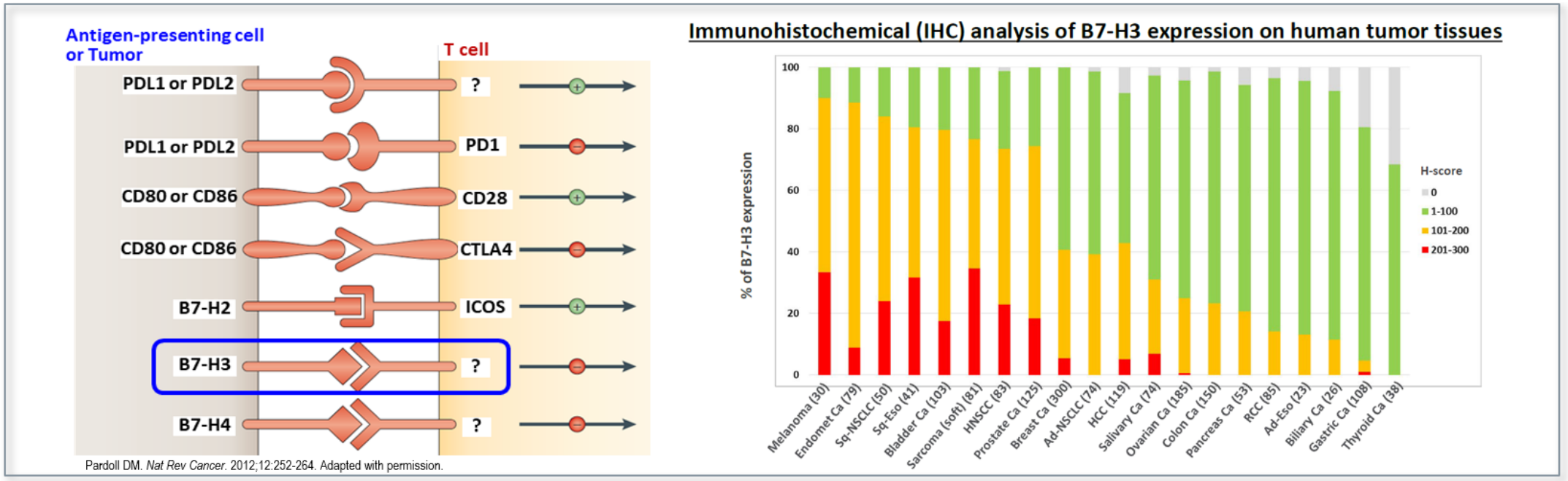
Background and Rationale

- B7 homologue 3 (B7-H3, CD276) is a transmembrane protein overexpressed in various cancers, including lung, prostate, esophageal, and breast cancers, and head and neck squamous cell carcinoma (HNSCC)[1-4]
  - B7-H3 overexpression is associated with poor prognosis[1,2,4]

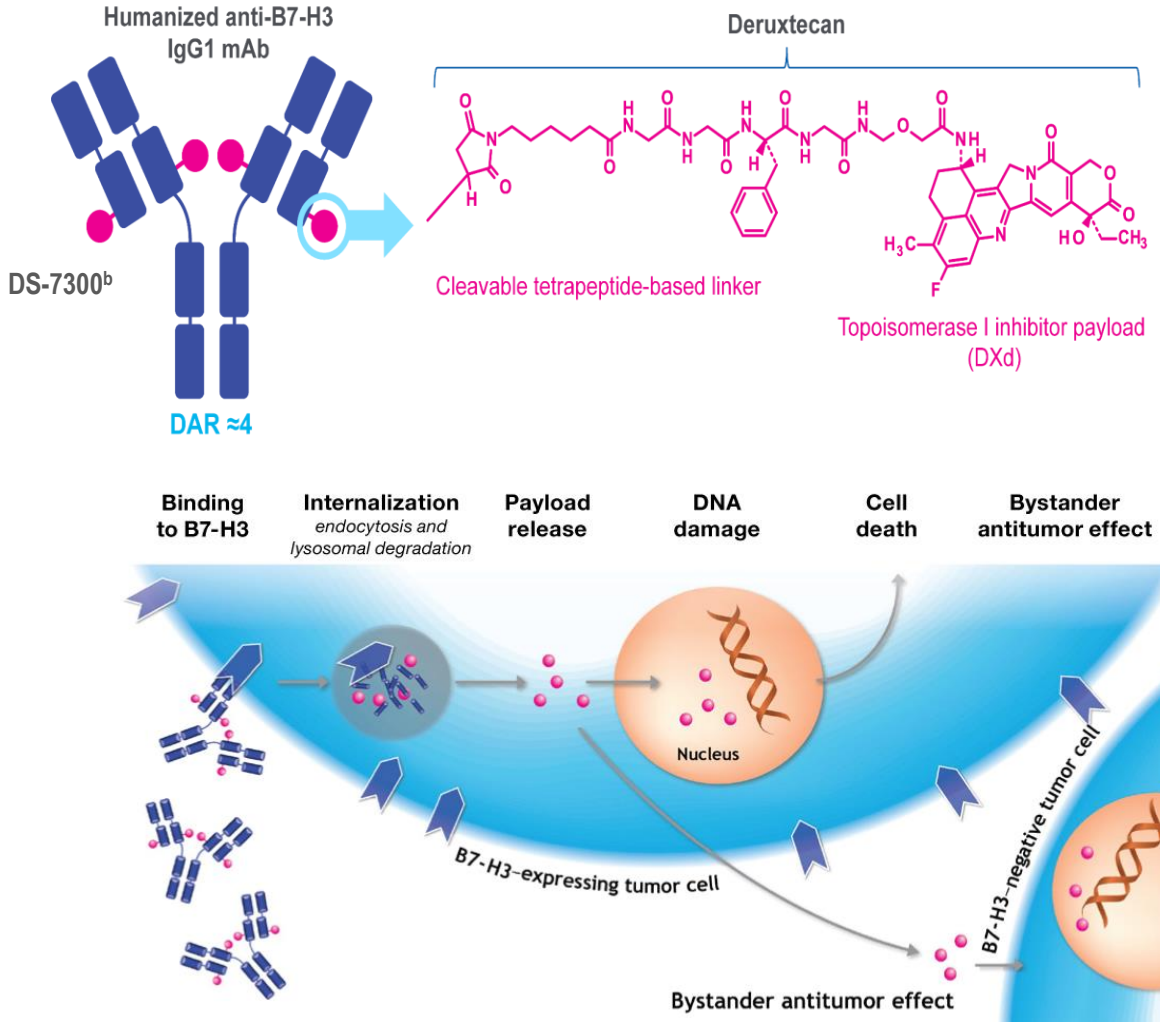


Ad, adenocarcinoma; Eso, esophageal cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; RCC, renal cell carcinoma; Sq, squamous cell carcinoma

1. Yamoto M, et al. EORTC-NCI-AACR 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 2020.

Background and Rationale: DS-7300

- Payload mechanism of action: topoisomerase I inhibitor [a,1-5]
- High potency of payload [a,2-5]
- Optimized drug-to-antibody ratio [a,c,1-4]
- Payload with short systemic half-life [a,c,2,3]
- Stable linker-payload [a,2,3,5]
- Tumor-selective cleavable linker [a,2-6]
- Bystander antitumor effect [a,2,7]



[a] The clinical relevance of these features is under investigation. [b] Image is for illustrative purposes only; actual drug-to-antibody ratio and drug positions may vary. [c] Based on animal data.

1. Okajima D, et al. Poster presented at: AACR-NCI-EORTC International Conference; October 26-30, 2019; Boston, MA. Abstract C026. **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.** Hashimoto Y, et al. *Clin Cancer Res.* 2019;25(23):7151-7161. **5.** Koganemaru S, et al. *Mol Cancer Ther.* 2019;18(11):2043-2050. **6.** Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. **7.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

A Multicenter, Open-Label, 2-Part, Multiple-Dose, First-in-Human, Phase 1/2 Study of DS-7300

Daiichi-Sankyo

NCT04145622

Part 1: Dose escalation

- DS-7300 IV Q3W monotherapy in advanced solid tumors
- Advanced/unresectable or metastatic solid tumors (unselected for B7-H3 expression)
- ECOG PS 0-1
- ≥1 measurable lesion according to RECIST version 1.1
- Key inclusion criteria
  - HNSCC, ESCC, squamous and adeno NSCLC, SCLC, bladder cancer, sarcoma, endometrial cancer, melanoma, CRPC, or BC that is refractory to or intolerant of standard treatment or for which no standard treatment is available

0.8 mg/kg → 1.6 mg/kg → 3.2 mg/kg → 4.8 mg/kg → 6.4 mg/kg → 8.0 mg/kg → 12.0 mg/kg → 16.0 mg/kg

MTD/RDE

Part 2: Dose expansion

- DS-7300 IV Q3W monotherapy in selected advanced solid tumors

Cohort 1: ESCC (up to n=25)

Cohort 2: mCRPC (up to n=40)

Cohort 3: SCLC (up to n≈40)

Key primary endpoints (Dose escalation):

- DLTs, SAEs, TEAEs, AESIs
- Here, we report initial results from the dose-escalation portion of the trial

AESI, adverse event of special interest; BC, breast cancer; CRPC, castration-resistant prostate cancer; DLT, dose-limiting toxicity; ECOG PS, Easter Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; IV, intravenous; mCRPC, metastatic castration-resistant prostate cancer; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; Q3W, every 3 weeks; RDE, recommended dose for expansion; SAE, serious adverse event; SCLC, small cell lung cancer; TEAE, treatment-emergent adverse event

Results: Baseline Demographics and Disease Characteristics

	DS-7300 Dose Level								Total (N=70)
	0.8 mg/kg (n=5)	1.6 mg/kg (n=5)	3.2 mg/kg (n=7)	4.8 mg/kg (n=5)	6.4 mg/kg (n=8)	8.0 mg/kg (n=12)	12.0 mg/kg (n=21)	16.0 mg/kg (n=7)	
Male, n (%)	3 (60)	4 (80)	5 (71.4)	3 (60)	7 (87.5)	11 (91.7)	17 (81)	5 (71.4)	55 (78.6)
Age, median (range), years	64 (46-67)	69 (35-73)	66 (41-77)	59 (56-60)	59.5 (44-74)	68 (56-77)	69 (43-82)	57 (53-70)	65 (35-82)
≥65 years, n (%)	2 (40)	3 (60)	5 (71.4)	0	3 (37.5)	9 (75)	14 (66.7)	1 (14.3)	37 (52.9)
ECOG PS, n (%)									
0	4 (80)	3 (60)	4 (57.1)	3 (60)	4 (50)	2 (16.7)	6 (28.6)	3 (42.9)	29 (41.4)
1	1 (20)	2 (40)	3 (42.9)	2 (40)	4 (50)	10 (83.3)	15 (71.4)	4 (57.1)	41 (58.6)
Cancer type, n (%)									
CRPC	0	1 (20)	1 (14.3)	0	4 (50)	5 (41.7)	12 (57.1)	1 (14.3)	24 (34.3)
HNSCC	1 (20)	1 (20)	3 (42.9)	0	1 (12.5)	1 (8.3)	3 (14.3)	2 (28.6)	12 (17.1)
Sarcoma	2 (40)	1 (20)	1 (14.3)	0	1 (12.5)	1 (8.3)	1 (4.8)	1 (14.3)	8 (11.4)
SCLC	0	0	1 (14.3)	0	1 (12.5)	2 (16.7)	3 (14.3)	1 (14.3)	8 (11.4)
Endometrial cancer	0	1 (20)	0	1 (20)	0	0	1 (4.8)	1 (14.3)	4 (5.7)
ESCC	1 (20)	0	0	1 (20)	0	2 (16.7)	0	0	4 (5.7)
Squamous NSCLC	0	0	1 (14.3)	1 (20)	0	0	1 (4.8)	1 (14.3)	4 (5.7)
Breast cancer	1 (20)	0	0	1 (20)	0	0	0	0	2 (2.9)
Melanoma	0	1 (20)	0	1 (20)	0	0	0	0	2 (2.9)
Bladder cancer	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
Prior lines of therapy, median (range)	4 (2-6)	3 (2-10)	3 (1-7)	5 (3-6)	5 (2-7)	4 (2-9)	5 (1-8)	4 (2-8)	4 (1-10)

Data cutoff July 21, 2021
ECOG PS, Eastern Cooperative Oncology Group performance status; ESCC, esophageal squamous cell carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer; SCLC, small cell lung cancer

Results: Summary of Overall Safety

- No DLTs[a] were observed in dose escalation
- All-grade AESIs of ILD/pneumonitis or IRRs occurred in 2 (2.9%) and 28 patients (40%), respectively; no hepatotoxicity occurred
- One case of grade 5 ILD (adjudicated as treatment related) occurred at 16 mg/kg and 1 case of grade 1 ILD (pending adjudication) occurred at 12 mg/kg

Patients, n (%)	DS-7300								Total (N=70)
	0.8 mg/kg (n=5)	1.6 mg/kg (n=5)	3.2 mg/kg (n=7)	4.8 mg/kg (n=5)	6.4 mg/kg (n=8)	8.0 mg/kg (n=12)	12.0 mg/kg (n=21)	16.0 mg/kg (n=7)	
Tx duration, median (range), weeks	13 (6-33)	12 (9-47.9)	12 (6-18)	12.1 (6-18)	17.1 (6-37)	21.1 (5.9-44)	14.9 (3-36)	6 (3-21.9)	13.1 (3-47.9)
TEAEs[b]	4 (80)	5 (100)	7 (100)	5 (100)	8 (100)	12 (100)	21 (100)	7 (100)	69 (98.6)
Grade ≥3 TEAEs[b]	0	0	1 (14.3)	1 (20)	1 (12.5)	5 (41.7)	9 (42.9)	5 (71.4)	22 (31.4)
Serious TEAEs[b]	1 (20)	0	2 (28.6)	1 (20)	1 (12.5)	3 (25)	4 (19.0)	3 (42.9)	15 (21.4)
TEAEs leading to death[b]	0	0	0	0	0	1 (8.3)	0	1 (14.3)	2 (2.9)
TEAEs leading to Tx discontinuation	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
AESIs[b]									
Infusion-related reactions	1 (20)	0	1 (14.3)	3 (60)	4 (50)	4 (33.3)	11 (52.4)	4 (57.1)	28 (40)
Interstitial lung disease	0	0	0	0	0	0	1 (4.8)	1 (14.3)	2 (2.9)

Data cutoff July 21, 2021

AESI, adverse event of special interest; ILD, interstitial lung disease; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event; Tx, treatment.

[a] A DLT is defined as any TEAE that occurs during the DLT evaluation period excluding toxicities clearly related to disease progression or intercurrent illness and is grade ≥3 according to NCI-CTCAE Version 5.0. [b] Regardless of causality.

Results: Most Common TEAEs (Any Grade)

- The most common TEAEs of any grade included nausea, IRRs, vomiting, and decreased appetite
  - All IRRs were grade ≤2

Most Common (Occurring in ≥10% of All Patients) Treatment-Emergent Adverse Events (Any Grade), Regardless of Causality

TEAEs, n (%)	0.8 mg/kg (n=5)	1.6 mg/kg (n=5)	3.2 mg/kg (n=7)	4.8 mg/kg (n=5)	6.4 mg/kg (n=8)	8.0 mg/kg (n=12)	12.0 mg/kg (n=21)	16.0 mg/kg (n=7)	Total N=70
Any TEAE	4 (80)	5 (100)	7 (100)	5 (100)	8 (100)	12 (100)	21 (100)	7 (100)	69 (98.6)
Nausea	3 (60)	1 (20)	3 (42.9)	2 (40)	3 (37.5)	6 (50)	16 (76.2)	5 (71.4)	39 (55.7)
IRR	1 (20)	0	1 (14.3)	3 (60)	4 (50)	4 (33.3)	11 (52.4)	4 (57.1)	28 (40)
Vomiting	2 (40)	1 (20)	2 (28.6)	0	1 (12.5)	5 (41.7)	7 (33.3)	1 (14.3)	19 (27.1)
Decreased appetite	1 (20)	1 (20)	3 (42.9)	1 (20)	3 (37.5)	3 (25)	6 (28.6)	2 (28.6)	20 (28.6)
Dehydration	0	1 (20)	1 (14.3)	0	1 (12.5)	2 (16.7)	3 (14.3)	0	8 (11.4)
Diarrhea	0	0	1 (14.3)	0	0	2 (16.7)	5 (23.8)	0	8 (11.4)
Chills	0	0	1 (14.3)	0	0	3 (25)	5 (23.8)	0	9 (12.9)
Fatigue	1 (20)	1 (20)	2 (28.6)	0	2 (25)	1 (8.3)	8 (38.1)	0	15 (21.4)
Pyrexia	1 (20)	2 (40)	2 (28.6)	0	0	3 (25)	1 (4.8)	0	9 (12.9)

Data cutoff July 21, 2021

Results: Grade ≥3 TEAEs

- The most common grade ≥3 TEAEs were anemia and lymphocyte count decreased
- The only Grade ≥3 treatment-related AEs were anemia (n=6), lymphocyte count decreased (n=2), neutropenia, asthenia, neutrophil count decreased, and ILD (n=1 each)

Grade ≥3 Treatment-Emergent Adverse Events, Regardless of Causality

Grade ≥3 TEAEs, n (%)	0.8 mg/kg (n=5)	1.6 mg/kg (n=5)	3.2 mg/kg (n=7)	4.8 mg/kg (n=5)	6.4 mg/kg (n=8)	8.0 mg/kg (n=12)	12.0 mg/kg (n=21)	16.0 mg/kg (n=7)	Total N=70
Anemia	0	0	0	0	1 (12.5)	3 (25)	5 (23.8)	2 (28.6)	11 (15.7)
Lymphocyte count decreased	0	0	0	0	0	0	2 (9.6)	0	2 (2.8)
Interstitial lung disease	0	0	0	0	0	0	1 (14.3)	0	1 (1.4)
Febrile neutropenia	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
Asthenia	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Blood creatinine increased	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
QT prolonged	0	0	1 (14.3)	0	0	0	0	0	1 (1.4)
Neutropenia[a]	0	0	0	0	0	0	2 (9.6)	0	2 (2.8)
Dehydration	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Hypercalcemia	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
Osteoarthritis	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
Dyspnea	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Hypoxia	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Pleural effusion	0	0	0	1 (20)	0	0	0	0	1 (1.4)
Arterial thrombosis	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
Myelosuppression	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
COVID-19	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
Sepsis	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Urinary tract infection	0	0	0	0	0	0	1 (4.8)	0	1 (1.4)
Wound infection	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
Cancer pain	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
Encephalopathy	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)
Ureteric obstruction	0	0	0	0	0	1 (8.3)	0	0	1 (1.4)
Embolism arterial	0	0	0	0	0	0	0	1 (14.3)	1 (1.4)

Data cutoff July 21, 2021. [a]Includes neutrophil count decreased.

Results: Initial Efficacy (Dose Escalation)

- Among 70 patients enrolled, 15 partial responses were observed[a]
- 32 patients had stable disease, including 24 patients ongoing on study treatment

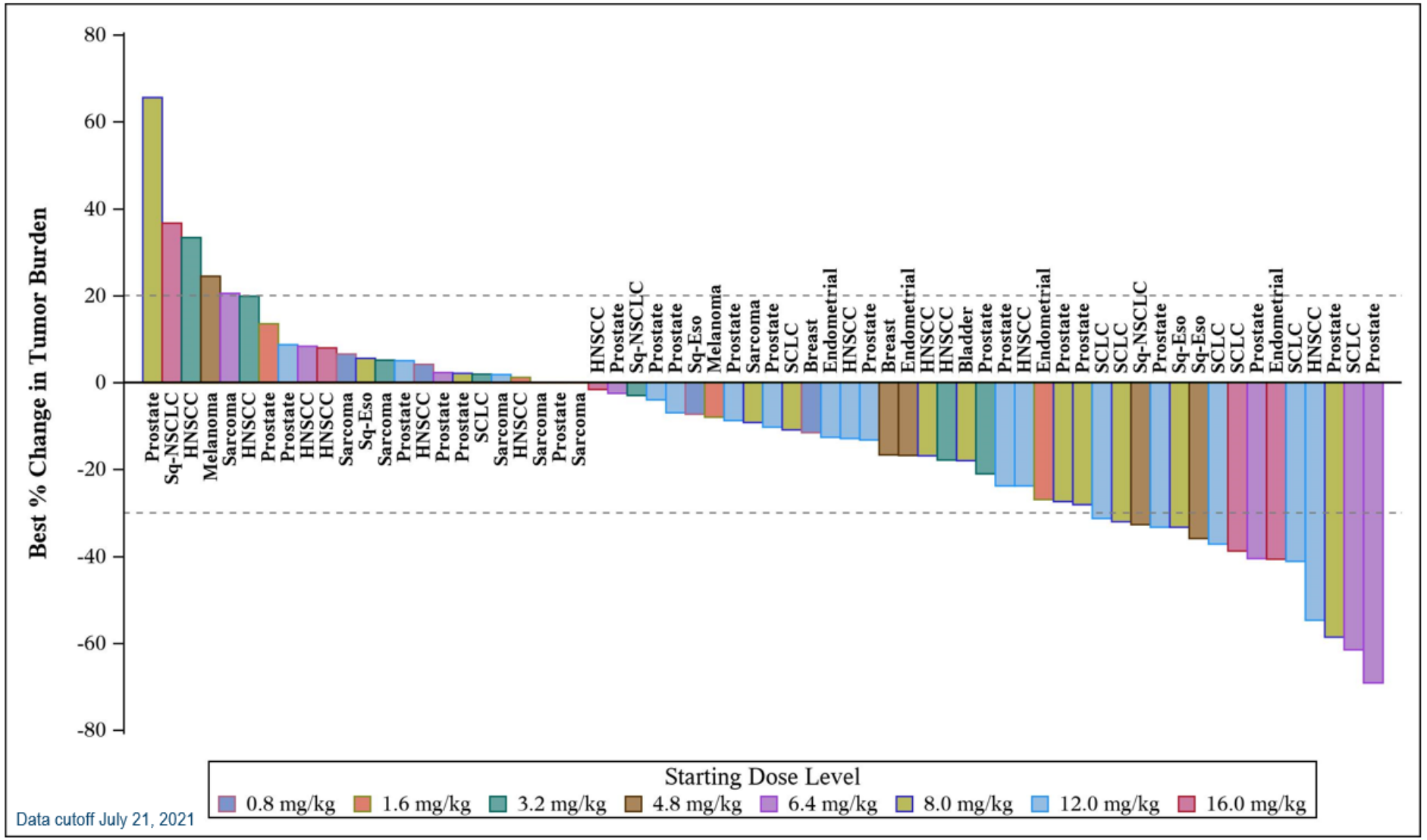
Summary of Efficacy in Dose Escalation (per RECIST v1.1)

Patients, n	DS-7300								
	0.8 mg/kg (n=5)	1.6 mg/kg (n=5)	3.2 mg/kg (n=7)	4.8 mg/kg (n=5)	6.4 mg/kg (n=8)	8.0 mg/kg (n=12)	12.0 mg/kg (n=21)	16.0 mg/kg (n=7)	Total (N=70)
Best response									
CR	0	0	0	0	0	0	0	0	0
PR[a]	0	0	0	2	3	3	5	2	15
SD	4	4	3	1	2	5	12	1	32
PD	1	1	4	2	2	4	1	2	17
NE[b]	0	0	0	0	1	0	3	2	6

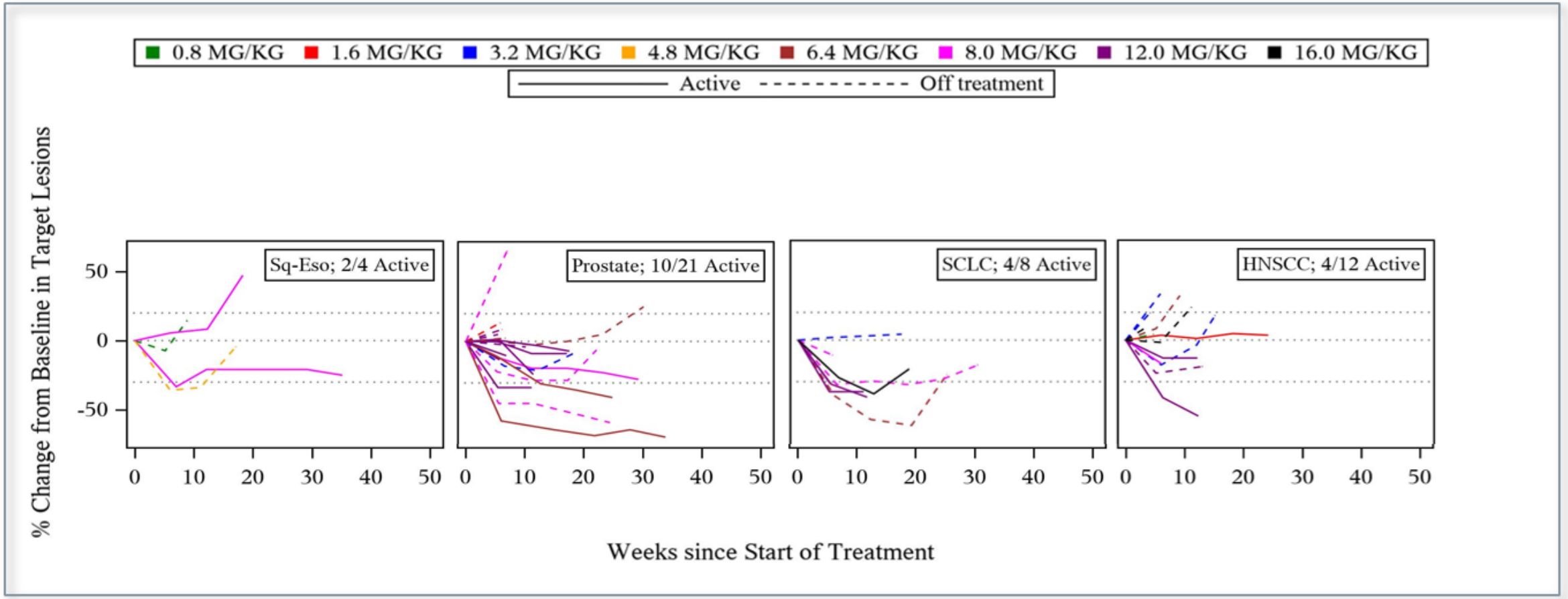
Data cutoff July 21, 2021

[a] Total confirmed and unconfirmed PRs was 10 and 5, respectively; unconfirmed partial responses are still ongoing. [b] Not evaluable per RECIST v 1.1.
CR, complete response; PD, progressive disease; NE, not evaluable; PR, partial response; SD, stable disease

Results: Initial Efficacy (Dose Escalation Cohorts)



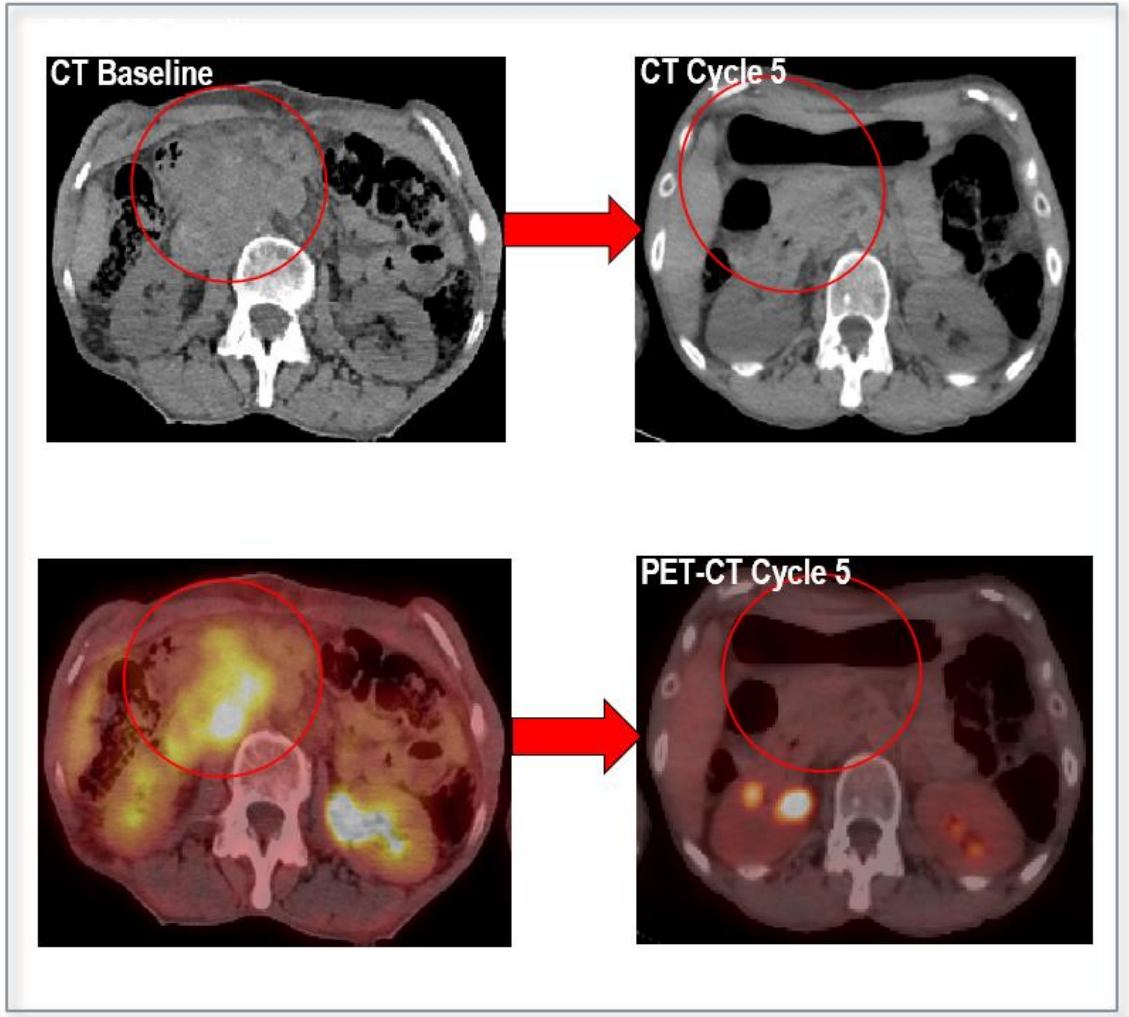
Results: Preliminary Efficacy (Dose Escalation Cohorts)



Data cutoff July 21, 2021

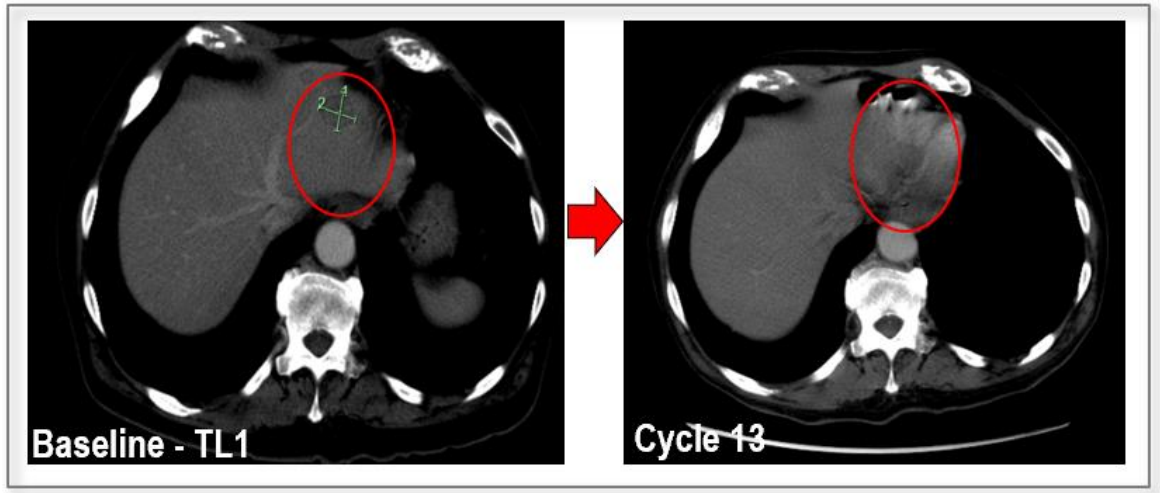
Case Summary: SCLC

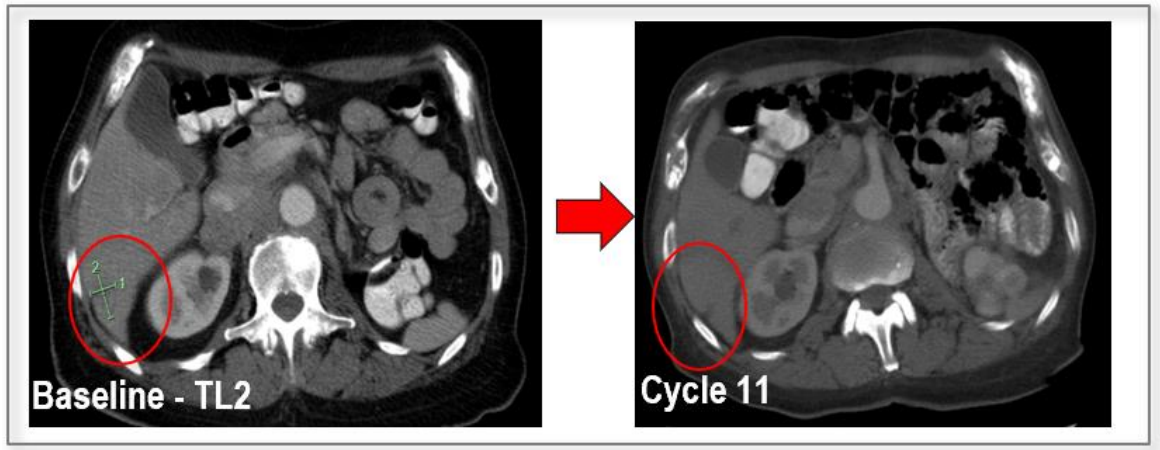
- 69-year-old female with SCLC
- 7 prior therapies
- Treated with DS-7300 8.0 mg/kg IV Q3W



Case Summary: mCRPC

- 72-year-old male with stage IV CRPC
- 5 prior therapies
- Treated with DS-7300 6.4 mg/kg IV Q3W





TL, target lesion

Conclusions

- In this first-in-human trial of single-agent DS-7300, a novel B7-H3 ADC, no DLTs were observed, and DS-7300 was generally well tolerated across all doses investigated to date in heavily pretreated patients with advanced solid tumors
- 15 PRs, including 10 confirmed and 5 unconfirmed, were observed in RECIST-evaluable patients at various doses during dose escalation
- Dose expansion of the study (part 2) is open and currently enrolling patients with select solid tumor types, including SCLC, ESCC, and mCRPC, to further evaluate DS-7300 efficacy, safety, and tolerability

本資料に関するお問い合わせ先

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