Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

ASCOハイライト

第一三共株式会社

2022年 6月 8日

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ASCOハイライト 2022: IRカンファレンスコール

眞鍋　淳
代表取締役 兼 CEO

竹下　健一
グローバル R&D ヘッド

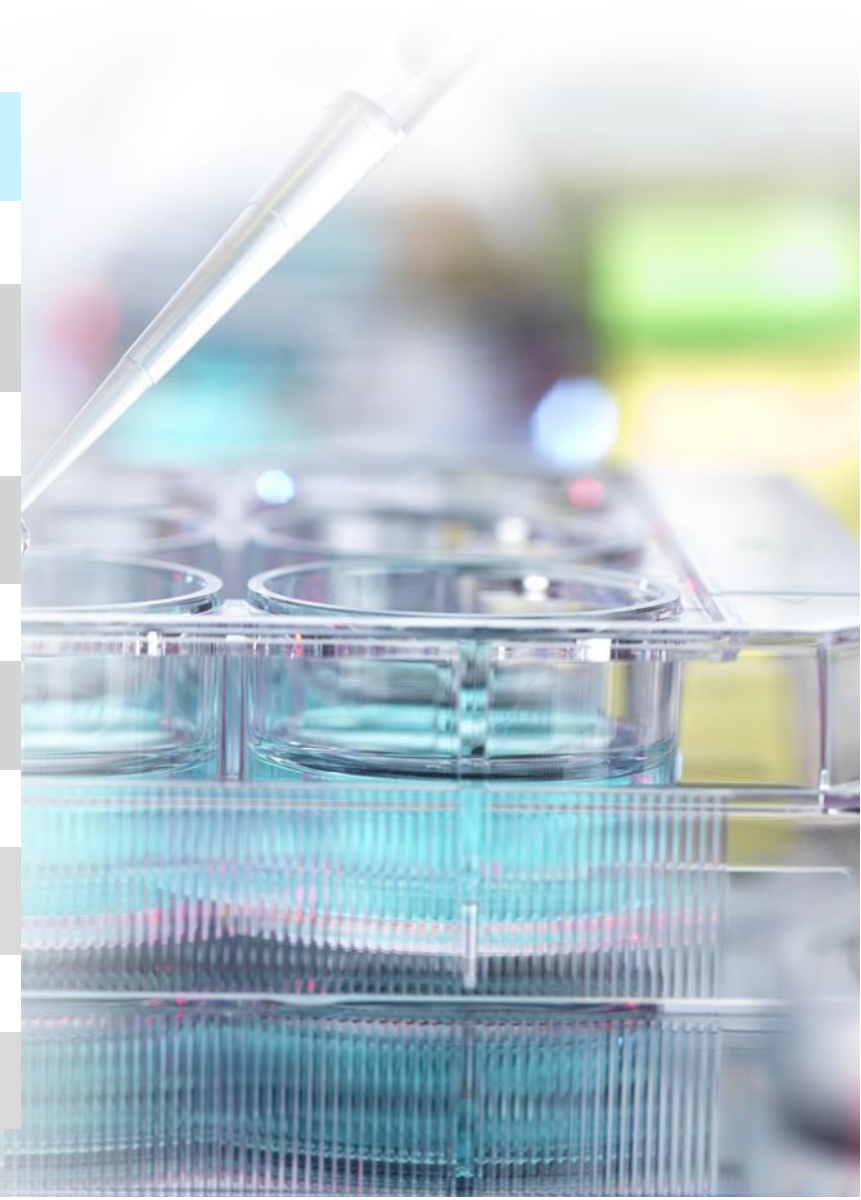
ジル　ギャラン
グローバル オンコロジー
臨床開発ヘッド

日時	2022年6月8日（水）7:30-9:00am JST
形式	バーチャル（Zoom）

本内容は後日オンデマンド配信予定

本日お話しする内容

1. イントロダクション
2. HER2低発現乳がん治療のパラダイムをシフトする
3. HER2陽性乳がんにおける信頼を構築する
4. 乳がんのさらなるニーズに対応する
5. Rising Stars
6. 今後のニュースフロー



持続的成長に向けた第5期中計の位置付け

第5期中計は、2025年度目標**「がんに強みを持つ先進的グローバル創薬企業」**を達成し、2030年ビジョン実現に向けた成長ステージに移行するための計画と位置づける

2020年現在

- がん事業立ち上げ
- エドキサバン拡大
- リージョナル・バリュー拡大
- AZアライアンス
- 研究開発投資拡大

2030年ビジョン

サステナブルな社会の発展に貢献する先進的グローバルヘルスケアカンパニー

- がん領域でグローバル top10
- 更なる成長の柱が収益源の一つ
- 各事業ユニットが新製品を軸とした収益構造
- 事業を通じたサステナブルな社会の発展への貢献

第5期中計　戦略の柱
第一の柱: 3ADC最大化の実現

2025年度目標を達成し成長ステージへ

3ADC最大化の実現
- アストラゼネカとの戦略的提携を通じたエンハーツ®、Dato-DXd最大化
- HER3-DXdの自社開発と最大化
- 製品ポテンシャルに合わせた効率的・段階的な要員・供給キャパシティ拡大

既存事業・製品の利益成長
- リクシアナ®利益最大化
- タリージェ®、Nilemdo®等の早期拡大
- 新薬を軸とした収益構造へのトランスフォーメーション
- アメリカン・リージェント、第一三共ヘルスケアの利益成長

更なる成長の柱の見極めと構築
- 3ADCに次ぐ成長ドライバーの見極め
- ポストDXd-ADCモダリティの選定

ステークホルダーとの価値共創
- 患者さん：Patient Centric Mindsetによる患者さんへの貢献
- 株主：バランスのとれた成長投資と株主還元
- 社会：バリューチェーン全体の環境負荷の低減、およびパンデミックリスクへの対応
- 従業員：One DS Cultureの醸成に向けたCore behaviorの実践

- DX推進によるデータ駆動型経営の実現と先進デジタル技術による全社の変革
- 新たなグローバルマネジメント体制による迅速な意思決定の実現

*3ADC：①エンハーツ®、トラスツズマブ デルクステカン（T-DXd、DS-8201）、②ダトポタマブ デルクステカン（Dato-DXd、DS-1062）および③パトリツマブ デルクステカン（HER3-DXd、U3-1402）

3ADCの上市計画
- 3ADCの幅広いがん種・治療ラインへの拡大-

~FY2020

エンハーツ®

- DESTINY-Breast01
- DESTINY-Gastric01

第5期中計 (FY2021-FY2025)

エンハーツ®

- DESTINY-Breast03
- DESTINY-Breast04
- DESTINY-Breast06
- DESTINY-Gastric04
- DESTINY-Lung01/02
- DESTINY-CRC01/02

Dato-DXd

- TROPION-Lung01

HER3-DXd

- HERTHENA-Lung01

FY2026 & Beyond

エンハーツ®

- DESTINY-Breast05
- DESTINY-Breast09
- DESTINY-Breast11
- DESTINY-Lung04

- 胃がん/NSCLC の早期ライン(併用含む)
- その他のがん種

Dato-DXd

- TROPION-Lung08
- TROPION-Breast01
- TROPION-Breast02

- NSCLC早期ライン，I/O 併用
- 乳がん（HER2陰性の早期ライン）
- その他のがん種

HER3-DXd

- HERTHENA-Lung02

- NSCLC早期ライン、オシメルチニブとの併用
- その他のがん種

2025年度目標の達成および2030年度に向けた成長ステージの移行へ順調なスタートを切った

新規適応取得のピボタル試験のみ記載

第5期中計　戦略の柱
第三の柱: 更なる成長の柱の見極めと構築

2025年度目標を達成し成長ステージへ

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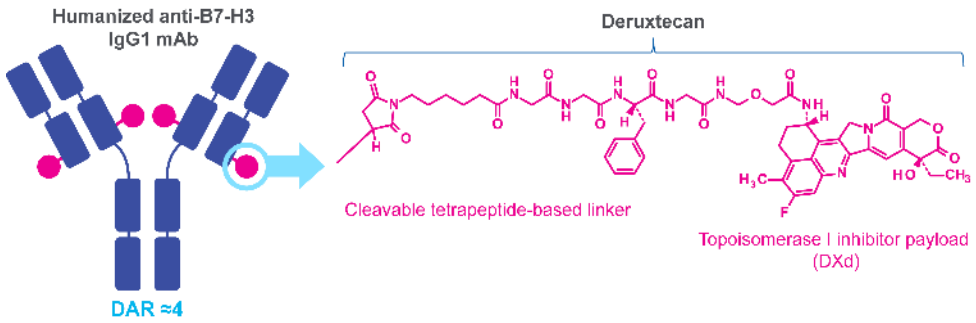
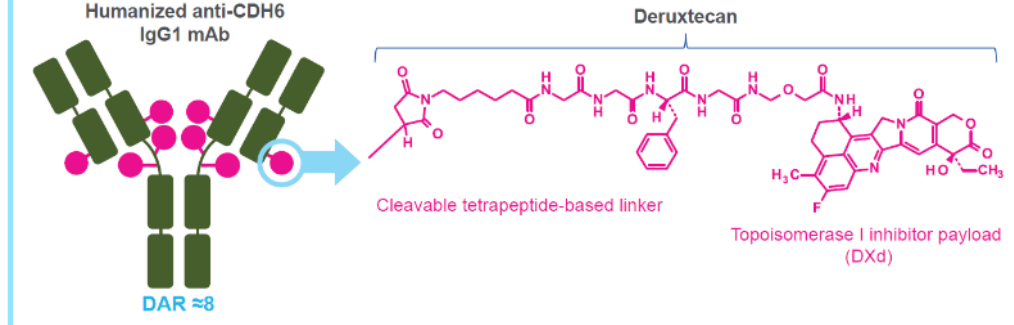
Rising Stars: DS-7300 & DS-6000

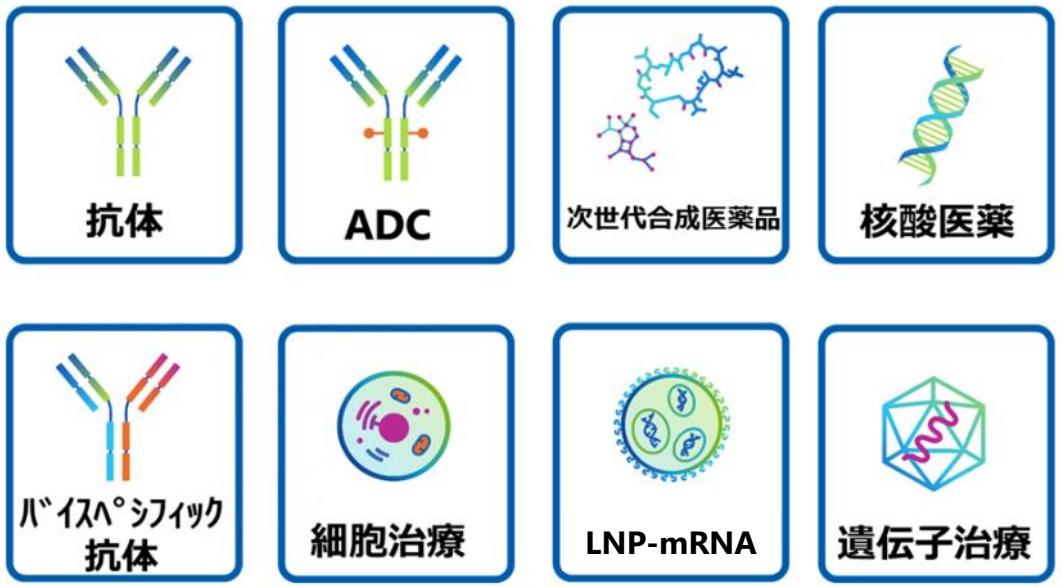
	DS-7300	DS-6000
構造		
開発ステージ & 適応症	**Ph1/2** 用量漸増パート: 固形がん 用量展開パート: 食道扁平上皮がん, 去勢抵抗性前立腺がん, 扁平上皮NSCLC **Ph2 (SCLC)** 2022年度上半期の開始を目指し準備中	**Ph1** 用量漸増& 用量展開パート: 腎細胞がん & 卵巣がん 現在用量展開パートを実施中

DAR: 薬物抗体比、mAb: モノクローナル抗体、NSCLC: 非小細胞肺がん、SCLC: 小細胞肺がん

Rising Starsは3ADCに次ぐ成長ドライバーとなる可能性を有しており、開発を加速化している

マルチモダリティ戦略

Optimized modality



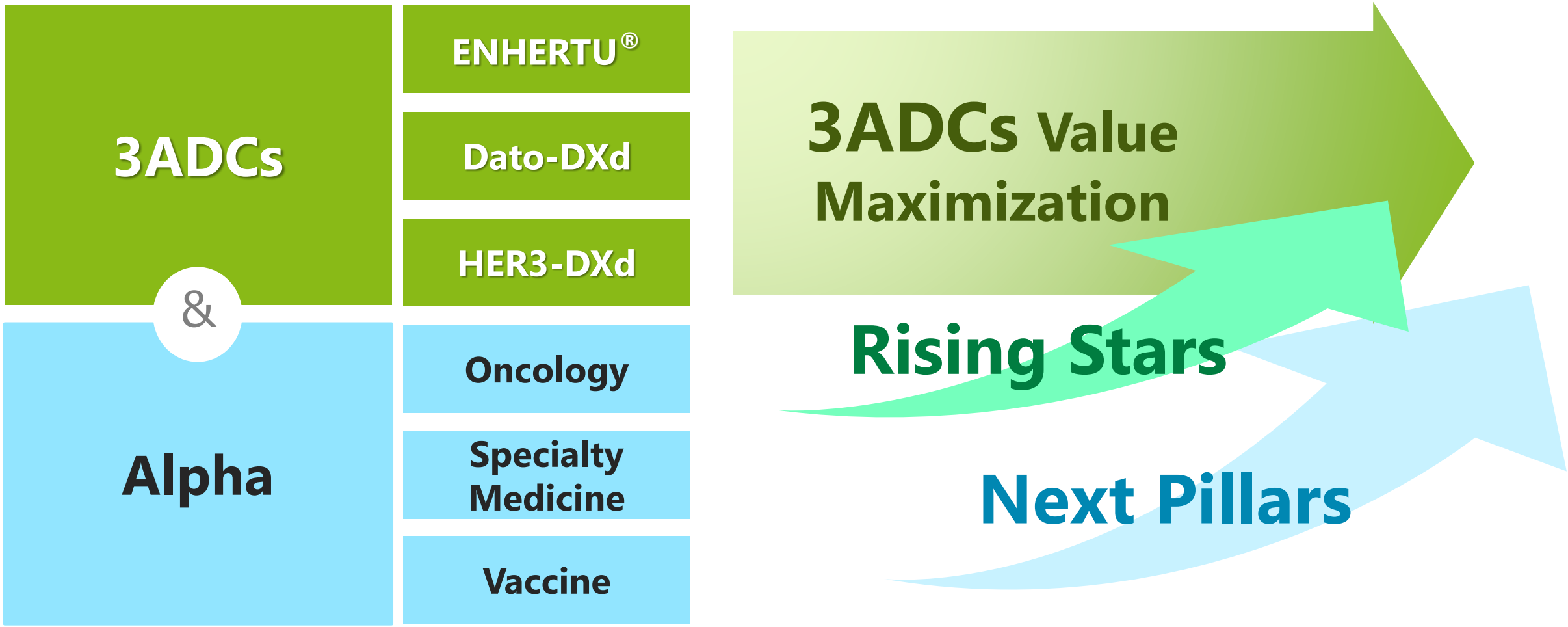
アンメット
メディカルニーズの
高い疾患

有望なポストDXd-ADCモダリティの選定が進行中

- 2021年度は**LNP-mRNA**技術の開発・製造に関する重要なノウハウが蓄積された
- その他のモダリティは研究早期の段階であり、可能性の見極めには更なるデータの蓄積が必要

患者さんへの貢献を高めるための第一三共の研究開発戦略

◆「3 and Alpha」 戦略の発展



第一三共のパーパスとR&Dビジョン

パーパス	世界中の人々の 健康で豊かな生活に貢献する
R&Dビジョン	患者さんによりよい人生をもたらす イノベーションの源泉となる

世界中の患者さんへの貢献

当社の強み **サイエンス&テクノロジー** の
グローバル展開によって

ASCO & ESMO BC　データ ハイライト

ESMO BC 2022
8 Abstracts

4 Oral Presentations
2 Mini Oral Presentations
2 Poster Presentations

4 on ENHERTU®
1 on Dato-DXd
2 on HER3-DXd

ASCO 2022
20 Abstracts

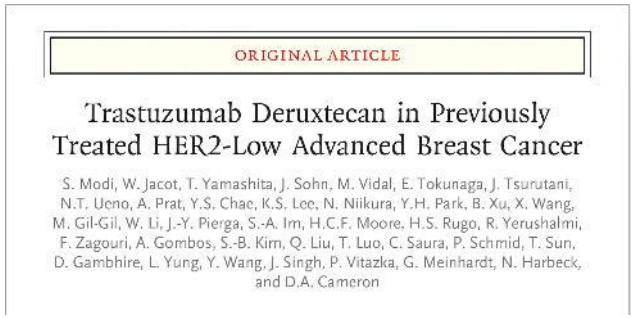
1 Plenary Session
4 Oral Presentations
13 Poster Presentations

9 on ENHERTU®
1 on Dato-DXd
5 on HER3-DXd

DESTINY-Breast04

エンハーツ®にとって5つ目の米国における画期的治療薬の指定

The NEW ENGLAND JOURNAL of MEDICINE


ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Low Advanced Breast Cancer

S. Modi, W. Jacot, T. Yamashita, J. Sohn, M. Vidal, E. Tokunaga, J. Tsurutani, N.T. Ueno, A. Prat, Y.S. Chae, K.S. Lee, N. Niikura, Y.H. Park, B. Xu, X. Wang, M. Gil-Gil, W. Li, J.-Y. Pierga, S.-A. Im, H.C.F. Moore, H.S. Rugo, R. Yerushalmi, F. Zagouri, A. Gombos, S.-B. Kim, Q. Liu, T. Luo, C. Saura, P. Schmid, T. Sun, D. Gambhire, L. Yung, Y. Wang, J. Singh, P. Vitazka, G. Meinhardt, N. Harbeck, and D.A. Cameron

本日お話しする内容

1. イントロダクション
2. **HER2低発現乳がん治療のパラダイムをシフトする**
3. HER2陽性乳がんにおける信頼を構築する
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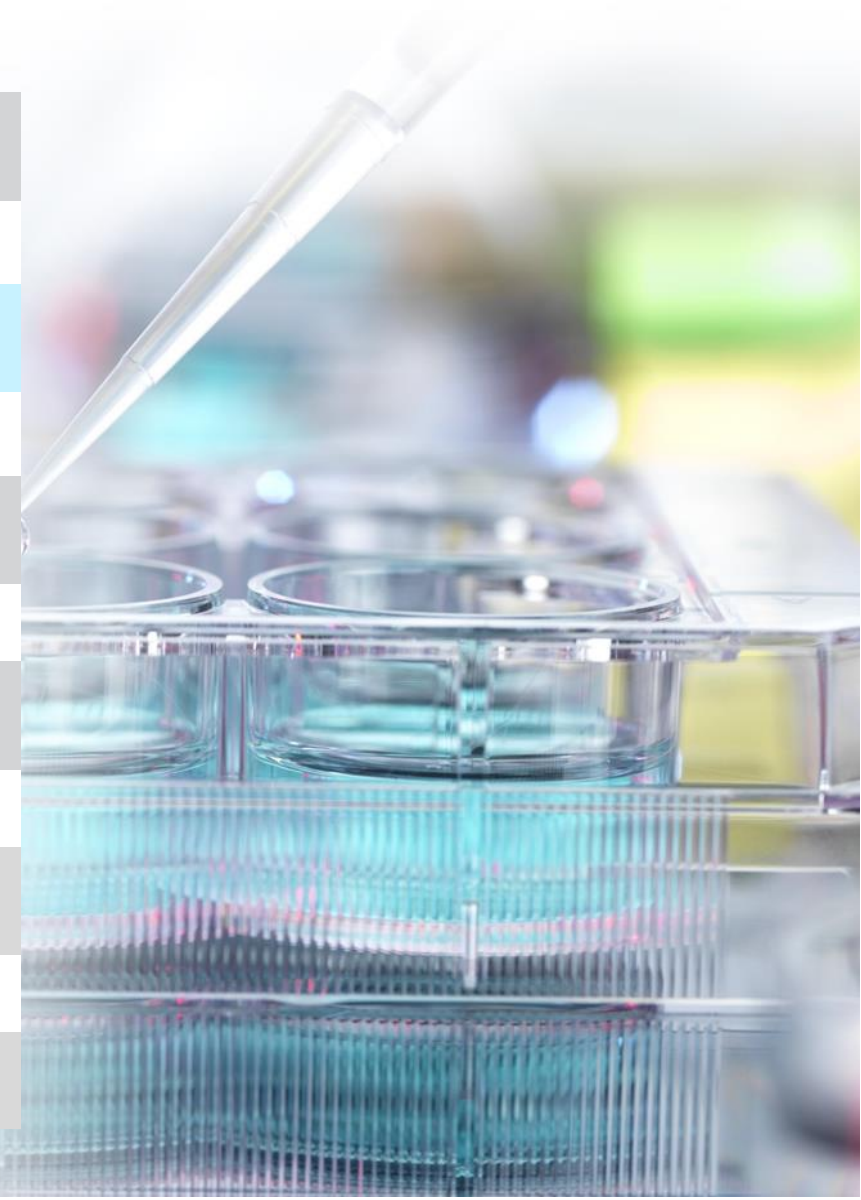


HER2低発現乳がん患者の新規治療パラダイムの扉が開かれる

Daiichi-Sankyo

DESTINY-Breast04

Trastuzumab Deruxtecan (T-DXd) vs Treatment of Physician's Choice in Patients with HER2-low Unresectable and/or Metastatic Breast Cancer: Results of DESTINY-Breast04, a Randomized, Phase 3 Study

Shanu Modi Memorial Sloan Kettering Cancer Center, Memorial Hospital, New York, USA

Additional authors: William Jacot, Toshinari Yamashita, Joo Hyuk Sohn, Maria Vidal, Eriko Tokunaga, Junji Tsurutani, Naoto Ueno, Yee Soo Chae, Keun Seok Lee, Naoki Niikura, Yeon Hee Park, Xiaojia Wang, Binghe Xu, Dhiraj Gambhire, Lotus Yung, Gerold Meinhardt, Yibin Wang, Nadia Harbeck, David Cameron

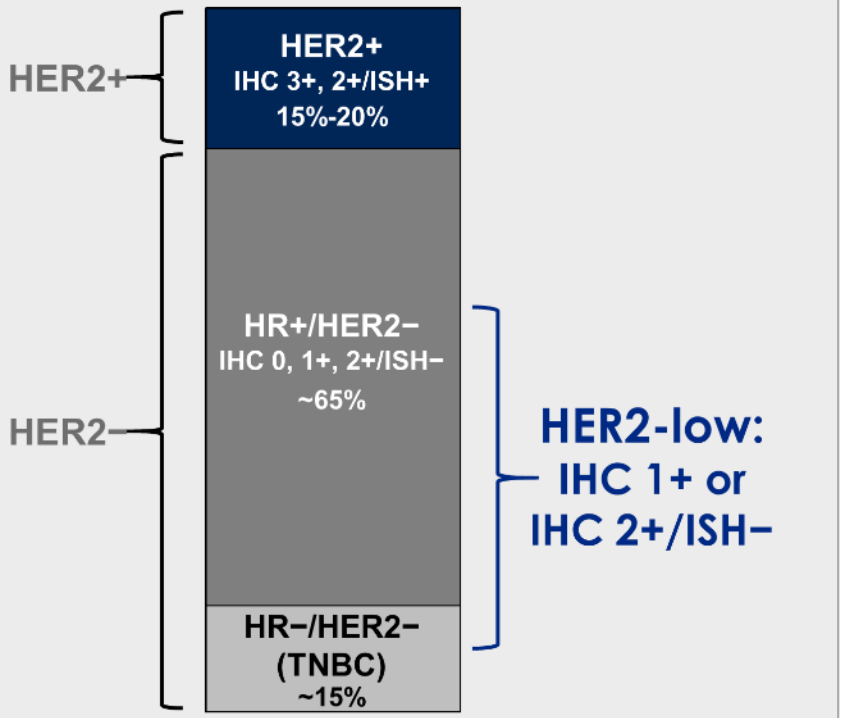
DESTINY-Breast04 概要とインパクト

DESTINY-Breast04

Daiichi-Sankyo

T-DXd treatment showed unprecedented improvement in efficacy for patients with HER2-low mBC

Current mBC paradigm[1,2]



The new mBC paradigm

- T-DXd is the first HER2-targeted therapy to demonstrate improved efficacy in HER2-low mBC
- DESTINY-Breast04 establishes T-DXd as the new standard of care for HER2-low mBC
- Potential improvement for ~50% of all mBC patients

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; T-DXd, trastuzumab deruxtecan; TNBC, triple-negative breast cancer; TPC, treatment of physician's choice.

1. Schettini F, et al. *NPJ Breast Cancer*. 2021;7(1):1. 2. Tarantino P, et al. *J Clin Oncol*. 2020;38(17):1951-1962.

DESTINY-Breast04: T-DXd 初のHER2低発現転移再発乳がんを対象としたPhase 3試験

DESTINY-Breast04

Daiichi-Sankyo

An open-label, multicenter study (NCT03734029)

Patients[a]
- HER2-low (IHC 1+ vs IHC 2+/ISH−), unresectable, and/or mBC treated with 1-2 prior lines of chemotherapy in the metastatic setting
- HR+ disease considered endocrine refractory

R 2:1

T-DXd
5.4 mg/kg Q3W
(n = 373)

HR+ ≈ 480
HR− ≈ 60

TPC
Capecitabine, eribulin, gemcitabine, paclitaxel, nab-paclitaxel[c]
(n = 184)

Primary endpoint
- PFS by BICR (HR+)

Key secondary endpoints[b]
- PFS by BICR (all patients)
- OS (HR+ and all patients)

Stratification factors
- Centrally assessed HER2 status[d] (IHC 1+ vs IHC 2+/ISH−)
- 1 versus 2 prior lines of chemotherapy
- HR+ (with vs without prior treatment with CDK4/6 inhibitor) versus HR−

ASCO/CAP, American Society of Clinical Oncology/College of American Pathologists; BICR, blinded independent central review; CDK, cyclin-dependent kinase; DOR, duration of response; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; mBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]If patients had HR+ mBC, prior endocrine therapy was required. [b]Other secondary endpoints included ORR (BICR and investigator), DOR (BICR), PFS (investigator), and safety; efficacy in the HR− cohort was an exploratory endpoint. [c]TPC was administered accordingly to the label. [d]Performed on adequate archived or recent tumor biopsy per ASCO/CAP guidelines using the VENTANA HER2/neu (4B5) investigational use only [IUO] Assay system.

患者背景

DESTINY-Breast04

Daiichi-Sankyo

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Age, median (range), years	57 (32-80)	56 (28-80)	58 (32-80)	56 (28-80)
Female, n (%)	329 (99)	163 (100)	371 (99)	184 (100)
Region, n (%)				
Europe + Israel	149 (45)	73 (45)	166 (45)	85 (46)
Asia	128 (39)	60 (37)	147 (39)	66 (36)
North America	54 (16)	30 (18)	60 (16)	33 (18)
HER2 status (IHC), n (%)				
1+	193 (58)	95 (58)	215 (58)	106 (58)
2+/ISH−	138 (42)	68 (42)	158 (42)	78 (42)
ECOG performance status, %				
0	187 (56)	95 (58)	200 (54)	105 (57)
1	144 (44)	68 (42)	173 (46)	79 (43)
Hormone receptor,[a] n (%)				
Positive	328 (99)	162 (99)	333 (89)	166 (90)
Negative	3 (1)	1 (1)	40 (11)	18 (10)
Brain metastases at baseline, n (%)	18 (5)	7 (4)	24 (6)	8 (4)
Liver metastases at baseline, n (%)	247 (75)	116 (71)	266 (71)	123 (67)
Lung metastases at baseline, n (%)	98 (30)	58 (36)	120 (32)	63 (34)

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Hormone receptor status is based on data collected using the interactive web/voice response system at the time of randomization, which includes misstratified patients.

前治療歴

DESTINY-Breast04

Daiichi-Sankyo

	Hormone receptor–positive		All patients	
	T-DXd (n = 331)	TPC (n = 163)	T-DXd (n = 373)	TPC (n = 184)
Lines of systemic therapy (metastatic setting)				
Number of lines, median (range)	3 (1-9)	3 (1-8)	3 (1-9)	3 (1-8)
Number of lines, n (%)				
1	23 (7)	14 (9)	39 (10)	19 (10)
2	85 (26)	41 (25)	100 (27)	53 (29)
≥3	223 (67)	108 (66)	234 (63)	112 (61)
Lines of chemotherapy (metastatic setting)				
Number of lines, median (range)	1 (0-3)	1 (0-2)	1 (0-3)	1 (0-2)
Number of lines, n (%)				
0	1 (0.3)	1 (0.6)	1 (0.3)	1 (0.5)
1	203 (61.3)	93 (57.1)	221 (59.2)	100 (54.3)
2	124 (37.5)	69 (42.3)	145 (38.9)	83 (45.1)
≥3	3 (0.9)	0	6 (1.6)	0
Lines of endocrine therapy (metastatic setting)				
Number of lines, median (range)	2 (0-7)	2 (0-6)	2 (0-7)	2 (0-6)
Number of lines, n (%)				
0	28 (8)	17 (10)	60 (16)	34 (18)
1	105 (32)	49 (30)	108 (29)	51 (28)
2	110 (33)	53 (33)	115 (31)	54 (29)
≥3	88 (27)	44 (27)	90 (24)	45 (24)
Prior targeted cancer therapy, n (%)				
Targeted therapy	259 (78)	132 (81)	279 (75)	140 (76)
CDK4/6 inhibitor	233 (70)	115 (71)	239 (64)	119 (65)

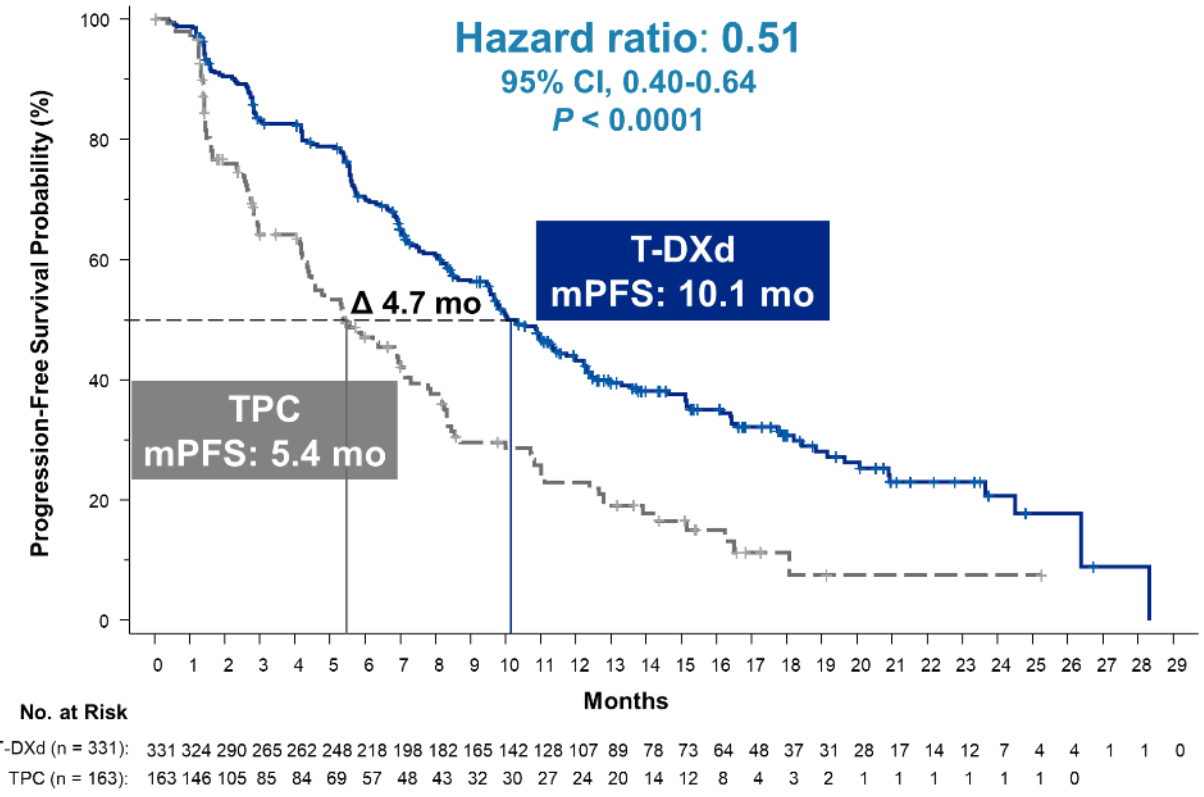
Based on derived data, which includes protocol deviations. CDK, cyclin-dependent kinase; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFS: HR+ および すべての患者

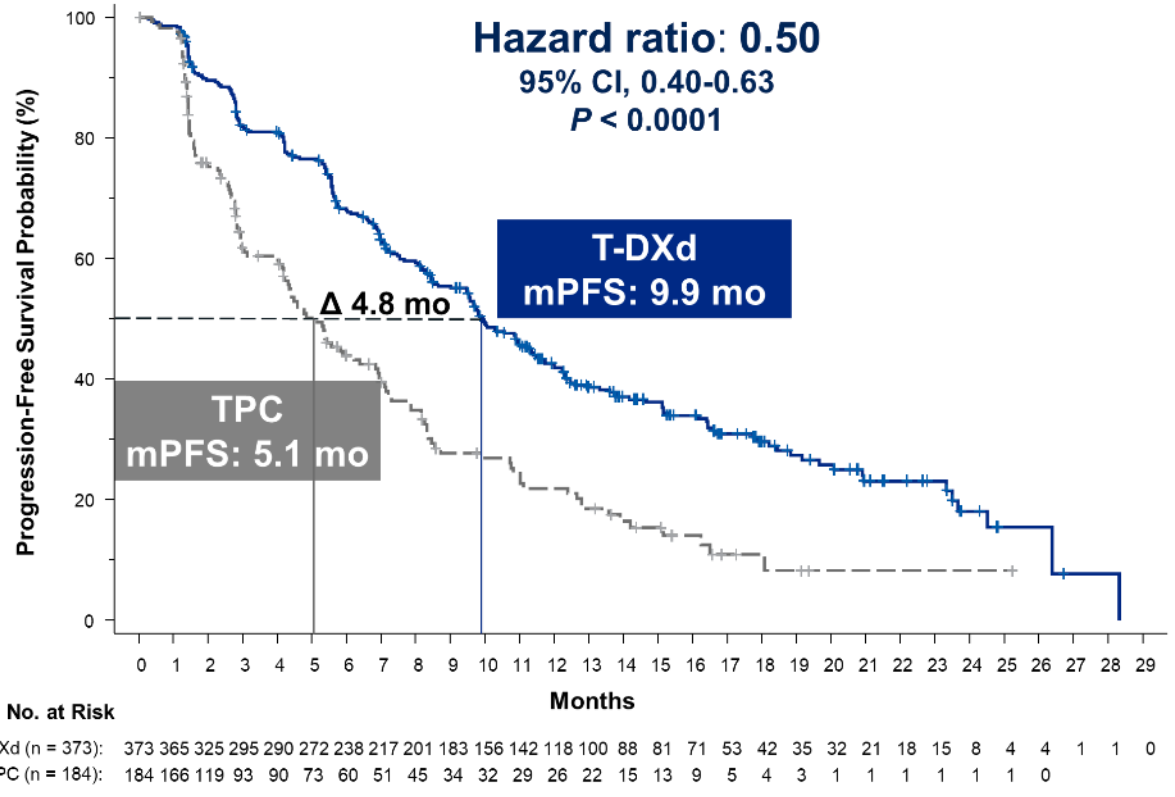
DESTINY-Breast04

Daiichi-Sankyo

Hormone receptor–positive



All patients



PFS by blinded independent central review.

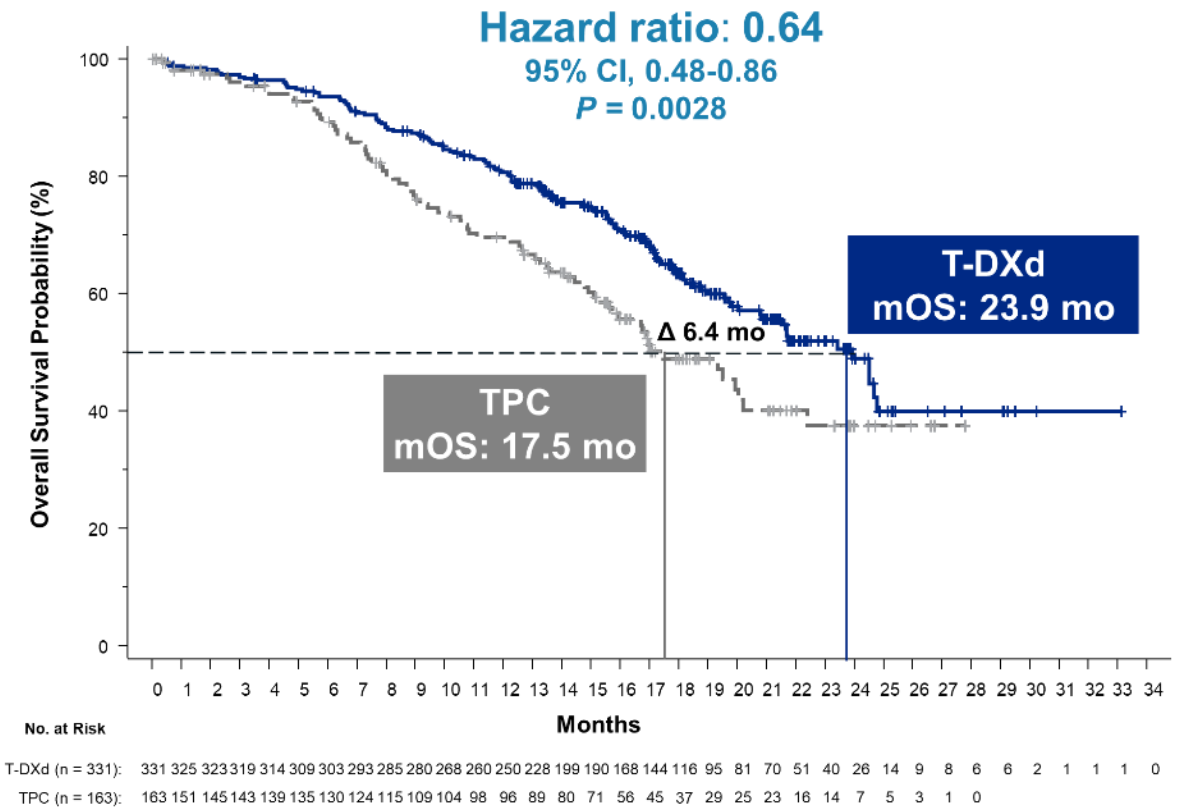
HR, hormone receptor; mPFS, median progression-free survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

OS: HR+ および すべての患者

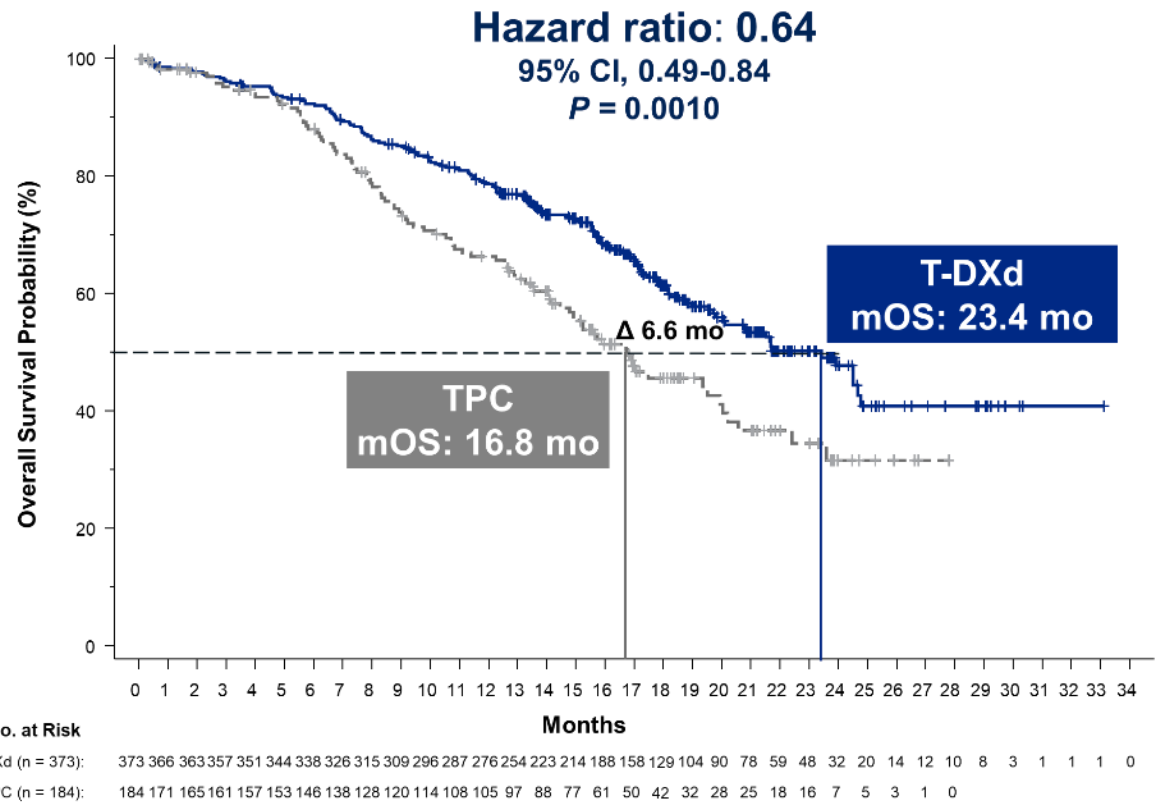
DESTINY-Breast04

Daiichi-Sankyo

Hormone receptor–positive



All patients



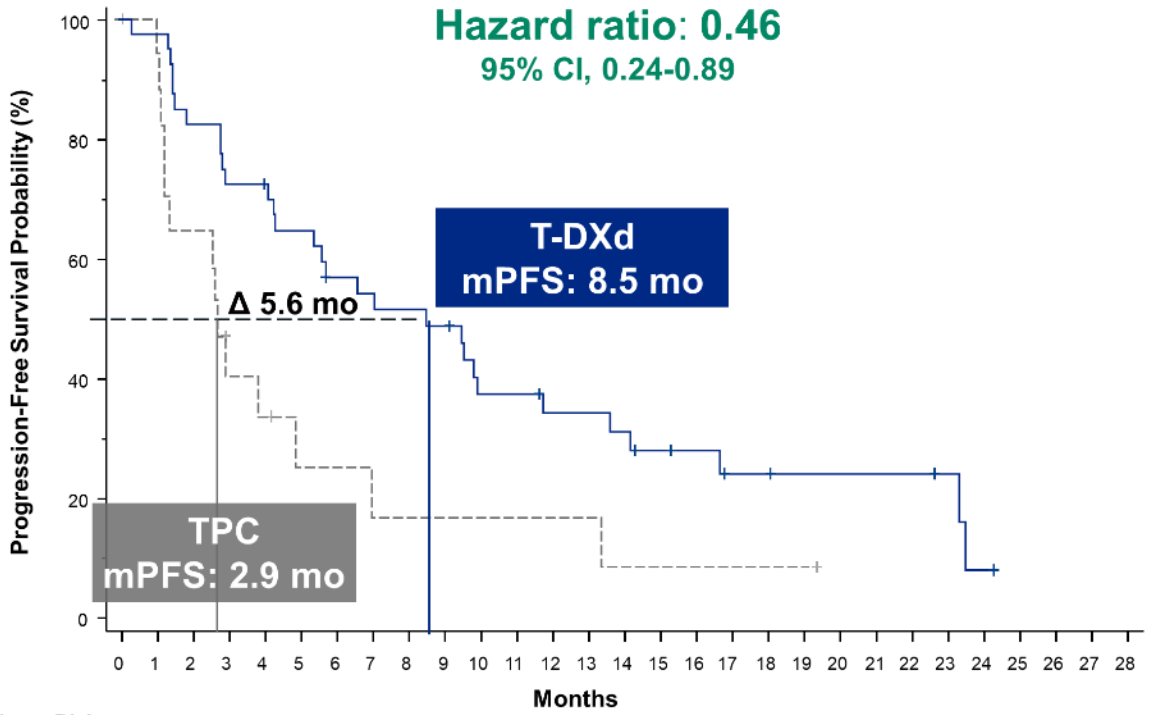
HR, hormone receptor; mOS, median overall survival; OS, overall survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

PFSおよびOS: HR- 患者（探索的評価項目）

DESTINY-Breast04

Daiichi-Sankyo

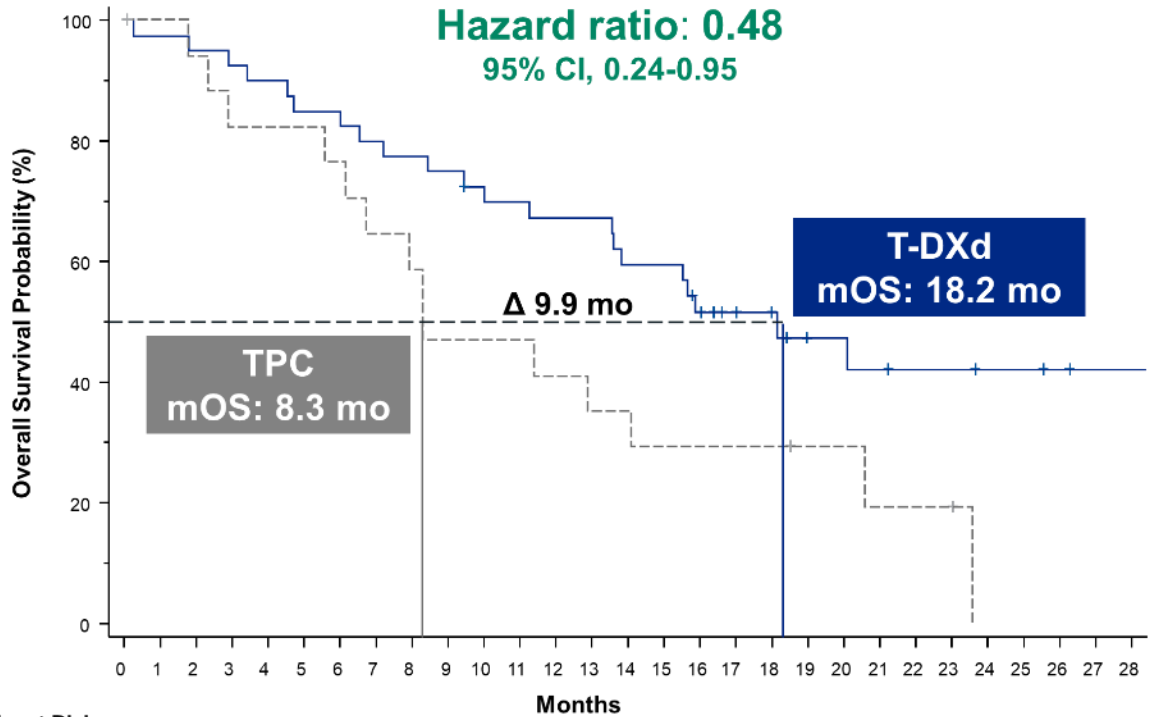
PFS



No. at Risk

T-DXd (n = 40):	40	39	33	29	28	25	21	20	19	18	13	13	11	11	10	8	7	5	5	4	4	4	3	1	0
TPC (n = 18):	18	17	11	7	6	4	3	3	2	2	2	2	2	2	1	1	1	1	1	1	0				

OS



No. at Risk

T-DXd (n = 40):	40	39	38	37	36	34	34	32	31	30	28	27	26	26	23	23	19	14	13	9	9	8	7	7	6	6	5	4	4
TPC (n = 18):	18	17	16	14	14	14	3	11	10	8	8	8	7	6	6	5	5	5	5	3	3	2	2	2	0				

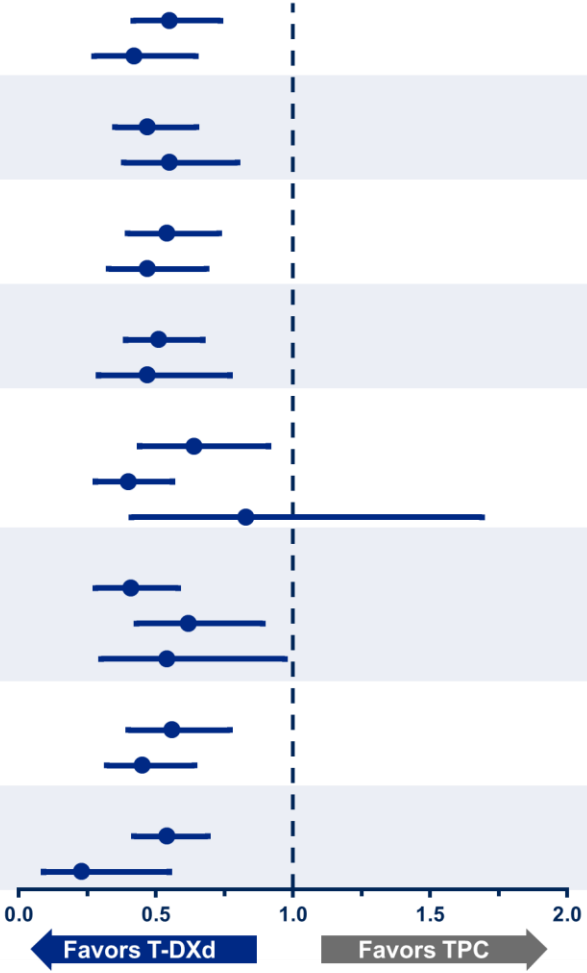
HR, hormone receptor; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
For efficacy in the hormone receptor–negative cohort, hormone receptor status is based on data from the electronic data capture corrected for misstratification.

サブグループ解析: HR+患者のPFS

DESTINY-Breast04

Daiichi-Sankyo

	No. of Events/No. of Patients		PFS, median (95% CI), mo		Hazard Ratio for Disease Progression or Death (95% CI)
	T-DXd	TPC	T-DXd	TPC	
Prior CDK4/6 inhibitors					
Yes	149/233	74/115	10.0 (8.3-11.4)	5.4 (4.0-7.8)	0.55 (0.42-0.73)
No	60/96	35/47	11.7 (9.5-17.7)	5.9 (4.3-8.2)	0.42 (0.28-0.64)
IHC status					
IHC 1+	119/192	66/96	10.3 (8.6-12.3)	5.3 (4.1-7.8)	0.48 (0.35-0.65)
IHC 2+/ISH−	92/139	44/67	10.1 (8.2-12.2)	5.9 (4.3-7.9)	0.55 (0.38-0.80)
Prior lines of chemotherapy					
1	129/203	63/93	10.9 (8.5-12.3)	6.8 (4.5-8.2)	0.54 (0.40-0.73)
≥2	81/127	47/69	9.9 (8.3-11.7)	4.6 (2.8-6.2)	0.47 (0.33-0.68)
Age					
<65 years	170/260	79/120	9.8 (8.4-11.3)	5.4 (4.1-7.8)	0.51 (0.39-0.67)
≥65 years	41/71	31/43	12.0 (9.5-14.7)	5.6 (4.3-10.8)	0.47 (0.29-0.77)
Race					
White	100/156	43/78	10.0 (8.5-12.2)	7.1 (4.0-10.0)	0.64 (0.44-0.91)
Asian	83/131	54/66	11.0 (8.4-13.8)	4.8 (4.2-6.4)	0.40 (0.28-0.56)
Other	25/37	11/16	6.0 (5.4-10.5)	7.0 (1.4-11.0)	0.83 (0.41-1.69)
Region					
Asia	81/128	48/60	10.9 (8.4-14.7)	5.3 (4.2-6.8)	0.41 (0.28-0.58)
Europe and Israel	90/149	44/73	10.8 (8.5-13.0)	7.1 (3.0-10.7)	0.62 (0.43-0.89)
North America	40/54	18/30	8.5 (6.3-11.3)	4.5 (2.9-8.2)	0.54 (0.30-0.97)
ECOG performance status					
0	116/187	55/95	10.9 (9.5-13.0)	7.0 (4.2-8.5)	0.56 (0.40-0.77)
1	95/144	55/68	9.7 (7.3-11.5)	4.6 (2.9-6.2)	0.45 (0.32-0.64)
Visceral disease at baseline					
Yes	196/298	100/146	9.8 (8.5-11.1)	5.8 (4.4-7.1)	0.54 (0.42-0.69)
No	15/33	10/17	17.9 (10.9-26.4)	4.5 (1.6-12.4)	0.23 (0.09-0.55)

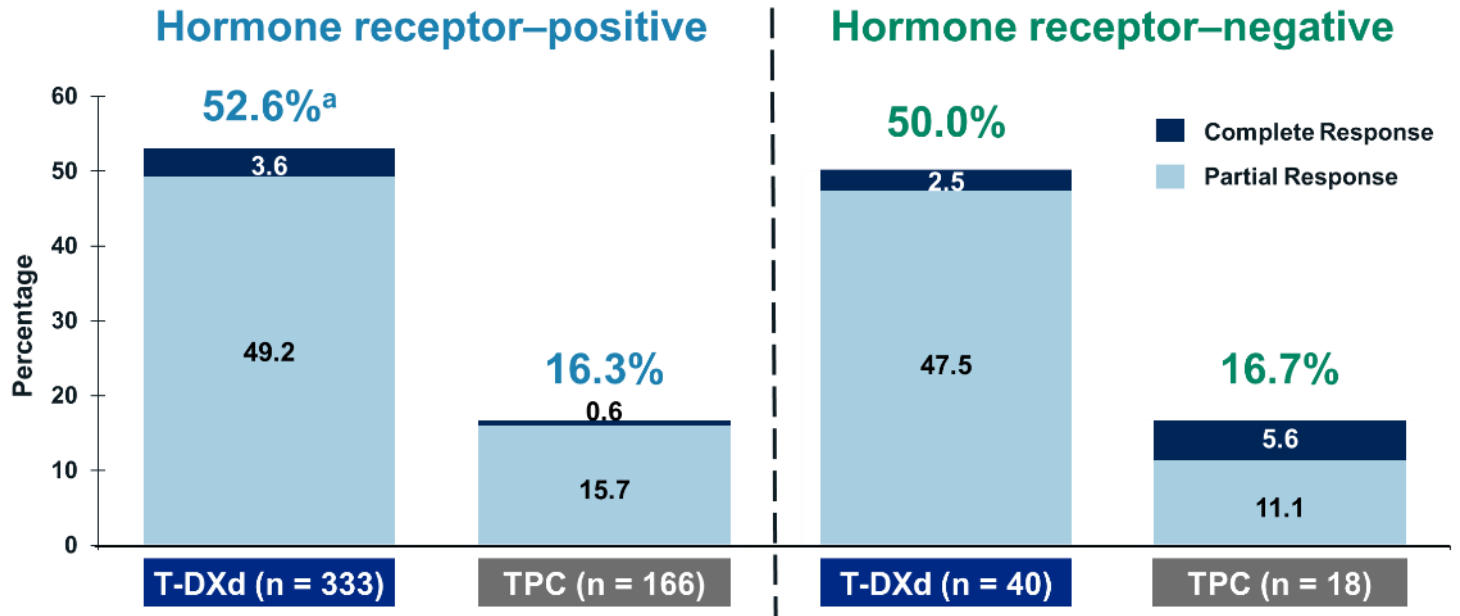


PFS by blinded independent central review. Based on derived data, which include protocol deviations.

CDK, cyclin-dependent kinase; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

確定 ORR

Confirmed Objective Response Rate



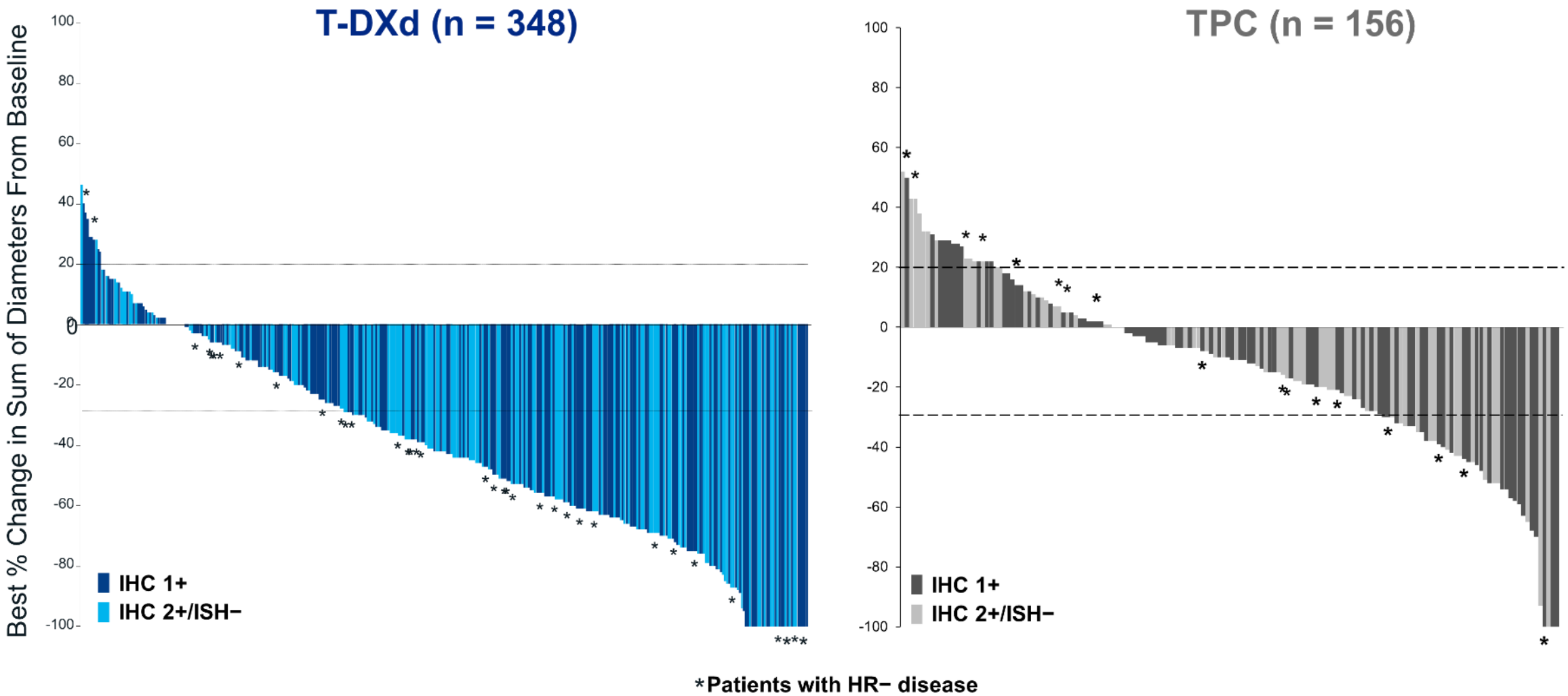
	T-DXd (n = 333)	TPC (n = 166)	T-DXd (n = 40)	TPC (n = 18)
Progressive disease, %	7.8	21.1	12.5	33.3
Not evaluable, %	4.2	12.7	7.5	5.6
Clinical benefit rate,[b] %	71.2	34.3	62.5	27.8
Duration of response, months	10.7	6.8	8.6	4.9

Hormone receptor status is based on data from the electronic data capture corrected for misstratification.
ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]The response of 1 patient was not confirmed. [b]Clinical benefit rate is defined as the sum of complete response rate, partial response rate, and more than 6 months' stable disease rate, based on blinded independent central review.

対象病変の最良の変化（すべての患者）

DESTINY-Breast04

Daiichi-Sankyo



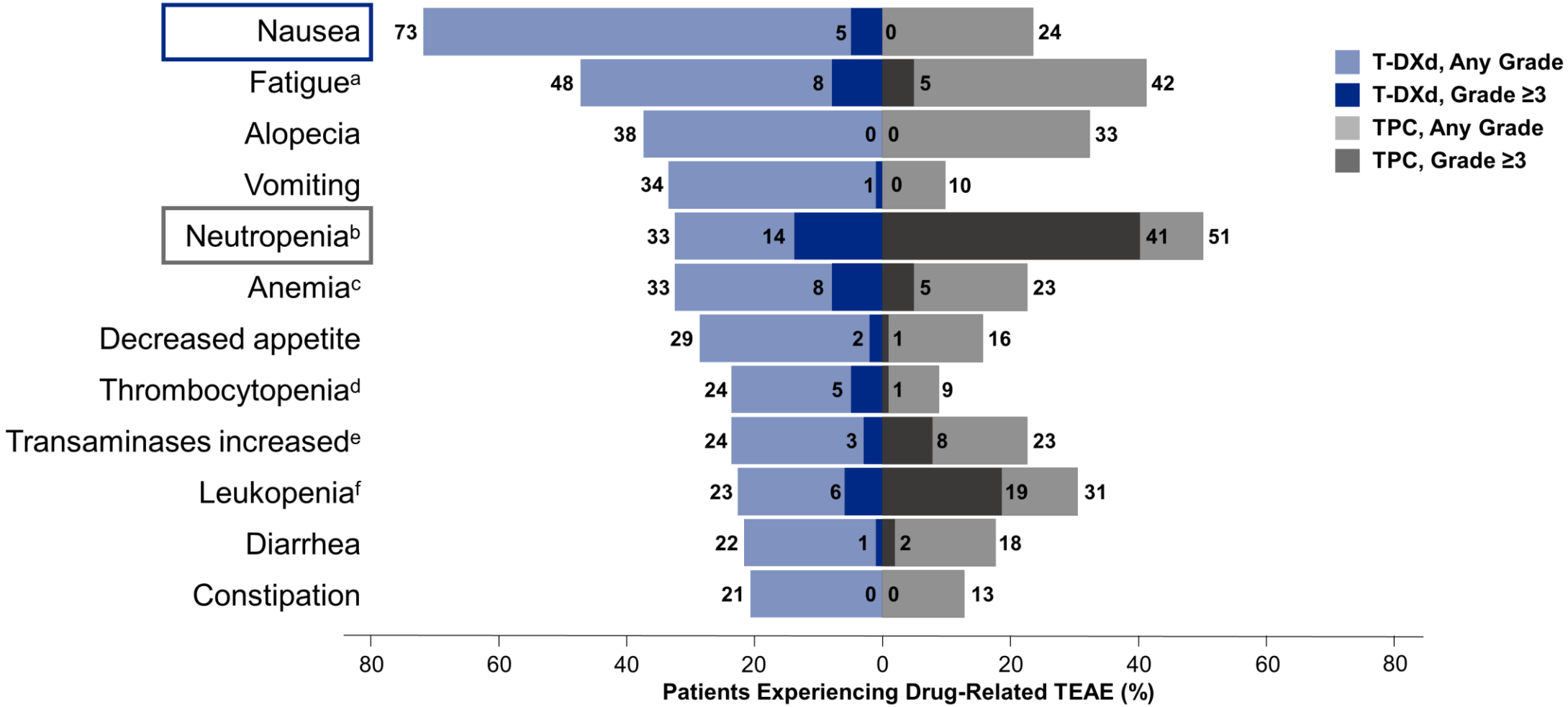
*Patients with HR− disease

Shown are the best percentage changes from baseline in the sum of the largest diameters of measurable tumors in patients for whom data from both baseline and postbaseline assessments of target lesions by independent central review were available. 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).

HR, hormone receptor; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.

20%以上の患者で確認された薬剤に関連する有害事象

DESTINY-Breast04



T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[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-cell count decreased, anemia, and hematocrit decreased. [d]This category includes the preferred terms platelet count decreased and thrombocytopenia. [e]This category includes the preferred terms transaminases increased, aspartate aminotransferase increased, alanine aminotransferase increased, gamma-glutamyltransferase increased, liver function test abnormal, hepatic function abnormal. [f]This category includes the preferred terms white-cell count decreased and leukopenia.

安全性の概要

DESTINY-Breast04

Daiichi-Sankyo

n (%)	Safety analysis set[a] T-DXd (n = 371)	TPC (n = 172)
Total patient-years of exposure, years[b]	283.55	63.59
TEAEs	369 (99)	169 (98)
Grade ≥3	195 (53)	116 (67)
Serious TEAEs	103 (28)	43 (25)
TEAEs associated with dose discontinuations	60 (16)	14 (8)
TEAEs associated with dose interruptions	143 (39)	72 (42)
TEAEs associated with dose reductions	84 (23)	66 (38)
TEAEs associated with deaths	14 (4)	5 (3)

- **Median treatment duration**
  - **T-DXd: 8.2 months (range, 0.2-33.3)**
  - **TPC: 3.5 months (range, 0.3-17.6)**
- Most common TEAE associated with treatment discontinuation
  - T-DXd: 8.2%, ILD/pneumonitis[c]
  - TPC: 2.3%, peripheral sensory neuropathy
- Most common TEAE associated with dose reduction
  - T-DXd: 4.6%, nausea and fatigue[d]
  - TPC: 14.0%, neutropenia[d]
- Total on-treatment deaths[e]
  - T-DXd: 3.8%
  - TPC: 4.7%

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TPC, treatment of physician's choice.
[a]Safety analyses were performed in patients who received ≥1 dose of a study regimen. [b]Patient-years of exposure are the treatment duration with year as unit. [c]Grouped term. [d]Fatigue includes the preferred terms fatigue, malaise, and asthenia; neutropenia included the preferred terms of neutropenia and neutrophil count decreased. [e]On-treatment death was defined as any death that occurred from the date of the first dose to 47 days after the last dose of study drug irrespective of the cause; the TEAEs associated with deaths represent a subset of on-treatment deaths reported by the investigators as adverse events.

注目すべき有害事象

DESTINY-Breast04

Daiichi-Sankyo

Adjudicated as drug-related ILD/pneumonitis[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
T-DXd (n = 371)	13 (3.5)	24 (6.5)	5 (1.3)	0	3 (0.8)	45 (12.1)
TPC (n = 172)	1 (0.6)	0	0	0	0	1 (0.6)

Left ventricular dysfunction[b]

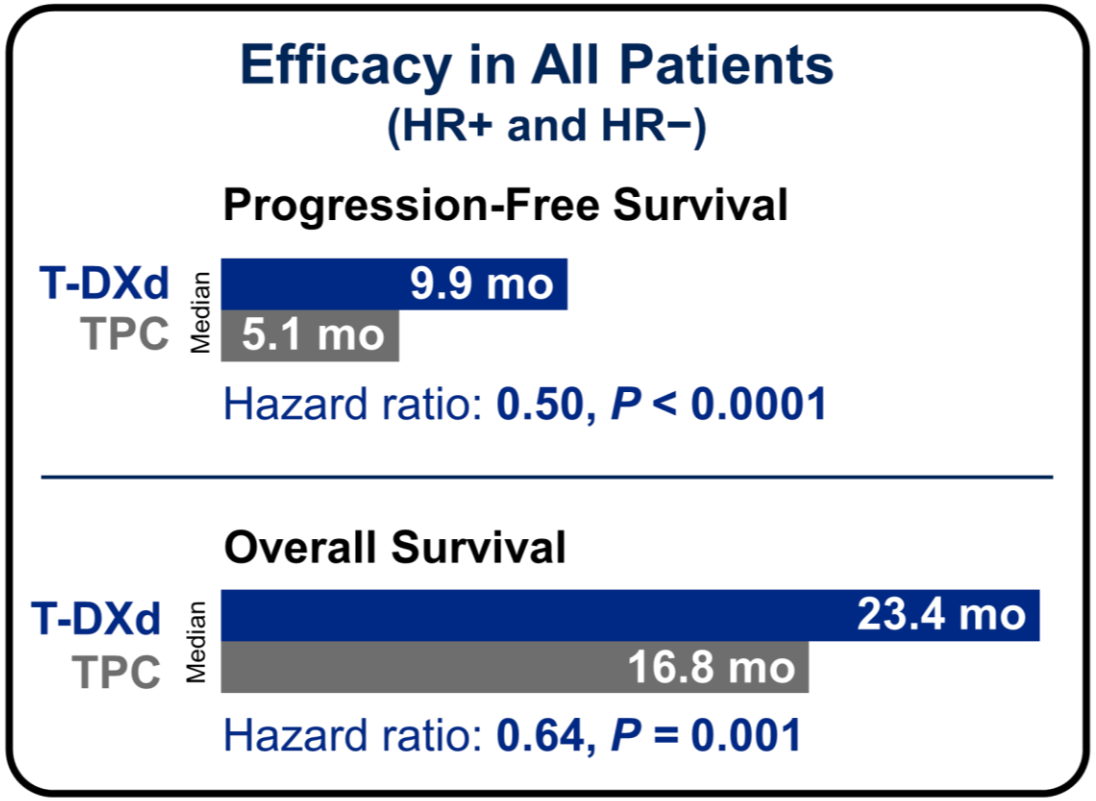
n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
Ejection fraction decreased						
T-DXd (n = 371)	1 (0.3)	14 (3.8)	1 (0.3)	0	0	16 (4.3)
TPC (n = 172)	0	0	0	0	0	0
Cardiac failure[c]						
T-DXd (n = 371)	0	1 (0.3)	1 (0.3)	0	0	2 (0.5)
TPC (n = 172)	0	0	0	0	0	0

ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TPC, treatment of physician's choice.
[a]Median time to onset of ILD/pneumonitis for patients with T-DXd was 129.0 days (range, 26-710). [b]Left ventricular dysfunction was reported in a total of 17 (4.6%) patients in the T-DXd arm. One patient initially experienced ejection fraction decrease, then later developed cardiac failure. [c]Both patients with cardiac failure were reported to have recovered.

DESTINY-Breast04により、 T-DXdはHER2低発現 HR+/HR− 転移再発乳がんの新たな標準治療になりうる

- T-DXdは、医師選択治療と比較して、統計学的に有意かつ臨床的意義のあるPFSおよびOSの前例のない改善を示す最初のHER2標的薬である。
- HER2 IHCステータスおよびCDK4/6阻害薬の前治療歴を含め、すべてのサブグループにおいて同程度のベネフィットが得られている。
- 得られた安全性データは既報の安全性プロファイルと同様であり、リスク・ベネフィットのバランスは総合的にポジティブである。
- DESTINY-Breast04により、 T-DXdはHER2低発現 (IHC 1+, IHC 2+/ISH−)転移再発乳がんという新たな患者層における標準治療になりうる。

DESTINY-Breast04



CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IHC, immunohistochemistry; OS, overall survival; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TPC, treatment with physician's choice.

Retrospective study to estimate the prevalence of HER2-low breast cancer (BC) and describe its clinicopathological characteristics

Giuseppe Viale, MD, FRCPath[1]; Naoki Niikura, MD, PhD[2]; Eriko Tokunaga, MD[3]; Mark Basik, MD[4]; Naoki Hayashi, MD[5]; JoohyukSohn, MD, PhD[6]; Ciara O'Brien, PhD[7]; Gavin Higgins, PhD[8]; Della Varghese, PhD[9]; Gareth D. James[10]; Akira Moh, MD, PhD[11]; Nana Scotto, MD[12]

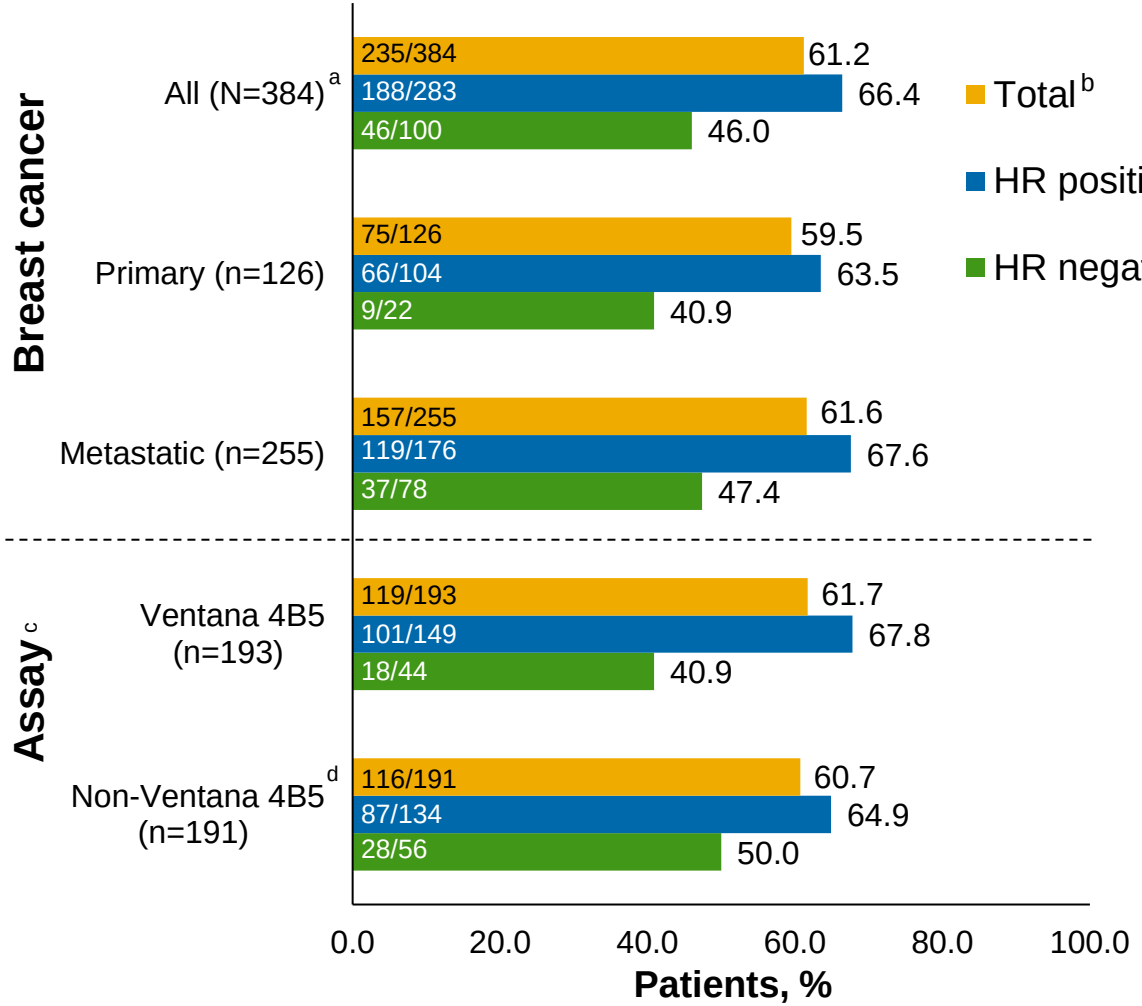
[1]European Institute of Oncology IRCCS and University of Milan, Milan, Italy; [2]Tokai University School of Medicine, Kanagawa, Japan; [3]National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; [4]Jewish General Hospital, McGill University, Montreal, QC, Canada; [5]St. Luke's International Hospital, Tokyo, Japan; [6]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea; [7]The Christie NHS Foundation Trust, Manchester, UK; [8]Victoria Cancer Biobank, Melbourne, VIC, Australia; [9]AstraZeneca Pharmaceuticals LP, Gaithersburg, MD; [10]Medical Statistics Consultancy Ltd, London, UK; [11]Daiichi Sankyo Inc., Basking Ridge, NJ; [12]AstraZeneca Pharmaceuticals, Cambridge, UK

ASCO 2022 #1087 Poster

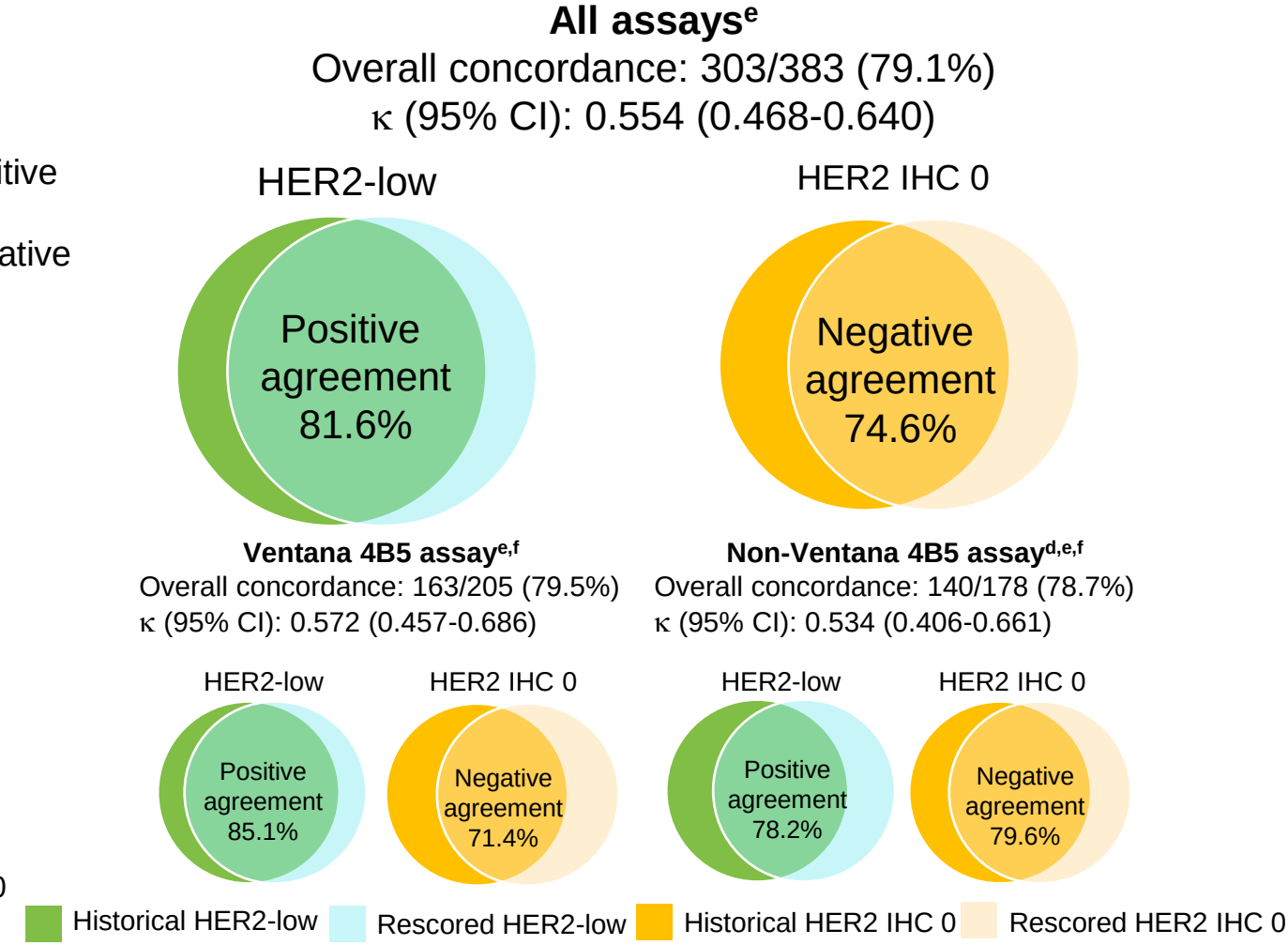
On behalf of the investigators

結果: 患者数および再スコアの一致率

Prevalence of HER2-low in HER2-neg mBC



Concordance between rescores and historical scores



HER2, human epidermal growth factor receptor 2; HR, hormone receptor, IHC, immunohistochemistry mBC, metastatic breast cancer. [a] Only patients with available HER2 score (HER2-low or HER2 IHC 0) contribute to prevalence calculations. [b] Patients with presently unknown HR status included in total category only. [c] Ventana and non-Ventana groups based on the rescore results. [d] Includes HercepTest, Bond Oracle, or unknown. [e] Only patients with available historical scores were included. [f] Ventana and non-Ventana groups based on the historical score.

まとめ

- 転移再発乳がんサンプルを用いた本試験では、HER2低発現の患者数の割合は61.2%であった
  - HER2低発現の患者数の割合は、HR+ 転移再発乳がんの方がHR- 転移再発乳がんよりも高かった（それぞれ66.4%と46.0%）
  - 乳がんにおけるHER2低発現の患者数の割合のデータは限定的であるが、本試験で推定された数字はHER2陰性乳がんサンプルを対象とした過去の試験 (≈60%)[1]と同等であった

- 過去の評価時と再スコア時のHER2発現分類における総合的な一致率は79.1% (κ [95% CI], 0.554 [0.468-0.640])であり、過去の評価においてもHER2低発現乳がん患者を比較的正確に同定できていた
  - 総合的な一致率はVentana 4B5とnon-Ventana 4B5 コホートで同程度 (それぞれ79.5% および 78.7%)
  - HER2低発現とHER2 IHC 0グループは同様の患者背景とベースラインの病態を有していた

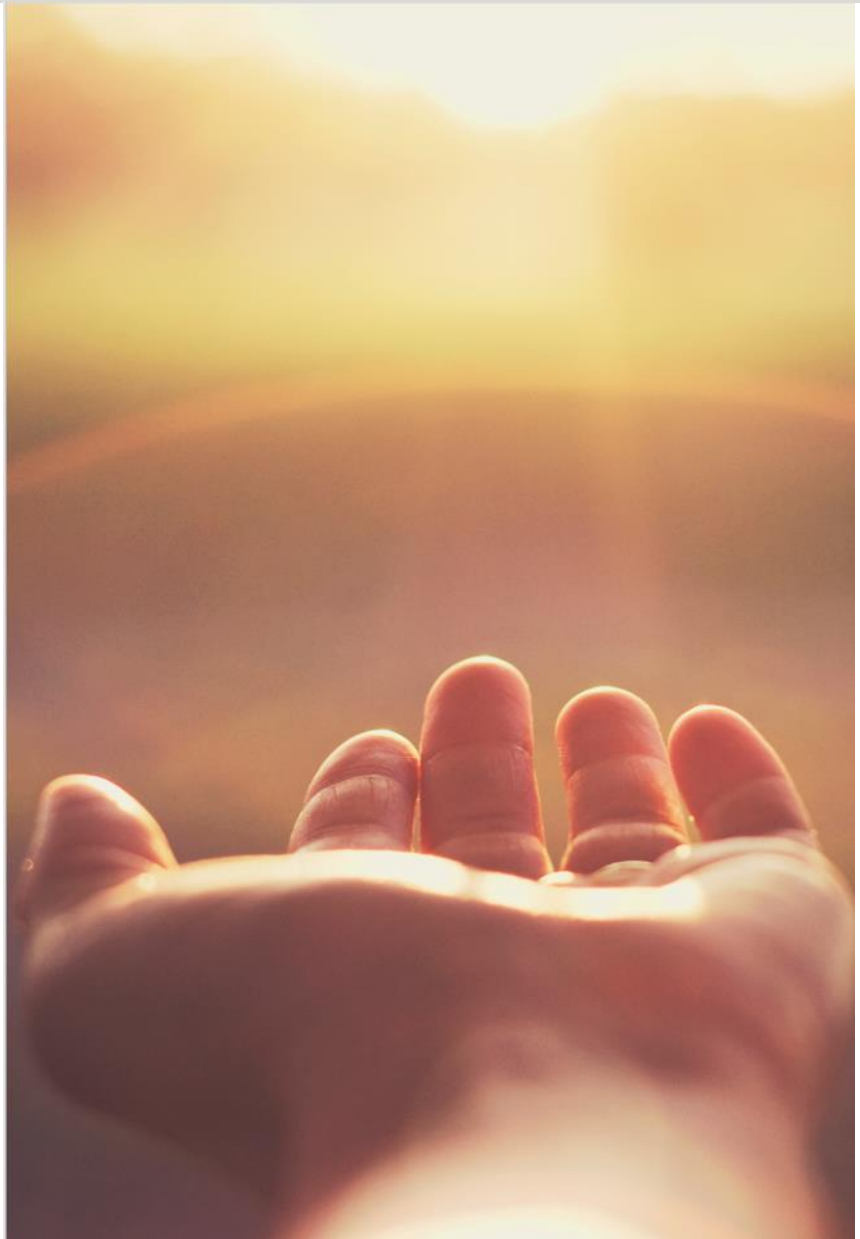
- HER2低発現乳がん患者に対してT-DXdのようなHER2を標的とした治療が現れたことにより[2-6]、これらの治療の恩恵を受けるであろうHER2低発現患者について理解を深めることが重要である

1. Schettini F, et al. *NPJ Breast Cancer*. 2021;7(1):1. 2. AstraZeneca. Enhertu significantly improved both progression-free and overall survival in DESTINY-Breast04 trial in patients with HER2-low metastatic breast cancer. Accessed April 26, 2022. https://www.astrazeneca.com/media-centre/press-releases/2022/enhertu-improves-pfs-and-os-in-her2-low-bc.html. 3. Modi S, et al. *J Clin Oncol*. 2020;38(17):1887-1896. 4. Diéras V, et al. Presented at: San Antonio Breast Cancer Symposium; December 7-10, 2021; San Antonio, Texas. Abstract PD8-02. 5. Bardia A, et al. Presented at: San Antonio Breast Cancer Symposium; December 8-11, 2020; virtual. Abstract OT-03-09. 6. Modi S, et al. Presented at: San Antonio Breast Cancer Symposium; December 10-14, 2019; San Antonio, Texas. Abstract OT1-07-02.

エンハーツ®: HER2低発現乳がん 臨床開発ハイライト

	Neoadjuvant	Post-neoadjuvant/Adjuvant	1L Metastatic	2L Metastatic	3L Metastatic
HER2＋ ~ 20% of patients	**DESTINY-Breast11** Phase 3 ENHERTU® vs ENHERTU® / THP vs AC / THP	**DESTINY-Breast05** Phase 3 Monotherapy vs T-DM1	**DESTINY-Breast09** Phase 3 ENHERTU® ± pertuzumab vs THP	**DESTINY-Breast03** Phase 3 Monotherapy vs T-DM1 APPROVED	**DESTINY-Breast01** Phase 2 Monotherapy LAUNCHED
			DESTINY-Breast07 Phase 1b/2 Combination (Part 2)		**DESTINY-Breast02** Phase 3 Monotherapy vs PC
					DESTINY-Breast07 Phase 1b/2 Combination(Part 1)
Hormone-receptor positive (HR+) ~ 65% of patients	**HER2 Low ~ 60% of patients that are not HER2+**			**DESTINY-Breast06** Phase 3 Monotherapy vs PC (chemotherapy naïve)	
			DESTINY-Breast08 Phase 1b Combination		**DESTINY-Breast04** Phase 3 Monotherapy vs PC (2L+ chemotherapy) **BTD in US**
Triple-negative (TNBC) ~ 15% of patients			**BEGONIA** Phase 1b/2 Combo with durvalumab		

HER2低発現乳がん Key Takeaways



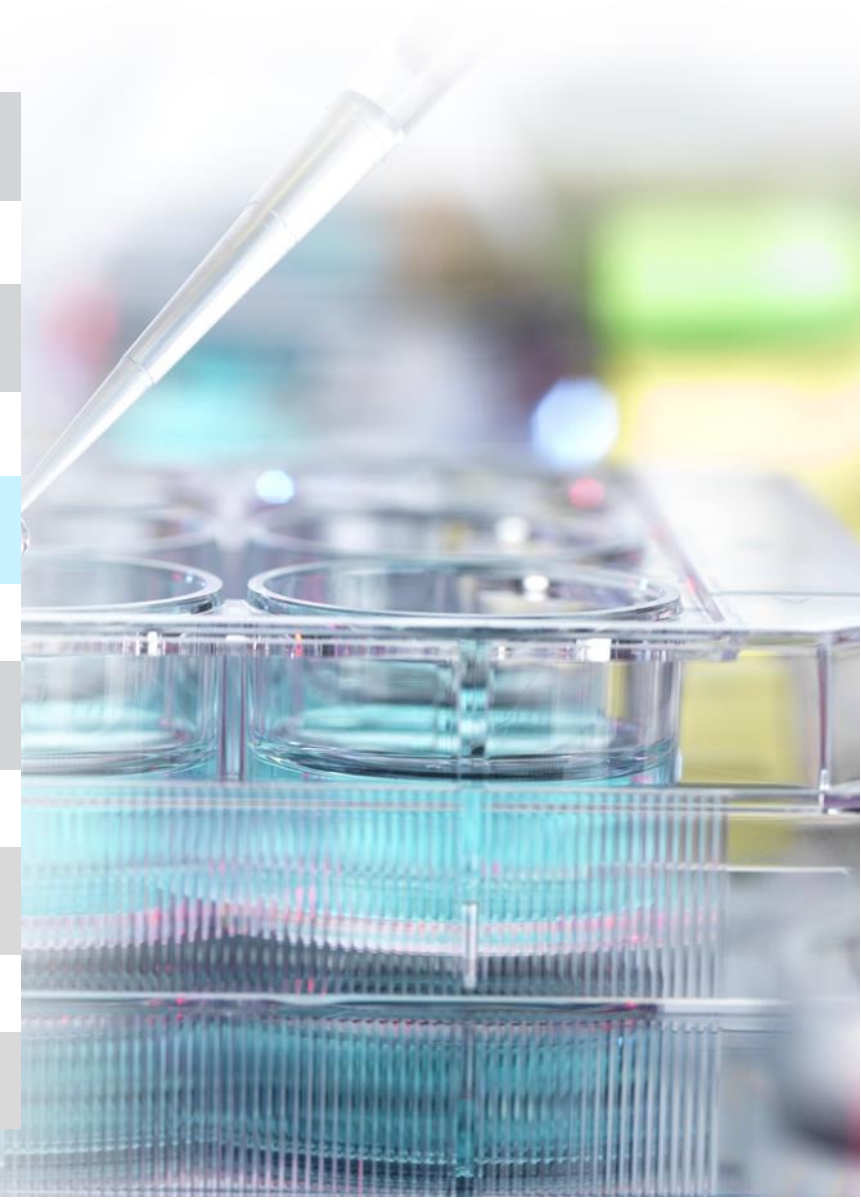
- DESTINY-Breast04: HER2低発現 転移再発乳がんにおいて、様々なホルモン受容体のステータスおよびIHCスコアに一貫して、 T-DXdは医師選択薬に対して統計的に有意かつ臨床的に意義のあるPFSとOSの改善を示した
  - FDAによる画期的治療薬の指定
- 乳がん患者の約50%が、新規の患者セグメントであるHER2低発現に再分類される
- 化学療法未治療の患者を対象としたフェーズ3試験(DESTINY-Breast06) を実施中であり、併用療法による早期治療ラインでの開発も検討中

エンハーツ®はHER2低発現乳がんに対する初めての標的療法を切り開いた

DB-04の承認申請は2022年度上半期を予定

本日お話しする内容

1. イントロダクション
2. HER2低発現乳がん治療のパラダイムをシフトする
3. **HER2陽性乳がんにおける信頼を構築する**
4. 乳がんのさらなるニーズに対応する
5. Rising Stars
6. 今後のニュースフロー



エンハーツ®は米国において HER2陽性乳がん二次治療の承認を取得した

DESTINY-Breast03

2022年5月5日

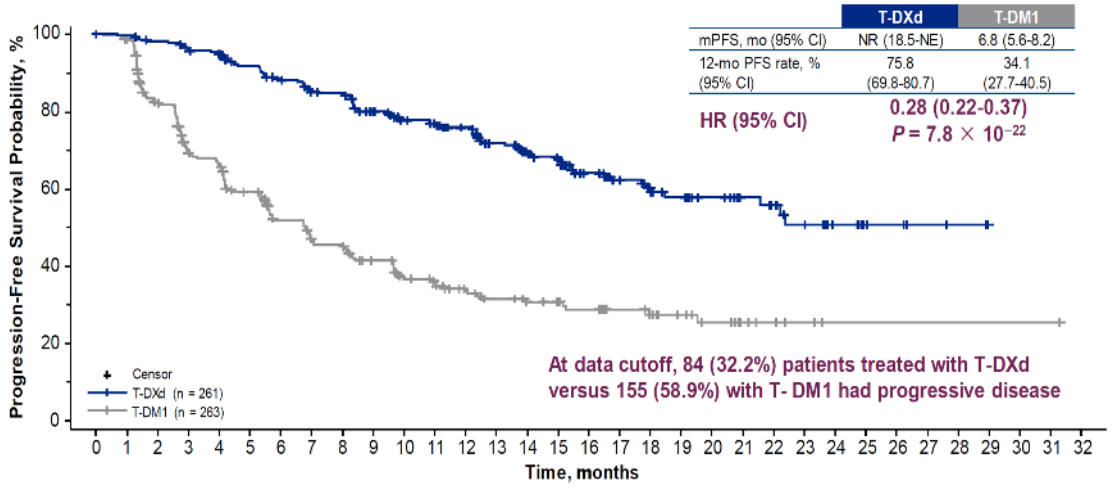
- 優先審査、画期的治療薬指定、およびリアルタイムオンコロジーレビュープログラムに基づき、FDAによる承認を受けた
- 本承認により、エンハーツ® はより早期の転移再発乳がんに適応を広げた
- DESTINY-Breast03試験の前例のない結果は、エンハーツ®がトラスツズマブ エムタンシン(T-DM1)に対し、病勢進行または死亡のリスクを72%減少させたことを示している

エンハーツ®: DESTINY-Breast03試験

DESTINY-Breast03

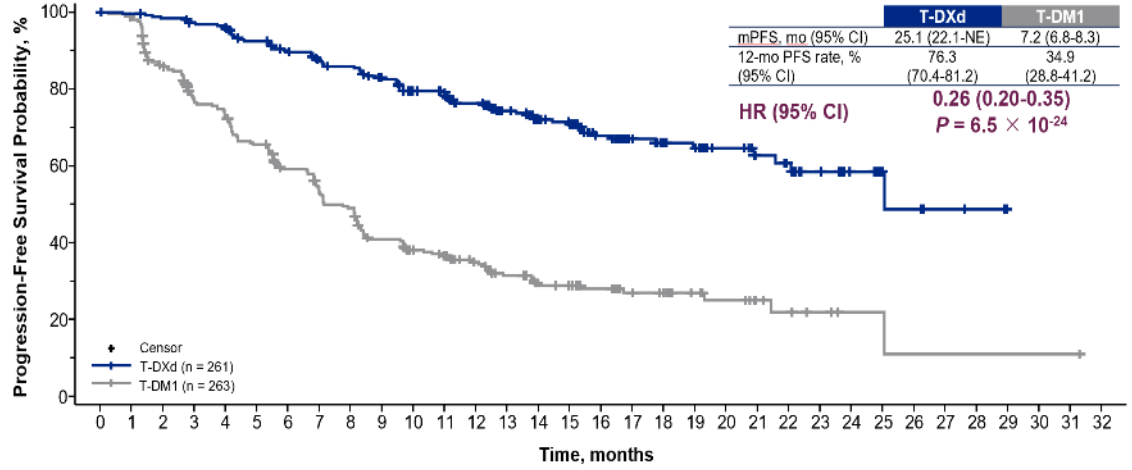
Daiichi-Sankyo

主要評価項目：PFS（盲検下独立中央判定） ESMO 2021



- エンハーツ®における病勢進行もしくは死亡のリスクは、T-DM1と比較して72%減少した

副次評価項目：PFS（主治医判定） ESMO 2021



- T-DM1のmPFSは7.2ヶ月に対し、エンハーツ®のmPFSは25.1ヶ月であった

BICR, blinded independent central review; HR, hazard ratio; mPFS, median progression-free survival; NE, not estimable; NR, not reached; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Median PFS follow-up for T-DXd was 15.5 months (range, 15.1-16.6) and was 13.9 months (range, 11.8-15.1) for T-DM1.
Cortés et al. *N Engl J Med*. 2022; 286:1143-54

- HER2陽性乳がん患者において、エンハーツ®はT-DM1と比較してPFSの**前例のない**改善を示し、グレード4/5のILDは確認されなかった。NEJMにデータ掲載。
- 2022年5月に米国にて承認取得、日欧にて今年度承認取得予定。

HER2陽性 乳がん治療の変革

NEJM: the New England Journal of Medicine

Daiichi-Sankyo

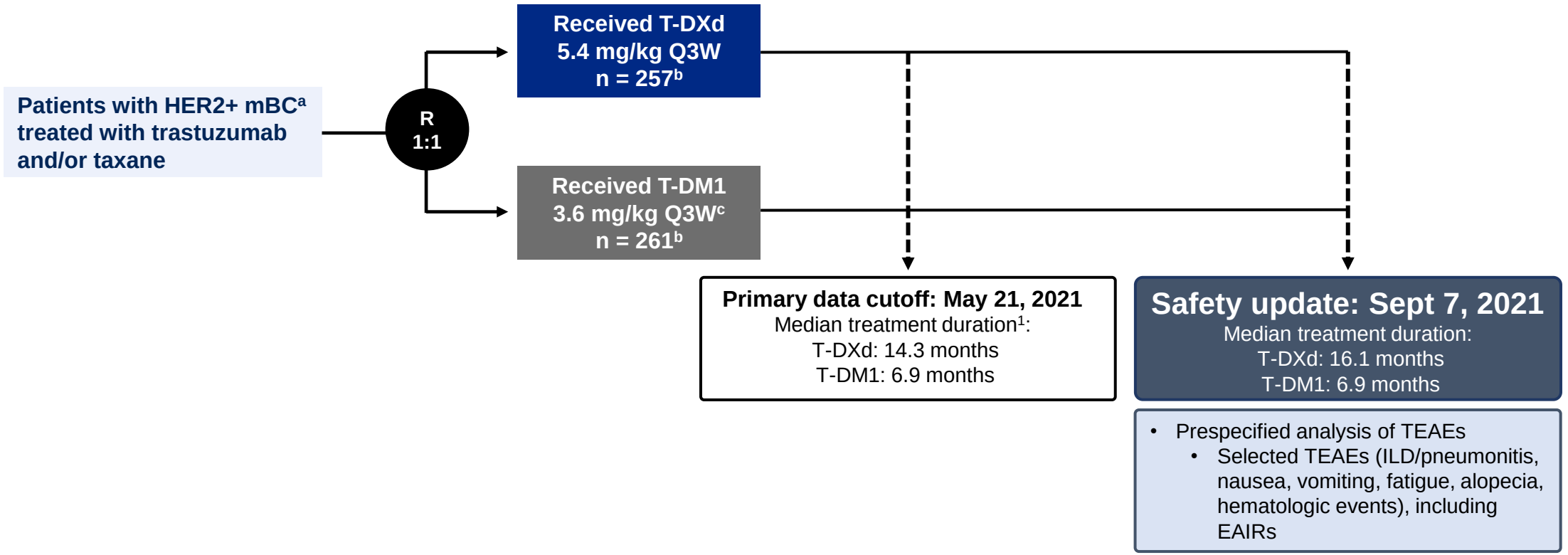
DESTINY-Breast03

Trastuzumab Deruxtecan vs Trastuzumab Emtansine in Patients With HER2-Positive Unresectable and/or Metastatic Breast Cancer: Safety Follow-up of the Randomized, Phase 3 Study DESTINY-Breast03

Erika Hamilton, MD,[a] Vanessa Petry, Winnie Yeo, Sung-Bae Kim, Giampaolo Bianchini, Toshinari Yamashita, Kan Yonemori, Kenichi Inoue, Giuseppe Curigliano, Sara A. Hurvitz, Javier Cortés, Hiroji Iwata, Jillian Cathcart, Yali Liu, Caleb Lee, Emarjola Bako, Rachel Kim, Seock-Ah Im
On behalf of the DESTINY-Breast03 investigators

[a]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, USA

DESTINY-Breast03 試験デザイン



Objective of the study was to provide updated safety data with additional analyses in patients with HER2+ mBC treated with T-DXd or T-DM1 in DESTINY-Breast03

EAIRs, exposure-adjusted incidence rates; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; mBC, metastatic breast cancer; Q3W, every 3 weeks; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

[a]Central testing of archived sample for HER2 status. [b]Number of treated patients (not the randomized number of patients). [c]Or in accordance with the local label.

1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

安全性アップデートの概要（2021年9月7日）

DESTINY-Breast03

Daiichi-Sankyo

n (%)	T-DXd n = 257	T-DM1 n = 261
Patients discontinued from study treatment	141 (54.9)	222 (85.1)
Any grade TEAE	256 (99.6)	249 (95.4)
Grade ≥3 TEAE	137 (53.3)	130 (49.8)
Any grade serious TEAE	54 (21.0)	50 (19.2)
Grade ≥3 serious TEAE	39 (15.2)	38 (14.6)
TEAE associated with drug discontinuation	38 (14.8)	19 (7.3)
TEAE associated with dose reduction	59 (23.0)	36 (13.8)

- Rates of TEAEs (any grade and grade ≥3) and serious TEAEs were similar between the T-DXd and T-DM1 arms
- TEAEs associated with drug discontinuation occurred in 38 patients (14.8%) in the T-DXd arm and 19 patients (7.3%) in the T-DM1 arm

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.

Safety update: Sept 7, 2021

曝露調整発現率 (EAIR)[a]

DESTINY-Breast03

Daiichi-Sankyo

	Exposure-adjusted incidence per total patient-years of exposure	
	T-DXd n = 257	**T-DM1 n = 261**
Patients remaining on treatment, n (%)	116 (45.1)	39 (14.9)
Treatment duration, median (range), months	**16.1 (0.7-33.0)**	**6.9 (0.7-28.5)**
Exposure, patient-years[b]	327.2	186.3
EAIR, grade ≥3 TEAE	0.42	0.70
EAIR, any grade serious TEAE	0.17	0.27
EAIR, grade ≥3 serious TEAE	0.12	0.20
EAIR, TEAE associated with drug discontinuation	0.12	0.10
EAIR, TEAE associated with dose reduction	0.18	0.19

- EAIRs were measured to account for differences in treatment duration exposure between T-DXd and T-DM1 and provide a more meaningful comparison
- EAIRs per patient-year were lower in the T-DXd arm than the T-DM1 arm except for TEAEs associated with drug discontinuation, which were primarily associated with ILD/pneumonitis in the T-DXd arm
  - EAIR for grade ≥3 TEAEs was 0.42 for T-DXd and 0.70 for T-DM1
  - EAIR for any grade serious TEAEs was 0.17 for T-DXd and 0.27 for T-DM1

EAIRs, exposure-adjusted incidence rates; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
[a]EAIR was the number of patients with at least 1 event incidence divided by the sum of patient-years of exposure over patients in the safety analysis set (total patient-years of exposure). [b]Patient years of exposure were the treatment duration with year as unit.

Safety update: Sept 7, 2021

いずれかの投与群で20%以上の患者に発現した薬剤に関連する有害事象[a]

DESTINY-Breast03

Daiichi-Sankyo

n (%)	T-DXd n = 257		T-DM1 n = 261	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	189 (73.5)	17 (6.6)	72 (27.6)	1 (0.4)
Fatigue	118 (45.9)	16 (6.2)	76 (29.1)	2 (0.8)
Vomiting	114 (44.4)	4 (1.6)	15 (5.7)	1 (0.4)
Neutropenia	111 (43.2)	51 (19.8)	30 (11.5)	8 (3.1)
Alopecia	97 (37.7)	1 (0.4)	7 (2.7)	0
Anemia	82 (31.9)	16 (6.2)	37 (14.2)	11 (4.2)
Leukopenia	79 (30.7)	17 (6.6)	21 (8.0)	2 (0.8)
Decreased appetite	68 (26.5)	3 (1.2)	34 (13.0)	0
Thrombocytopenia	65 (25.3)	19 (7.4)	137 (52.5)	65 (24.9)
Diarrhea	61 (23.7)	1 (0.4)	11 (4.2)	2 (0.8)
Constipation	60 (23.3)	0	25 (9.6)	0

- Most of the selected drug-related TEAEs in either treatment arm were hematologic or gastrointestinal

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse events.
Selected TEAEs (and preferred terms included): anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased); neutropenia (neutrophil count decreased, neutropenia); thrombocytopenia (platelet count decreased, thrombocytopenia); fatigue (fatigue, asthenia, malaise).
[a]Based on nonclinical data, clinical data, epidemiology data, and reported data from drugs in a similar class (anti-HER2 therapies), selected TEAEs for T-DXd were reviewed for additional characterization.

Safety update: Sept 7, 2021

有害事象の初回発現までの時間

DESTINY-Breast03

Daiichi-Sankyo

Median time to event, days	T-DXd n = 257	T-DM1 n = 261
TEAE associated with treatment discontinuation	224	147
TEAE associated with first dose reduction	96	19
Selected TEAEs		
Anemia	70.0	42.0
Lymphopenia	196.0	168.0
Thrombocytopenia	132.0	8.0
Fatigue	22.0	24.0
Leukopenia	74.5	92.0
Neutropenia[a]	64.0	105.0
Nausea	2.0	3.0
Vomiting	10.0	6.0
Alopecia	27.0	43.0

- TEAEs associated with first drug discontinuation or first dose reduction occurred later with T-DXd treatment than with T-DM1 treatment
- Median time to any TEAE associated with first dose reduction was longer in the T-DXd arm at 96 days compared with the T-DM1 arm at 19 days

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event.
Selected TEAEs (and preferred terms included): anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased); lymphopenia (lymphocyte count decreased, lymphopenia); neutropenia (neutrophil count decreased, neutropenia); thrombocytopenia (platelet count decreased, thrombocytopenia); leukopenia (white blood cell count decreased, leukopenia); fatigue (fatigue, asthenia, malaise).
[a]11.7% of patients in the T-DXd group and 2.3% of patients in the T-DM1 group were treated with G-CSF within 28 days after onset of neutropenia, including febrile neutropenia.

Safety update: Sept 7, 2021

薬剤に関連すると判定されたILD/肺臓炎

DESTINY-Breast03

	T-DXd n = 257	T-DM1 n = 261
Any grade, n (%)	28 (10.9)	5 (1.9)
Grade 1	7 (2.7)	4 (1.5)
Grade 2	19 (7.4)	1 (0.4)
Grade 3	2 (0.8)	0
Grade 4	0	0
Grade 5	0	0
Time to first onset, median (range), days	181 (33-507)	289 (80-499)
Outcome of worst event, n (%)		
Fatal	0	1 (20.0)[a]
Not recovered/not resolved	8 (28.6)	0
Ongoing	0	0
Recovering/resolving	2 (7.1)	0
Recovered/resolved with sequelae	2 (7.1)	0
Recovered/resolved	16 (57.1)	4 (80.0)

For this safety update:

- Majority of adjudicated ILD/pneumonitis cases were low grade and no new grade 4 or 5 events occurred in either treatment arm
- One additional grade 2 adjudicated drug-related ILD/pneumonitis occurred
- The majority of events resolved with ongoing follow-up

ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

[a]Patient had an event of pulmonary embolism that the investigator considered to be grade 5. This was initially reported as respiratory failure but subsequently updated to pulmonary embolism. The ILD adjudication committee adjudicated this event as drug-related grade 1 ILD/pneumonitis. The death was not evaluable for adjudication. The investigator recorded disease progression as the primary cause of death.[1]

1. Cortés J et al. *N Engl J Med.* 2022;386:1143-1154 (supplementary appendix).

Safety update: Sept 7, 2021

まとめ

今回の安全性アップデートにおいて、T-DXdを投与したHER2陽性 転移再発乳がんの患者で新たな安全性シグナルは観察されず[1-3]、詳細な解析により以下のことが示された：

- ほとんどの有害事象はグレード1もしくは2であり、グレード3以上あるいは重篤な有害事象の曝露調整発現率はT-DM1と比較してT-DXdの方が低かった。
- 悪心、嘔吐、倦怠感、および脱毛のリスクは、初回治療サイクルにおいてT-DXdの方が高かった。
- 倦怠感および嘔吐の発現率は、初回治療サイクルにおいてT-DXdの方が高く、脱毛および倦怠感については経時的に続いていた。
  - T-DXd群において、これらの有害事象のリスク増加および高い発現率は治療期間に渡って持続しており、継続的な支持療法が必要である。
- T-DXd群において、新たにグレード3のILD/肺臓炎と判定された患者はいなかった（全体的な発現割合 0.8%）。また、本試験ではグレード4もしくは5のILD/肺臓炎は確認されなかった

これらのデータは、HER2陽性 転移再発乳がんにおいてT-DM1と比較して良好なリスク・ベネフィットプロファイルの確立を強固にした

HER2, human epidermal growth factor receptor-2; ILD, interstitial lung disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

1. Modi S et al. *J Clin Oncol*. 2020;38:1887-1896. 2. Modi S et al. *N Engl J Med*. 2020;382:610-621. 3. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154.

Safety update: Sept 7, 2021

T-DXd投与患者におけるILD/肺臓炎の診断および管理のためのガイドラインと勧告 (1/2)

Daiichi-Sankyo

Workup

In the following situations, ILD/pneumonitis should be considered:

- Patient develops radiographic changes potentially consistent with ILD/pneumonitis
- Patient develops an acute onset of new or worsening pulmonary or other related signs/symptoms such as dyspnea, cough, or fever

Patient evaluations should include the following:

- High-resolution CT
- Pulmonologist consultation
- Infectious disease consultation as clinically indicated
- Blood culture and CBC; other blood tests could be considered as needed
- Consider bronchoscopy and bronchoalveolar lavage if clinically indicated and feasible
- Pulmonary function tests and pulse oximetry (SpO_2)
- Arterial blood gases if clinically indicated
- One blood sample collection for PK analysis as soon as ILD/pneumonitis is suspected, if feasible
- Other tests could be considered, as needed

We suggest:

- **Use of a multidisciplinary team in evaluating for an ILD/pneumonitis diagnosis, including the medical oncologist, primary physician, nurse practitioner, pulmonologist, thoracic surgeon, pathologist, infectious disease specialist, and radiologist**
- **If blood tests are being considered, consider tests for atypical infection, such as serum beta-d glucan and galactomannan, and for serum markers such as KL-6, SP-A, and SP-D[a]**

If the event is confirmed to have an etiology other than ILD/pneumonitis, follow routine clinical practice. If the event is confirmed to be ILD/pneumonitis, follow the ILD/pneumonitis management guidelines according to ILD/pneumonitis severity as outlined below

Continued on the next slide

These guidelines are based on guidelines published by Modi et al 2020 and the US, EU, and Canada prescribing information. Minor updates to the guidelines from Modi et al were published by Li et al 2021 and are included here.. [a] KL-6, SP-A, and SP-D are used as markers in Japan but may not be used clinically in all countries. [b] In the event a dose reduction is needed, per the US, EU, and Canada prescribing information, dose reductions from the indicated dose of 5.4 mg/kg for patients with breast cancer are 4.4 and 3.2 mg/kg for the first and second dose-level reductions, respectively. Per the US prescribing information, dose reductions from the indicated dose of 6.4 mg/kg for patients with gastric cancer are 5.4 and 4.4 mg/kg for the first and second dose-level reductions, respectively. If further dose reductions are required, treatment should be discontinued. [c] The EU and Canada prescribing information and Li et al indicate that for grade ≥ 2 ILD, steroids should be continued for ≥ 14 days or until complete resolution of clinical and chest CT findings, while the US prescribing information indicates that steroids should be continued for ≥ 14 days. CBC, complete blood count; CT, computed tomography; ILD, interstitial lung disease; IV, intravenous; KL-6, Krebs von den Lungen-6; PK, pharmacokinetics; SP-A, surfactant protein-A; SP-D, surfactant protein-D; SpO2, oxygen saturation; T-DXd, trastuzumab deruxtecan.

Source: Swain SM et al. Cancer Treatment Reviews (2022): 102378

T-DXd投与患者におけるILD/肺臓炎の診断および管理のためのガイドラインと勧告(2/2)

ILD/pneumonitis severity	Grade 1	Grade 2	Grade 3 or 4
	We suggest that the medical oncologist manage and treat the ILD/pneumonitis jointly with a multidisciplinary team, including a primary care physician, nurse practitioner, pulmonologist, pathologist, pharmacist, infectious disease specialist, and radiologist. The pulmonologist should be involved early to benefit from their expertise in managing the lung injury		
T-DXd dosing modification	• **Interrupt T-DXd** • T-DXd can be resumed if the ILD/pneumonitis fully resolved to grade 0 – If resolved in ≤28 days from day of onset, maintain dose – If resolved in >28 days from day of onset, reduce dose 1 level[b] – If ILD/pneumonitis occurs beyond day 22 and has not resolved within 49 days from the last infusion, discontinue T-DXd	**Permanently discontinue T-DXd**	**Permanently discontinue T-DXd**
ILF/pneumonitis management	• Monitor and closely follow up in 2-7 days for onset of clinical symptoms and pulse oximetry • Consider follow-up imaging in 1-2 weeks or as clinically indicated • Consider starting systemic steroids (eg. ≥0.5 mg/kg/day of prednisone or equivalent) until improvement, followed by gradual taper over ≥4 weeks *If diagnostic observations worsen despite initiation of steroids, then follow grade 2 guidelines*	• Promptly start systemic steroids (eg. ≥1.0 mg/kg/day of prednisone or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks[c] • Monitor symptoms closely • Reimage as clinically indicated • If worsening or no improvement in clinical or diagnostic observations in 5 days: – Consider increasing dose of steroids (eg. 2.0 mg/kg/day of prednisone or equivalent), and administration may be switched to IV (eg. methylprednisolone) – Reconsider additional workup for alternative etiologies as described above – Escalate care as clinically indicated	• Hospitalization required • Promptly start empirical high-dose methylprednisolone IV treatment (eg. 500-1000 mg/day for 3 days), followed by ≥1.0 mg/kg/day of prednisone (or equivalent) for ≥14 days or until complete resolution of clinical and chest CT findings, followed by gradual taper over ≥4 weeks • Reimage as clinically indicated • If still no improvement within 3-5 days: – Reconsider additional workup for alternative etiologies as described above – Consider other immunosuppressants (eg. infliximab or mycophenolate mofetil) and/or treat per local practice
	We suggest considering steroids for selected grade 1 cases that show extensive lung involvement or in patients at increased risk for progression of ILD/pneumonitis		

Patients with ILD/pneumonitis regardless of severity or seriousness should be followed up until complete resolution of clinical and/or chest CT findings, including after drug discontinuation

Refer to footnotes on the previous slide

Source: Swain SM et al. Cancer Treatment Reviews (2022): 102378

PATIENT-REPORTED OUTCOMES FROM DESTINY-Breast03, A RANDOMIZED PHASE 3 STUDY OF TRASTUZUMAB DERUXTECAN (T-DXd) VS TRASTUZUMAB EMTANSINE (T-DM1) IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

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ESMO BC 2022 #1630 Oral

On behalf of the investigators

DESTINY-Breast03 患者報告アウトカム & 入院エンドポイント&分析

DESTINY-Breast03

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Endpoint	Description	Measures of interest	Main analyses
EORTC QLQ-C30	Oncology-specific questionnaire	• Global health status (GHS)/QoL[a] • Functioning scales: physical, role, emotional, cognitive, and social • Symptom scales: pain	• Change from baseline • Time to definitive deterioration (TDD)[b,c]
EORTC QLQ-BR45	Breast cancer-specific questionnaire	• Symptom scales: arm and breast	• TDD[b,c]
EQ-5D-5L	Generic questionnaire	• Self-rated health status (visual analog scale [VAS])	• TDD[c]
Hospitalization	Records assessment	• Date of admission to hospital • Status/date of discharge	• Time to first hospitalization • Length of stay

- Completion compliance for HRQoL patient questionnaires was high in both treatment groups, with **>97% completion at baseline** and **>82% completion from cycles 3-27** in both arms

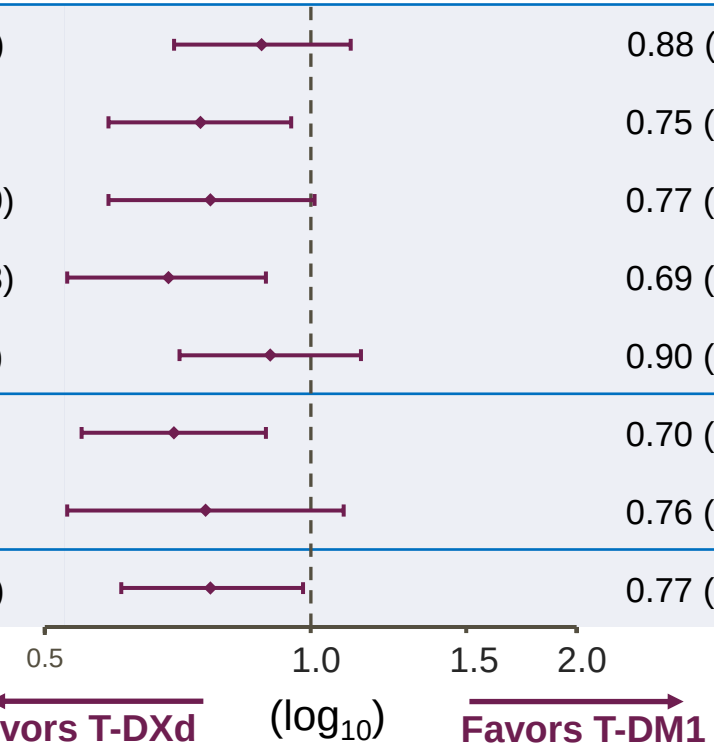
EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health status; HRQoL, health-related quality of life; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Primary PRO variable of interest. [b]Clinically meaningful deterioration defined as a change of 10 points or more in the GHS and subscale scores. [c]Not all variables measured were assessed for TDD.

患者報告アウトカムにおける病態悪化までの期間

DESTINY-Breast03

Daiichi-Sankyo

		Median (95% CI) TDD, months		HR (95% CI)	Nominal *P* value
		T-DXd (n = 261)	T-DM1 (n = 263)		
EORTC QLQ-C30	Global health status/QoL[a]	9.7 (7.3-12.5)	8.3 (7.0-10.3)	0.88 (0.70-1.11)	0.2829
	Pain symptoms[b]	10.8 (8.3-14.0)	8.3 (6.6-9.8)	0.75 (0.59-0.95)	0.0146
	Physical functioning[b]	16.7 (14.5-NE)	10.3 (8.3-21.0)	0.77 (0.59-1.01)	0.0529
	Emotional functioning[b]	16.4 (14.1-19.9)	10.5 (9.0-13.8)	0.69 (0.53-0.89)	0.0049
	Social functioning[b]	11.1 (7.3-13.4)	9.0 (7.1-11.3)	0.90 (0.71-1.14)	0.3577
EORTC QLQ-BR45	Arm symptoms[b]	11.1 (8.5-14.8)	7.0 (5.6-9.3)	0.70 (0.55-0.89)	0.0033
	Breast symptoms[b]	26.4 (26.4-NE)	NE (NE-NE)	0.76 (0.53-1.09)	0.1329
EQ-5D-5L	VAS[b]	13.2 (10.1-15.3)	8.5 (7.3-10.4)	0.77 (0.61-0.98)	0.0354



EORTC, European Organization for Research and Treatment of Cancer; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire; GHS, global health status; HR, hazard ratio; PRO, patient-reported outcome; QLQ-BR45, Quality of Life Breast cancer questionnaire; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; VAS, visual analog scale.
P values are not adjusted for multiple testing. TDD is defined as a >10-point change from baseline. [a]Primary PRO variable of interest. [b]Secondary PRO variable of interest.

入院関連エンドポイント

DESTINY-Breast03

Daiichi-Sankyo

Parameter	T-DXd (n = 261)	T-DM1 (n = 263)
Subjects with hospitalization, n (%)	18 (6.9)	19 (7.2)
Median (range) time to first hospitalization,[a] days	219.5 (0-723)	60.0 (0-399)
Median (range) length of hospital stay, days	10.5 (1-181)	9.0 (2-25)
Died, n (%)	2 (0.8)	1 (0.4)
Discharged home, n (%)	15 (5.7)	16 (6.1)
Discharged to home health care, n (%)	1 (0.4)	1 (0.4)

T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
[a]Time to first hospitalization is defined as the time from the date of randomization to the date of the first hospitalization during the study treatment (from date of first dose to 47 days after last dose). Time for subjects whose first hospitalization date was prior to treatment start date was calculated as 0.

ESMO BC 2022 #1630 Oral

まとめ

DESTINY-Breast03

Daiichi-Sankyo

- EORTC QLQ-C30 GHSスコア (関心のある主要な患者報告アウトカムの変数) およびその他の特定された関心のあるサブスケールのベースラインからの変化の平均値から、**総合的な健康状態とQOLはT-DXd群で保持されていた**
- 治療期間の中央値はT-DXd群 (14.3 [0.7-29.8] ヶ月) においてT-DM1群 (6.9 [0.7-25.1] ヶ月)[1]より長かった
- 全ての事前に特定した患者報告アウトカム変数について、無作為化から回復が見られない悪化までの時間（TDD）のハザード比はT-DXdの方が T-DM1に対し数値的に勝っており (HR range, 0.69-0.90), **T-DXdによる治療が転移再発乳がん患者における QOLの悪化を遅延させる**ことが示された
  - **T-DXd群における痛みの症状のTDDの遅延** (HR, 0.75)は、QOLへの重大な影響[2,3]を考慮すれば特に顕著であった
- **T-DXd群における初回入院までの期間はT-DM1群と比較して遅延していた**（各中央値：219.5 日 および 60.0 日）(両群の入院比率が少ないことにより結果解釈が限定される)
- **T-DXdによる治療においてQOLが維持されていること、およびT-DM1に対し、事前に設定した様々な指標において回復が見られない悪化までの時間が延長した**というエビデンスは、T-DM1を上回るT-DXdの効果（PFSの改善を含む）および管理可能な安全性プロファイル[1]をさらに強く裏付けるものであり、**T-DXdがHER2陽性転移再発乳がん患者の治療において標準治療となり得ることを示している**

EORTC, European Organization for Research and Treatment of Cancer; GHS, global health status; HR, hazard ratio; QLQ-C30, Quality of Life Core 30 questionnaire; QoL, quality of life; TDD, time to definitive deterioration; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.

1. Cortés J et al. *N Engl J Med*. 2022;386:1143-1154. 2. Dueñas M, et al. *J Pain Res.* 2016;9:457–467. 3. Dams L et al. *Supportive Care Cancer.* 2022;doi: 10.1007/s00520-022-06805-0.

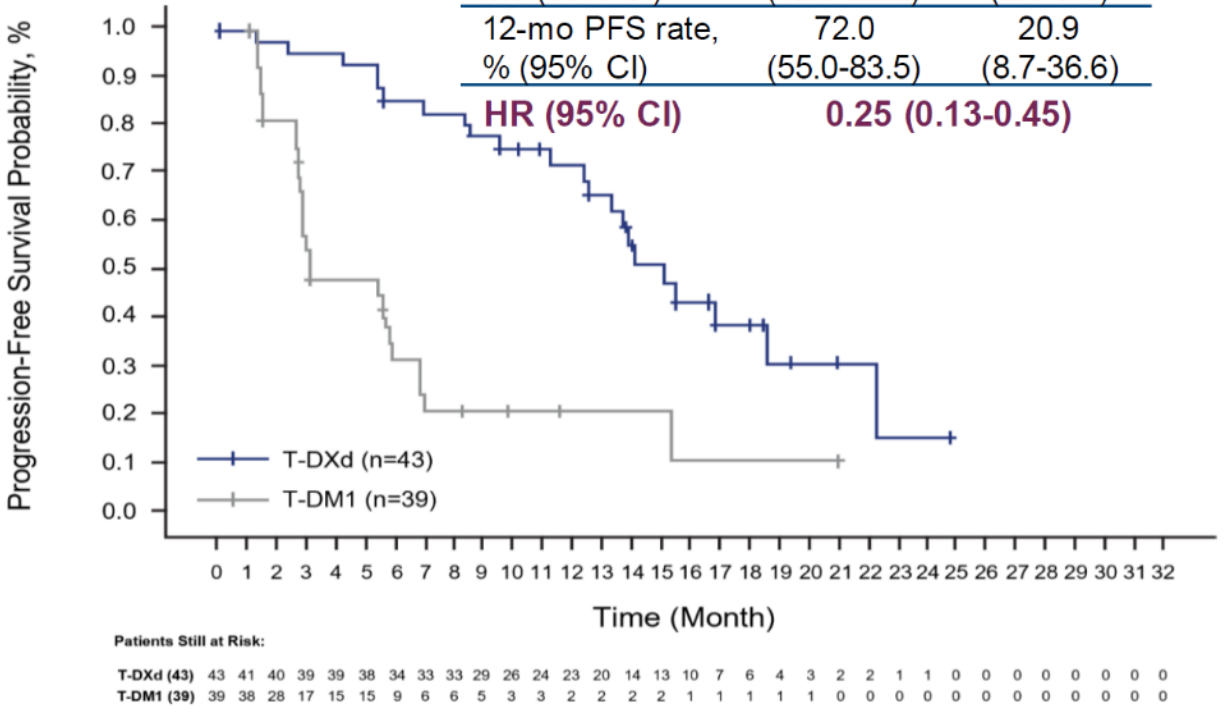
”エンハーツ®は脳転移にも薬効を示すのか？”

脳転移の有無別のPFS カプラン・マイヤー曲線

DESTINY-Breast03サブグループ解析 (非活動性の脳転移患者のみ)

Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	15.0 (12.5-22.2)	3.0 (2.8-5.8)
12-mo PFS rate, % (95% CI)	72.0 (55.0-83.5)	20.9 (8.7-36.6)
HR (95% CI)	0.25 (0.13-0.45)	

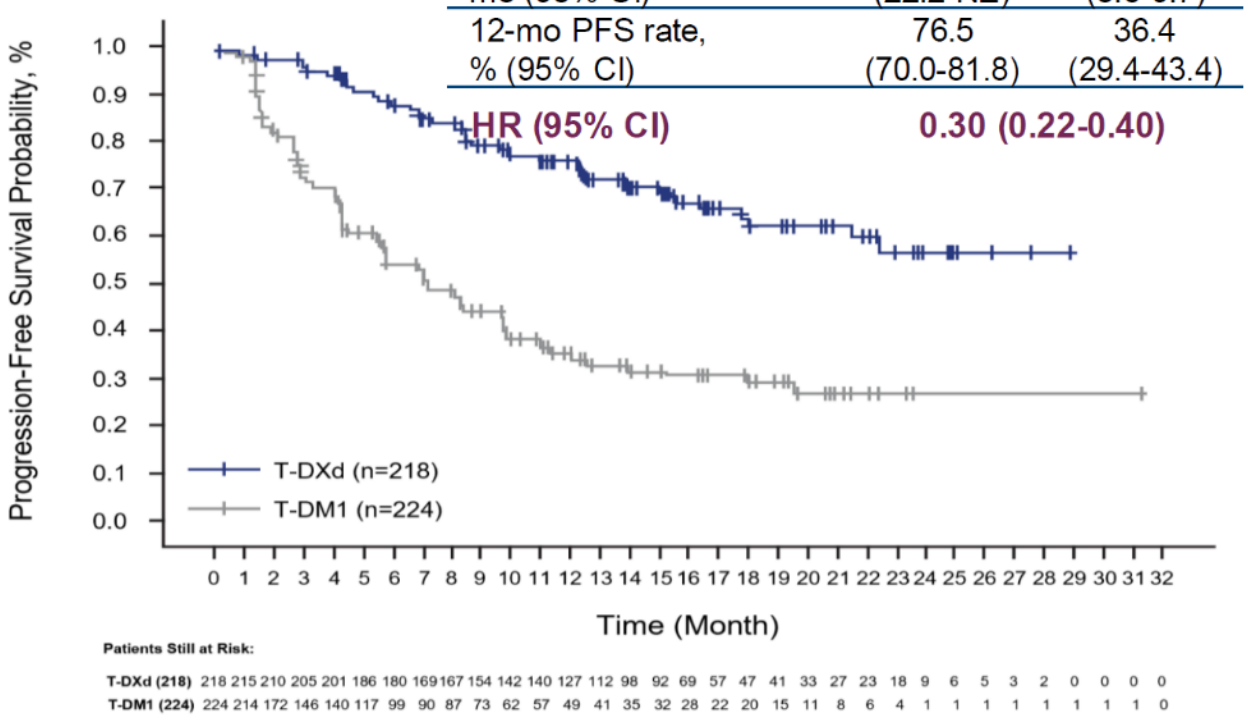


At data cutoff, in patients with BM at baseline, PD was observed:

- In 21/43 treated with T-DXd versus 27/39 with T-DM1
  - In the brain in 9/21 treated with T-DXd versus 11/27 with T-DM1

No Brain Metastases at Baseline

	T-DXd	T-DM1
mPFS, mo (95% CI)	NE (22.2-NE)	7.1 (5.6-9.7)
12-mo PFS rate, % (95% CI)	76.5 (70.0-81.8)	36.4 (29.4-43.4)
HR (95% CI)	0.30 (0.22-0.40)	

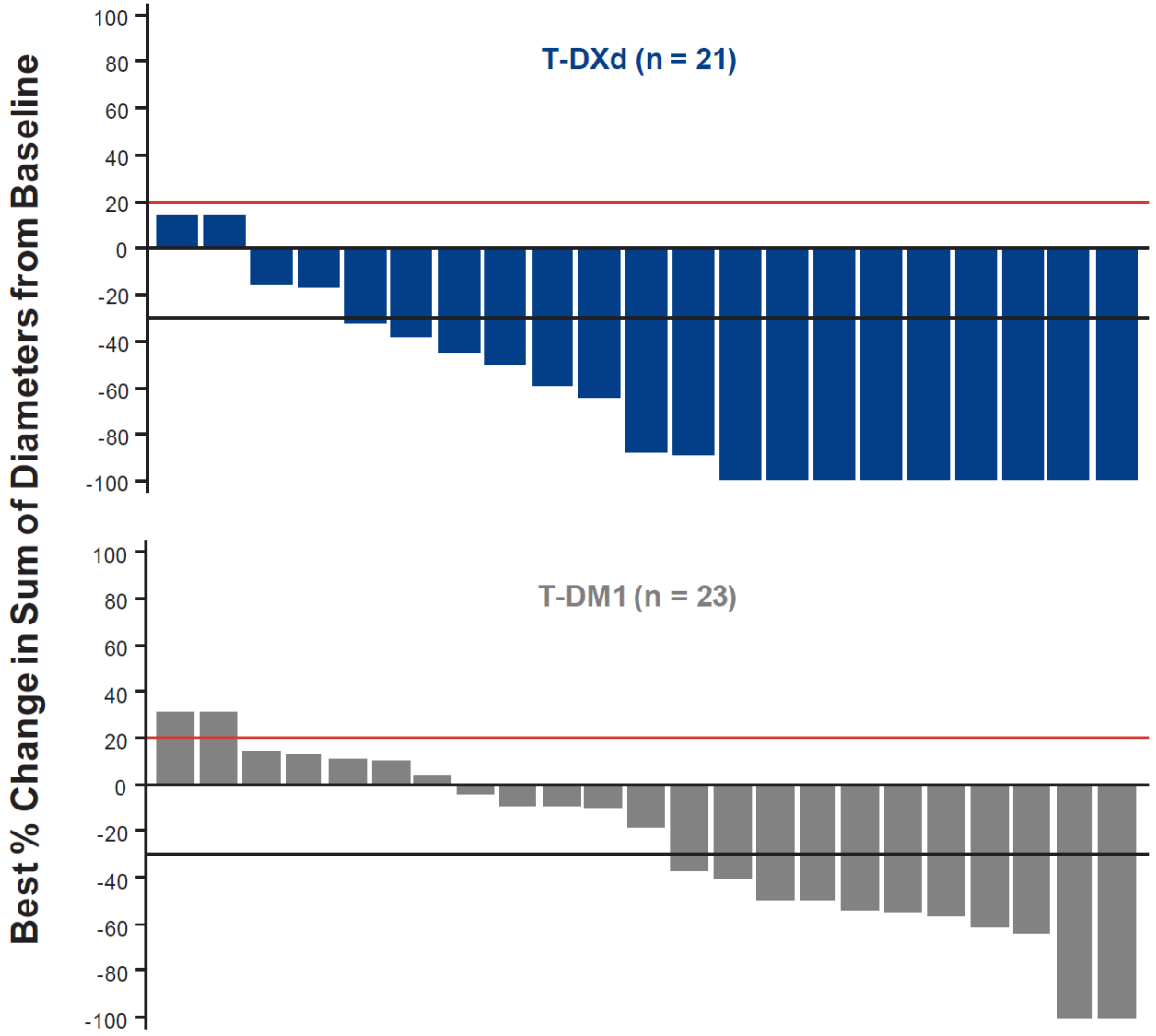


At data cutoff, in patients without BM at baseline, PD was observed:

- In 63/218 treated with T-DXd versus 128/224 with T-DM1
  - In the brain in 4/63 treated with T-DXd versus 1/128 with T-DM1

mPFS, median progression-free survival; PD, progressive disease; PFS, progression-free survival; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan

RECIST 1.1を用いた盲検独立中央判定における頭蓋内奏功率



	T-DXd (n = 36)	T-DM1 (n = 36)
Best Overall Response, n (%)[a]		
CR	10 (27.8)	1 (2.8)
PR	13 (36.1)	11 (30.6)
Non-CR/Non-PD	6 (16.7)	7 (19.4)
SD	4 (11.1)	7 (19.4)
PD	1 (2.8)	8 (22.2)
Not Evaluable	0	1 (2.8)
Missing	2 (5.6)	1 (2.8)
Subjects with Objective Response of CR or PR, n	23	12

CR, complete response; DCR, disease control rate; mDOR, median duration of response; PD, progressive disease; PR, partial response; SD, stable disease; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan.
Table includes target and non-target lesions. Only patients with target lesion assessments are eligible for inclusion in waterfall.
Red line at 20% indicates progressive disease; black line at -30% indicates partial response.
[a]Denominator for percentages is the number of subjects in the full analysis set with brain metastases tumor assessment

Trastuzumab-deruxtecan (T-DXd) in HER2-positive breast cancer patients with active brain metastases: Primary outcome analysis from the TUXEDO-1 trial

Rupert Bartsch[1], Anna Sophie Berghoff[1], Julia Furtner[2], Maximilian Marhold[1], Elisabeth Sophie Bergen[1], Sophie Roider-Schur[3], Angelika Martina Starzer[1], Heidrun Forstner[1], Beate Rottenmanner[1], Karin Dieckmann[4], Zsuzsanna Bago-Horvath[5], Georg Widhalm[6], Aysegül Ilhan-Mutlu[1], Christoph Minichsdorfer[1], Thorsten Fuereder[1], Christian Singer[7], Ansgar Weltermann[8], Rainer Puhr[1], Matthias Preusser[1]

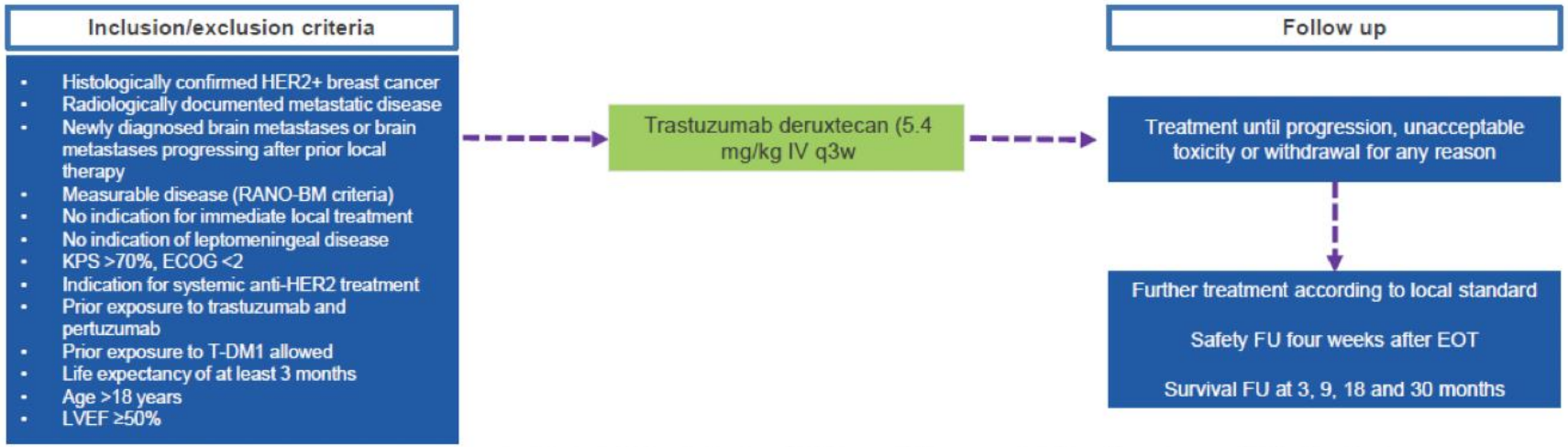
[1] Department of Medicine 1, Division of Oncology, Medical University of Vienna; [2] Department of Radiology, Medical University of Vienna, Vienna, Austria; [3] Department Oncology, St. Joseph's Hospital, Vienna, Austria; [4] Department of Radio-Oncology, Medical University of Vienna, Vienna, Austria; [5] Department of Pathology, Medical University of Vienna, Vienna, Austria; [6] Department of Neurosurgery, Medical University of Vienna, Vienna, Austria; [7] Department of Gynaecology, Medical University of Vienna, Vienna, Austria; [8] Department of Medicine 1, Elisabethinen Hospital Linz, Ordensklinkum Linz, Linz, Austria

Investigator-Initiated Study

試験デザイン

Primary Endpoint: ORR (CNS) by RANO-BM criteria
Secondary Endpoints:
- Clinical Benefit Rate (CR+PR+SD ≥6 months)
- Extracranial Response rate
- PFS
- OS
- Safety
- Ouality of Life

TUXEDO-1 (NCT04752059)



BM, brain metastasis; BW, body weight; CNS, central nervous system; D1, day 1; EOT, end of treatment; FU, follow up; IV, intravenous; KPS, Karnofsky performance; LVEF, left ventricular ejection fraction; q3w, once every 3 weeks; RANO, response assessment in neuro-oncology; T-DXd, trastuzumab deruxtecan.
EudraCT: 2020-000981-41.

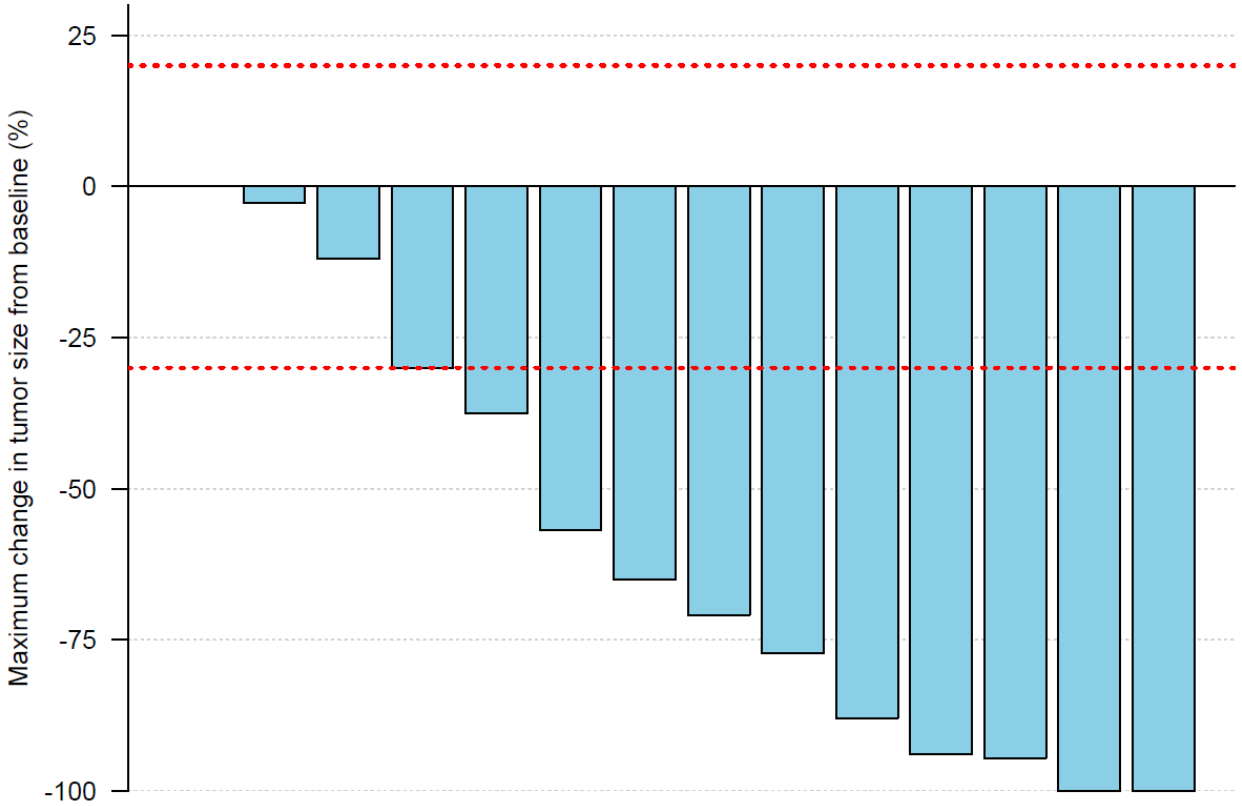
Simon Two Stage Design
- RR (CNS) >60% suggests clinically relevant activity
- RR (CNS) <26% suggests no benefit compared to previous systemic treatment options
- Stage 1: 6 pts. (at least three responses); Stage 2: 9 pts; overall 15 pts. (at least 7 responses)
- Type 1 error rate 5%; power 80%

主要評価項目

TUXEDO-1

Objective Response Rate (RANO-BM criteria)

ORR (intention-to-treat population; *n*=15): 73.3% (95% CI 48.1-89.1)



One patient with dural metastases

RR (per-protocol-population; *n*=14): 78.6%

ESMO BC 2022 #165 Mini Oral

まとめ
TUXEDO-1

- トラスツズマブ デルクステカンは脳転移を有するHER2陽性乳がんの患者においても有効であった
  - TUXEDO-1 は主要評価項目を達成した
  - 奏効率（試験の治療からの脱落者も含めた患者層） 73.3%
  - 頭蓋外および頭蓋内奏効率は同程度
  - 病勢コントロールの延長
- 新たな安全性シグナルは検出されなかった
- 治療期間を通じてQOLは維持された
- 脳転移を有するHER2陽性乳がんにおいて全身治療が可能であるというエビデンスを獲得した
- 脳転移に対するADCの更なる開発を支持する

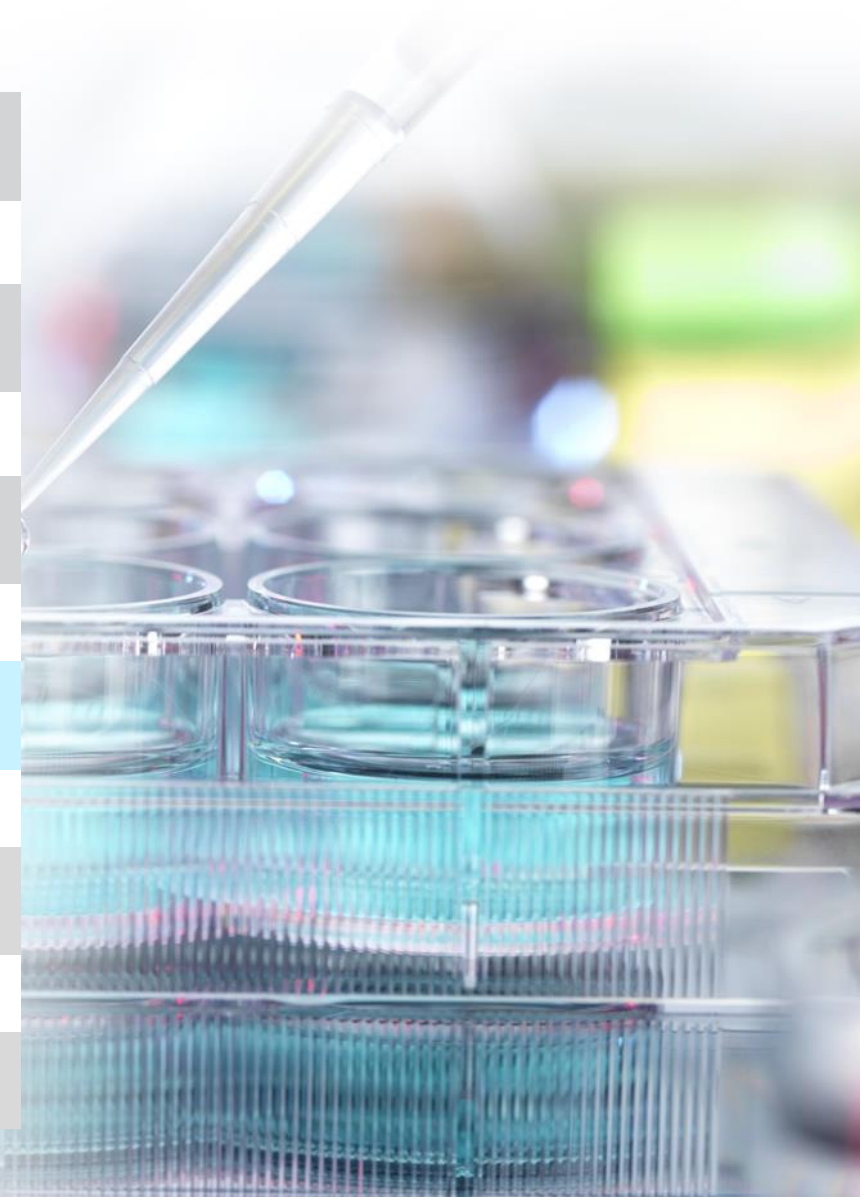
HER2陽性乳がん Key Takeaways

- DESTINY-Breast03: 安全性評価のフォローアップと患者報告アウトカムの結果は、既報の有効性データと合わせてHER2陽性乳がんにおけるエンハーツ®のベネフィットを示した
- エンハーツ®は活動性の脳転移を有する患者においても予備的な有効性を示した
  - さらなるエビデンス取得のため臨床試験を実施中
- ILDのマネジメントと教育はエンハーツ®の安全な使用のために引き続き重要である

エンハーツ® はHER2陽性乳がんにおいて引き続き信頼を構築していく

本日お話しする内容

1. イントロダクション
2. HER2低発現乳がん治療のパラダイムをシフトする
3. HER2陽性乳がんにおける信頼を構築する
4. **乳がんのさらなるニーズに対応する**
5. Rising Stars
6. 今後のニュースフロー



乳がんのさらなるニーズに対応する

エンハーツ®

- **併用および早期がんでの可能性の追求**
  - Support safety of nivolumab combination
    - – Hamilton E et al., ESMO BC #1620 Oral
  - Preliminary data of combo dose-finding in HER2+ (DB-07) and HER low BC (DB-08)
    - – Andre F et al., ASCO #3025 Poster
  - TALENT Ph2 neoadjuvant in HR+/HER2 Low early BC (IIS)
    - – Hurvitz S et al., ASCO #TPS623 Poster
- **サイエンスの深化**
  - Biomarker analyses from patients from DAISY trial
    - – Mosele F et al., ESMO BC #LBA1 Oral

乳がんのさらなるニーズに対応する

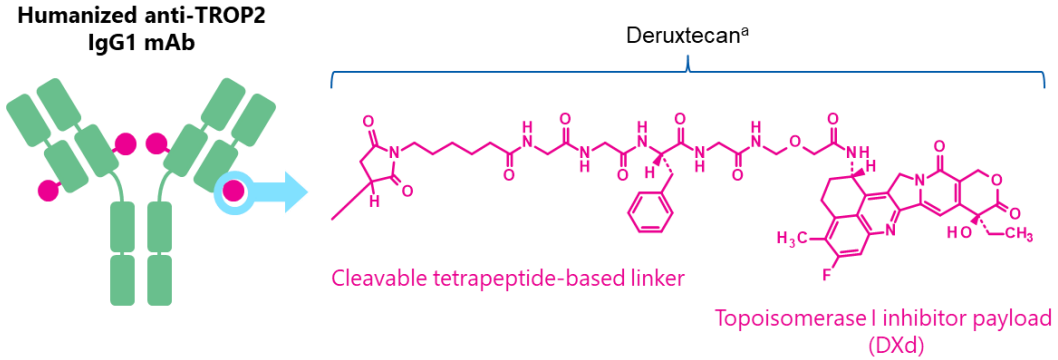
Dato-DXd

- **TNBCにおける有望な併用の可能性**
  - Initial results from BEGONIA study of Dato-DXd and durvalumab combo in 1L TNBC - Schmid P et al., ESMO BC #166 Mini Oral*

*次頁以降で紹介

- **TNBCおよびHR+/HER2- 乳がんおいて単剤の臨床試験が進行中**
  - 将来の学会でデータを開示予定

Datopotamab deruxtecan (Dato-DXd)



Designed With Key 7 Attributes

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

- **Potential Best-In-Class TROP2 ADC**
- **Developing for BC, NSCLC and other solid tumors**

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

Datopotamab deruxtecan + durvalumab as first-line treatment for unresectable locally advanced/metastatic triple-negative breast cancer

Initial results from BEGONIA, a phase 1b/2 study

Peter Schmid, FRCP, MD, PhD

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

K. H. Jung,[1] P. J. Wysocki,[2] J. Jassem,[3] C. X. Ma,[4] R. Fernandes,[5] R. Huisden,[6] R. Stewart,[6] P. Vukovic,[6] A. Tablante Nunes,[7] Z. Nowecki[8]

[1]Asan Medical Center - University of Ulsan, College of Medicine, Seoul, Korea; [2]Jagiellonian University - Medical College, Krakow, Poland; [3]Medical University of Gdańsk, Gdańsk, Poland; [4]Washington University School of Medicine, St. Louis, MO, USA; [5]Schulich School of Medicine & Dentistry, Western University, London Health Sciences Centre, London, Canada; [6]AstraZeneca, Cambridge, UK; [7]AstraZeneca, Gaithersburg, MD, USA; [8]Maria Skłodowska-Curie National Research Institute of Oncology, Warsaw, Poland

BEGONIA (NCT03742102) 試験デザイン

- Females aged ≥18 years
- Unresectable a/mTNBC
- No prior treatment for Stage IV TNBC
- ≥12 months since prior taxane therapy
- ECOG PS 0-1
- Adequate organ function
- Measurable disease per RECIST v1.1
- No prior treatment with checkpoint inhibitor or TOPO I-based ADC[a]

Part 1 (this presentation includes results from part 1)

First 20 patients
- Paclitaxel + Durvalumab (P + D) (N=20)
- **Dato-DXd + D[c]** (N=30) Q3W until PD

All others randomized to an open cohort
- Capivasertib + P + D (N=30)
- Oleclumab + P + D (N=30)
- T-DXd + D (N=30)

Each novel combination cohort

Primary endpoint: Safety and tolerability
Secondary endpoints: ORR, PFS, DoR, OS

Simon 2-stage futility analysis for Part 2 expansion[c]

Part 2 expansion (currently active/ongoing)

Randomized if multiple cohorts open
- **Dato-DXd + D[b]** Q3W until PD
- T-DXd + D

Enroll additional 27 patients in each arm

Primary endpoint: ORR
Secondary endpoints: PFS, DoR, PFS6, OS

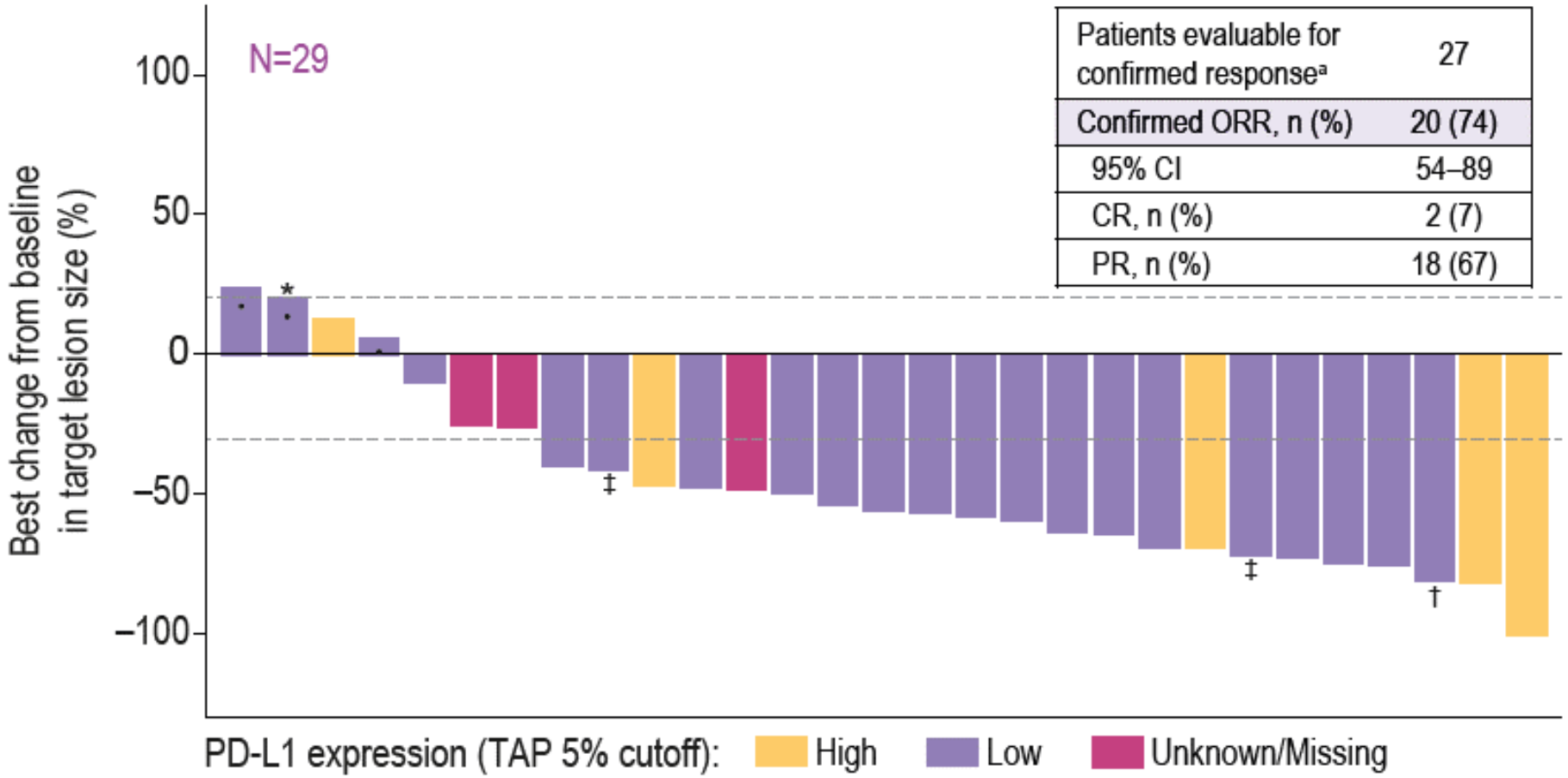
[a]ADC-cohort-specific criteria. [b]Dato-DXd 6 mg/kg + D 1120 mg. [c]Novel treatment combinations may enter Part 2 expansion if confirmed ORR is at least 57%.

ADC, antibody-drug conjugate; a/mTNBC, locally advanced/metastatic triple negative breast cancer; DLT, dose-limiting toxicity; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance scale; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PD, progressive disease; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; T-DXd, trastusumab deruxtecan; TOPO I, topoisomerase I.

Data cutoff: November 15, 2021

抗腫瘍効果

Dato-DXd + Durvalumab in BEGONIA Part 1



Patients evaluable for confirmed response[a]	27
Confirmed ORR, n (%)	20 (74)
95% CI	54–89
CR, n (%)	2 (7)
PR, n (%)	18 (67)

- Confirmed ORR was observed in 20/27 (74%) patients

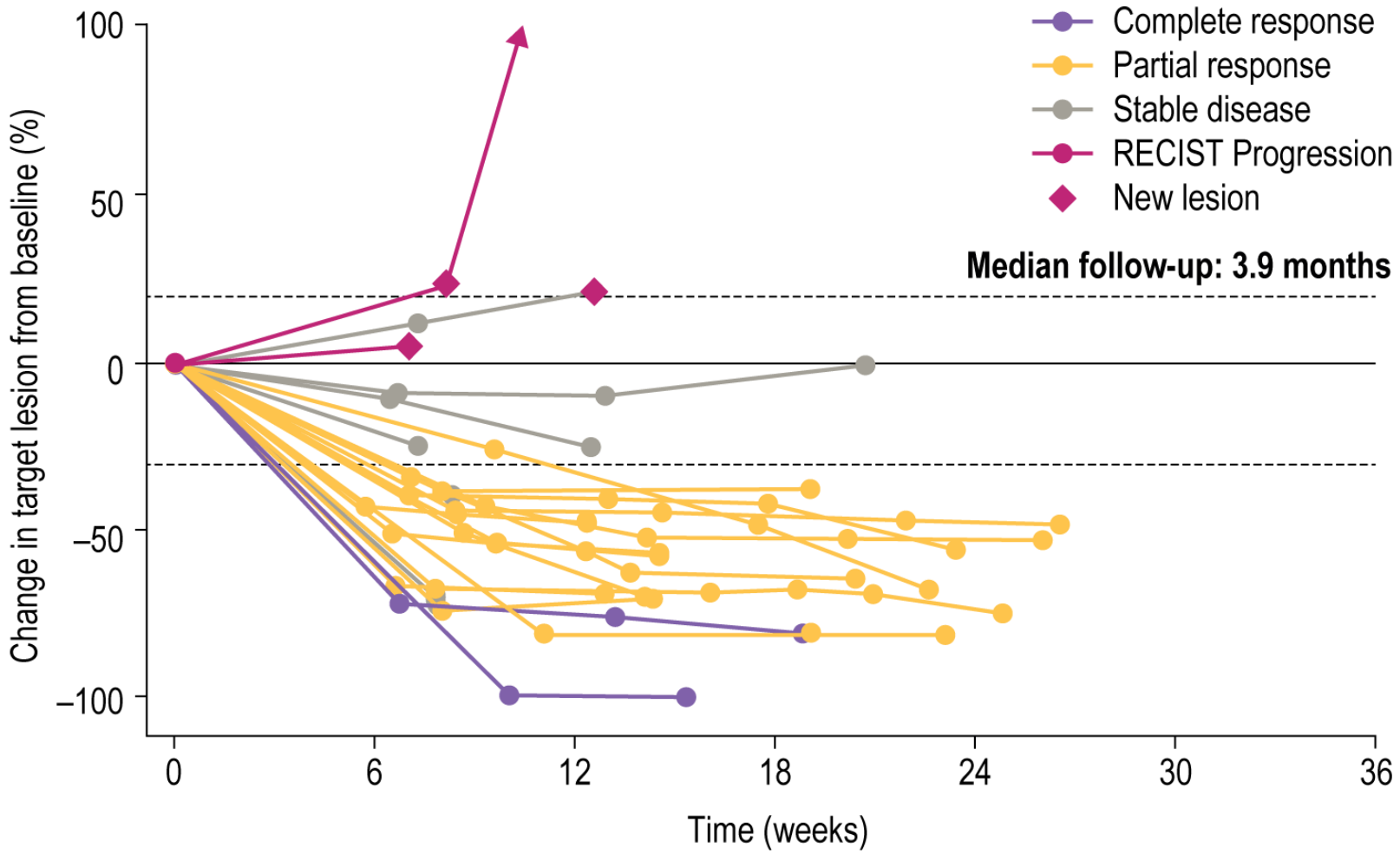
[a]Had the opportunity to have 2 postbaseline scans.
Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%).
*If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal, or death, the value is imputed at +20%.
"•" Patients with PD as best overall response. †CR with lymph node disease (CR per RECIST in lymph nodes, is <10mm). ‡ Unconfirmed response.
CR, complete response; ORR, objective response rate; PR, partial response.

Data cutoff: November 15, 2021

ESMO BC 2022 #166 Mini Oral

抗腫瘍効果

Dato-DXd + Durvalumab in BEGONIA Part 1



- Median time to response was 1.4 mos. (95% CI, 1.35–1.58)
- All patients with a response had an ongoing response at data cutoff
- Median duration of response was not reached

Data cutoff: November 15, 2021

Dotted lines indicate thresholds for partial response (−30%) and progressive disease (20%).

安全性の概要

Dato-DXd + Durvalumab in BEGONIA Part 1

No dose limiting toxicities	
Patients, n (%)	**Dato-DXd + D N=29**
Any grade AEs	29 (100)
Grade 3/4	8 (28)
Any grade treatment-related AEs	27 (93)
Grade 3/4	8 (28)
Dose adjustments	
Dato-DXd dose reduction[a]	4 (14)
Dato-DXd dose delay	1 (3)
Durvalumab dose delay	4 (14)
Serious AEs	5 (17)
AEs leading to death	1 (3)[b]
AEs leading to discontinuation of all treatments[c]	2 (7)

[a] All 4 Dato-DXd dose reductions were due to stomatitis.
[b] One patient died due to hypotension unrelated to treatment.
[c] Includes 1 case of anaphylactic reaction and 1 case of troponin increase.

Data cutoff: November 15, 2021

最も報告されている有害事象 （≥15% すべてのグレード)

Dato-DXd + Durvalumab in BEGONIA Part 1

Preferred term, n (%) AEs all causes	Dato-DXd + D N=29			
	All Grades, ≥15% of patients	Grade 1	Grade 2	Grade 3
Stomatitis	20 (69)	8 (28)	8 (28)	4 (14)
Alopecia	19 (66)	13 (45)	6 (21)	0
Nausea	19 (66)	13 (45)	6 (21)	0
Constipation	11 (38)	8 (28)	3 (10)	0
Fatigue	11 (38)	9 (31)	2 (6.9)	0
Rash	9 (31)	8 (28)	1 (3)	0
Vomiting	5 (17)	3 (10)	2 (6.9)	0

- Low rates of diarrhea reported (4 [14%]; all Grade 1)
- No cases of ILD/pneumonitis or neutropenic events were reported
- 13.7% of patients required dose reduction due to stomatitis
- Updated TMGs and prophylaxis for stomatitis are being implemented

Data cutoff: November 15, 2021

ILD, interstitial lung disease; TMG, trial management guide.

まとめ

Dato-DXd + Durvalumab in BEGONIA Part 1

- バイオマーカーによる選別を行っていないTNBC患者の一次治療を対象としたBEGONIA試験の中間結果において、Dato-DXd + デュルバルマブは高い奏効率を示した。
  - 確定ORRは74%で、データカットオフの時点ですべての患者が治療を継続していた
  - PD-L1発現に関わらず抗腫瘍効果が確認された
- Dato-DXdとデュルバルマブの併用療法は、個々の薬剤の既知の安全性プロファイルと同様の管理可能な安全性プロファイルを示し、新たな安全性シグナルは認められなかった。
  - 用量制限毒性なし
  - 主な有害事象は口内炎および軽度の悪心・脱毛症であった
  - 下痢の発現率は低く、ILD/肺炎もしくは好中球減少は報告されなかった
- パート2への患者登録が進行中。奏効期間およびPFS/OSを決定するために試験のフォローアップを継続する。

Dato-DXd: 乳がん 臨床開発ハイライト

	Neoadjuvant	Post-neoadjuvant/Adjuvant	1L Metastatic	2L Metastatic	3L Metastatic
HER2+ ~ 20% of patients		Adjuvant			
Hormone-receptor positive (HR+) ~ 65% of patients					TROPION-PanTumor01 Phase 1 Monotherapy TROPION-Breast01 Phase 3 Monotherapy vs CTx PC
Triple-negative (TNBC) ~ 15% of patients			BEGONIA Phase 1b/2 Combo with durvalumab New Study ➔ TROPION-Breast02 Phase 3 Monotherapy vs CTx	TROPION-PanTumor01 Phase 1 Monotherapy	

エンハーツ® & Dato-DXd: 乳がん 臨床開発ハイライト

ENHERTU®
Dato-DXd

Daiichi-Sankyo

	Neoadjuvant	Post-neoadjuvant/Adjuvant	1L Metastatic	2L Metastatic	3L Metastatic
HER2+ ~ 20% of patients	**DESTINY-Breast11** Phase 3 ENHERTU® vs ENHERTU® / THP vs AC / THP	**DESTINY-Breast05** Phase 3 Monotherapy vs T-DM1	**DESTINY-Breast09** Phase 3 ENHERTU® ± pertuzumab vs THP	**DESTINY-Breast03** Phase 3 Monotherapy vs T-DM1 APPROVED	**DESTINY-Breast01** Phase 2 Monotherapy LAUNCHED
			DESTINY-Breast07 Phase 1b/2 Combination (Part 2)		**DESTINY-Breast02** Phase 3 Monotherapy vs PC
					DESTINY-Breast07 Phase 1b/2 Combination(Part 1)
Hormone-receptor positive (HR+) ~ 65% of patients					**TROPION-PanTumor01** Phase 1 Monotherapy
				DESTINY-Breast06 Phase 3 Monotherapy vs PC (chemotherapy naïve)	**TROPION-Breast01** Phase 3 Monotherapy vs CTx PC
			DESTINY-Breast08 Phase 1b Combination		**DESTINY-Breast04** Phase 3 Monotherapy vs PC (2L+ chemotherapy)
Triple-negative (TNBC) ~ 15% of patients			**BEGONIA** Phase 1b/2 Combo with durvalumab		
			BEGONIA Phase 1b/2 Combo with durvalumab		
			TROPION-Breast02 Phase 3 Monotherapy vs CTx	**TROPION-PanTumor01** Phase 1 Monotherapy	

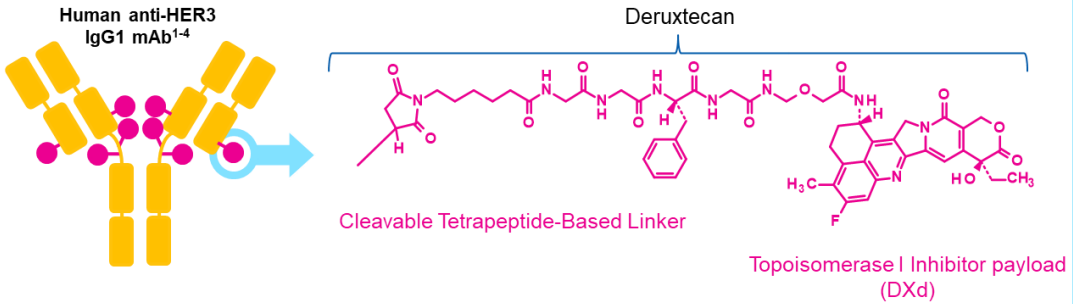
もう一つの乳がん治療オプションとしての可能性を探索

HER3-DXd

- **乳がんに関するASCO/ESMO BCでの発表**
  - HER3-expressing mBC pooled analysis – Krop I et al., ASCO #1002 Oral*

    *次頁以降で紹介
  - “Window of opportunity study” in pre-operative BC
    – Prat A et al., ESMO BC #LBA3 Oral

Patritumab Deruxtecan (HER3-DXd)



Designed With Key 7 Attributes

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

- **Potential First-In-Class HER3 ADC**
- **BTD by FDA for EGFR mutated NSCLC 3L+**
- **Exploring potential in BC and other solid tumors**

[a] The clinical relevance of these features is under investigation. [b] Based on animal data.

Results From the Phase 1/2 Study of Patritumab Deruxtecan, a HER3-Directed Antibody-Drug Conjugate (ADC), in Patients With HER3-Expressing Metastatic Breast Cancer

Ian E. Krop,[1] Norikazu Masuda,[2] Toru Mukohara,[3] Shunji Takahashi,[4] Takahiro Nakayama,[5] Kenichi Inoue,[6] Hiroji Iwata,[7] Tatsuya Toyama,[8] Yutaka Yamamoto,[9] Damien Hansra,[10] Masato Takahashi,[11] Akihiko Osaki,[12] Kumiko Koyama,[13] Tatsuya Inoue,[14] Takatoshi Yonekura,[13] Joseph Mostillo,[15] Shoichi Ohwada,[13] Yoshimi Tanaka,[13] David Sternberg,[15] Kan Yonemori[16]

[1] Yale University, Hartford, CT; [2] Nagoya University Graduate School of Medicine, Nagoya, Japan; [3] National Cancer Center Hospital East, Kashiwa, Japan; [4] The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan; [5] Osaka International Cancer Institute, Osaka, Japan; [6] Saitama Cancer Center, Saitama Japan; [7] Aichi Cancer Center Hospital, Nagoya, Japan; [8] Nagoya City University, Nagoya, Japan; [9] Kumamoto University Hospital, Kumamoto, Japan; [10] Piedmont Physicians Medical Oncology, Fayetteville, GA; [11] National Hospital Organization, Hokkaido Cancer Center, Sapporo, Japan; [12] Saitama Medical University International Medical Center; Hidaka, Japan; [13] Daiichi Sankyo Co., Ltd., Tokyo, Japan; [14] Daiichi Sankyo RD Novare Co., Ltd., Edogawa-Ku, Japan; [15] Daiichi Sankyo, Inc., Basking Ridge, NJ; [16] National Cancer Center Hospital, Tokyo, Japan

ASCO 2022 #1002 Oral

On behalf of the investigators

試験デザイン

Patritumab Deruxtecan : U31402-A-J101

KEY ELIGIBILITY CRITERIA

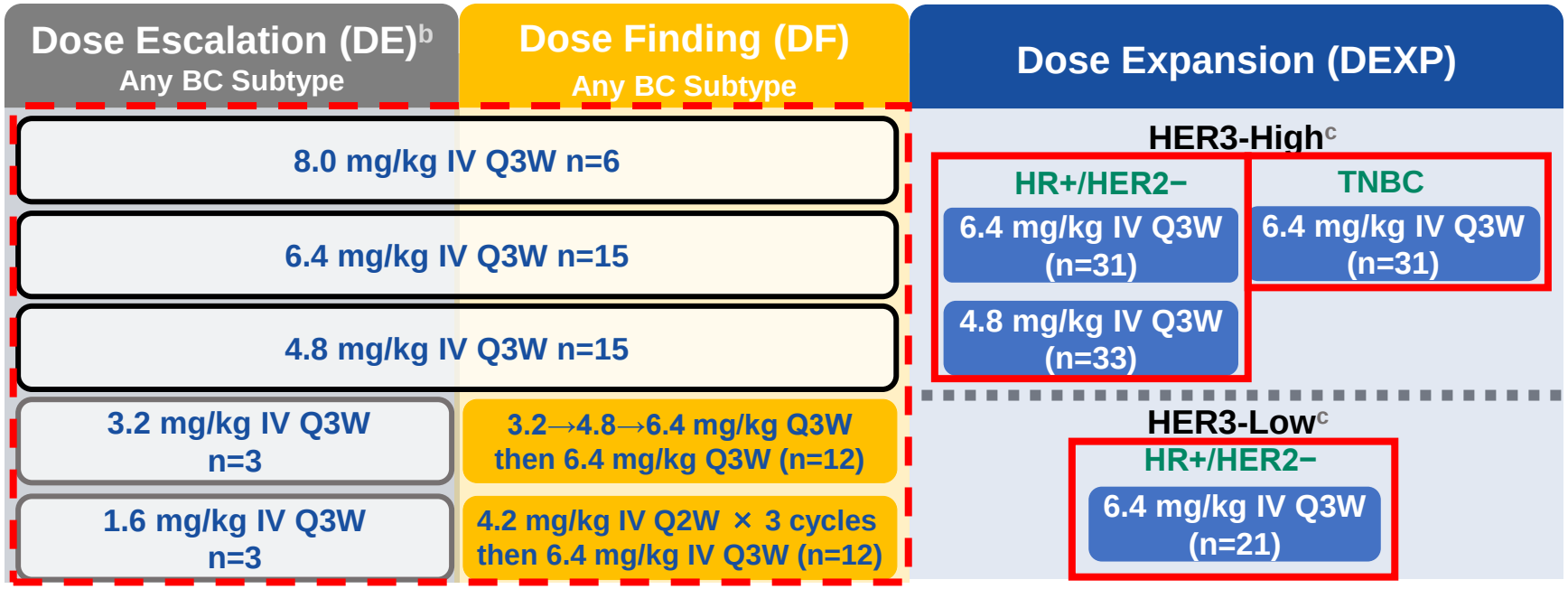
- Advanced/unresectable or metastatic breast cancer
- HER3-positive[a]

DE/DF & HR+/HER2− DEXP

- ≥2 and ≤6 lines of prior chemotherapy; ≥2 for advanced disease

Dose expansion: TNBC

- 1 to 2 prior chemotherapy regimens for advanced disease



Data for all 3 phases were pooled

- **Efficacy** is reported by BC subtype: HR+/HER2− (n=113), TNBC (n=53), and HER2+ (n=14)
- **Safety** is reported for patients who received HER3-DXd 4.8 mg/kg (n=48), 6.4 mg/kg (n=98), and all patients (N=182[d])

DE, dose escalation; DEXP, dose expansion; DF, dose finding; EWOC, escalation with overdose control; HR, hormone receptor; IHC, immunohistochemistry; mCRM, modified continuous reassessment method; Q2W, once every 2 weeks; Q3W, once every 3 weeks; R, randomized; TNBC, triple-negative breast cancer.

[a] HER3 status was determined by IHC; HER3-positive was defined as IHC 2+ and IHC 3+ for DE/DF cohorts and as ≥25% membrane positivity at 10x for DEXP cohorts. [b] Guided by mCRM with EWOC. [c] HER3-high was defined as >75% membrane positivity at 10x; HER3-low was defined as ≥25% and ≤75% membrane positivity at 10x. [d] Includes two patients with unknown BC subtype.

様々な乳がんサブタイプにおけるHER3-DXdの有効性データ

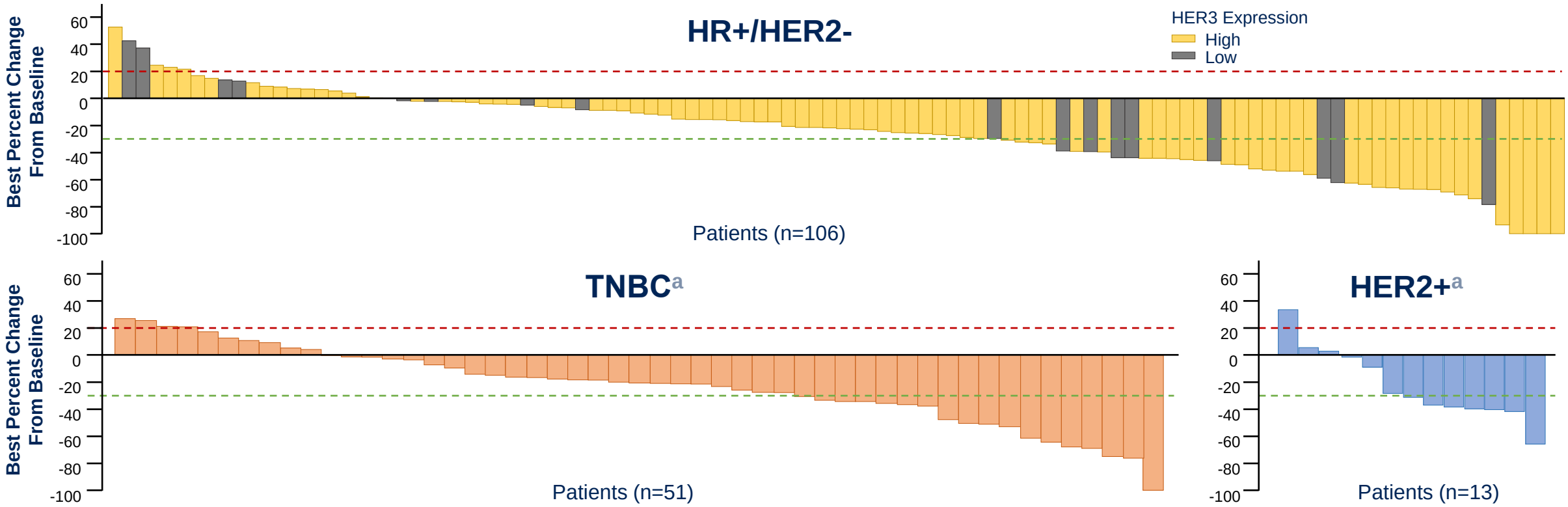
Outcomes (BICR per RECIST 1.1)	HR+/HER2− (n=113) HER3-High and -Low	TNBC (n=53) HER3-High	HER2+ (n=14) HER3-High
Confirmed ORR, % (95% CI[a])	30.1 (21.8-39.4)	22.6 (12.3-36.2)	42.9 (17.7-71.1)
Best overall response, %[b]			
PR	30.1	22.6	42.9
SD	50.4	56.6	50.0
PD	11.5	17.0	7.1
NE	8.0	3.8	0.0
DOR, median (95% CI), mo	7.2 (5.3-NE)	5.9 (3.0-8.4)	8.3 (2.8-26.4)
PFS, median (95% CI), mo	7.4 (4.7-8.4)	5.5 (3.9-6.8)	11.0 (4.4-16.4)
6-month PFS rate, % (95% CI)	53.5 (43.4-62.6)	38.2 (24.2-52.0)	51.6 (22.1-74.8)
OS, median (95% CI), mo	14.6 (11.3-19.5)	14.6 (11.2-17.2)	19.5 (12.2-NE)

HER3-DXd demonstrated durable antitumor activity across BC subtypes

- Confirmed ORR for all patients (N=182), 28.6% (95% CI, 22.1%-35.7%); median DOR, 7.0 mo (95% CI, 5.5-8.5 months)

CR, confirmed response; DOR, duration of response; NE, not evaluable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.
[a] 95% exact binomial confidence interval (by Clopper-Pearson method).
[b] No patients had a CR.

ベースラインからの腫瘍サイズの変化



HER3-DXd induced a clinically meaningful decrease in tumor size by BICR in most patients across BC subtypes[b]

[a] Patients with TNBC and HER2+ were all HER3-high.
[b] Best percentage change from baseline in sum of diameters based on BICR for all target lesions identified is represented by patient. If any lesion measurement is missing at a post-baseline tumor assessment visit, that visit is not taken into consideration for best percent change from baseline in sum of diameters.

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HER3-DXdの安全性プロファイル

- HER3-DXd was associated with a manageable safety profile
- There was a low rate of TEAEs associated with treatment discontinuation (9.9%)
  - 18 patients had TEAEs associated with treatment discontinuation across all doses: pneumonitis (n=6), disease progression (n=2), ejection fraction decreased (n=2), ILD, malaise, peripheral edema, hepatotoxicity, gastric cancer, mental status changes, extradural hematoma, and general physical health deterioration (all n=1)
- 6.6% of patients had treatment-related ILD events[a]
  - Most were grade 1 and 2 (4.4%)
  - There was one grade 5 ILD event (0.5%)

Patients, n (%) **Median treatment duration: 5.9 mo (range 0.7-30.6 mo)**	**4.8 mg/kg n=48**	**6.4 mg/kg n=98**	**All Doses N=182**
Any TEAE	47 (97.9)	98 (100)	181 (99.5)
Associated with discontinuation	5 (10.4)	8 (8.2)	18 (9.9)
Associated with dose reduction	6 (12.5)	22 (22.4)	35 (19.2)
Associated with drug interruption	23 (47.9)	57 (58.2)	100 (54.9)
Associated with death	1 (2.1)[b]	6 (6.1)[b]	7 (3.8)[b]
Grade ≥3 TEAE	31 (64.6)	80 (81.6)	130 (71.4)
Treatment-related TEAE	47 (97.9)	97 (99.0)	180 (98.9)
Associated with death	0	1 (1.0)[c]	1 (0.5)[c]
Grade ≥3	27 (56.3)	76 (77.6)	120 (65.9)
Serious TEAE	7 (14.6)	23 (23.5)	38 (20.9)
Adjudicated treatment-related ILD[d]			
Grade 1	0	2 (2.0)	3 (1.6)
Grade 2	1 (2.1)	2 (2.0)	5 (2.7)
Grade 3	0	2 (2.0)	3 (1.6)
Grade 4	0	0	0
Grade 5	0	1 (1.0)	1 (0.5)
Total	**1 (2.1)**	**7 (7.1)**	**12 (6.6)**

ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] As determined by an independent adjudication committee. [b] TEAEs associated with death included disease progression (n=4), neutropenic sepsis (n=1), extradural hematoma (n=1), and choking (n=1). [c] Treatment-related TEAE associated with death was neutropenic sepsis (n=1). [d] Median time to onset, 141.5 days (95% CI; 36-584 days).

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4.8 mg/kg および 6.4 mg/kgを投与後に発現した有害事象

- GI and hematologic toxicity were the most common TEAEs
- Rates of non-hematologic toxicity were similar at both doses and generally low grade
- Rates of grade ≥3 neutropenia, thrombocytopenia and leukopenia were numerically higher at 6.4 mg/kg vs 4.8 mg/kg
  - All events were managed by dose delay or reduction and were not associated with treatment discontinuation
  - No grade ≥3 TEAE of thrombocytopenia resulted in a grade ≥3 bleeding event

TEAEs (≥25% of all patients), (%)	4.8 mg/kg n=48		6.4 mg/kg n=98	
	All grade	Grade ≥3	All grade	Grade ≥3
TEAEs	**97.9**	**64.6**	**100**	**81.6**
Nausea	68.8	4.2	80.6	5.1
Platelet count decreased[a]	60.4	27.1	71.4	38.8
Neutrophil count decreased[a]	62.5	27.1	66.3	52.0
Decreased appetite	56.3	6.3	53.1	6.1
Vomiting	47.9	4.2	46.9	1.0
White blood cell count decreased[a]	45.8	10.4	45.9	23.5
Diarrhea	41.7	4.2	43.9	3.1
Anemia[a]	43.8	20.8	43.9	21.4
Aspartate aminotransferase increased	43.8	4.2	34.7	6.1
Stomatitis	25.0	0.0	34.7	1.0
Fatigue	31.3	0.0	33.7	3.1
Alanine aminotransferase increased	41.7	2.1	31.6	7.1
Constipation	22.9	0.0	29.6	0.0
Alopecia	20.8	NA	28.6	NA
Malaise	22.9	0.0	26.5	1.0

GI, gastrointestinal; NA, not applicable.
[a] Grouped terms: platelet count decreased (platelet count decreased, thrombocytopenia); neutrophil count decreased (neutrophil count decreased, neutropenia); white blood cell count decreased (leukopenia, white blood cell decreased); anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased).

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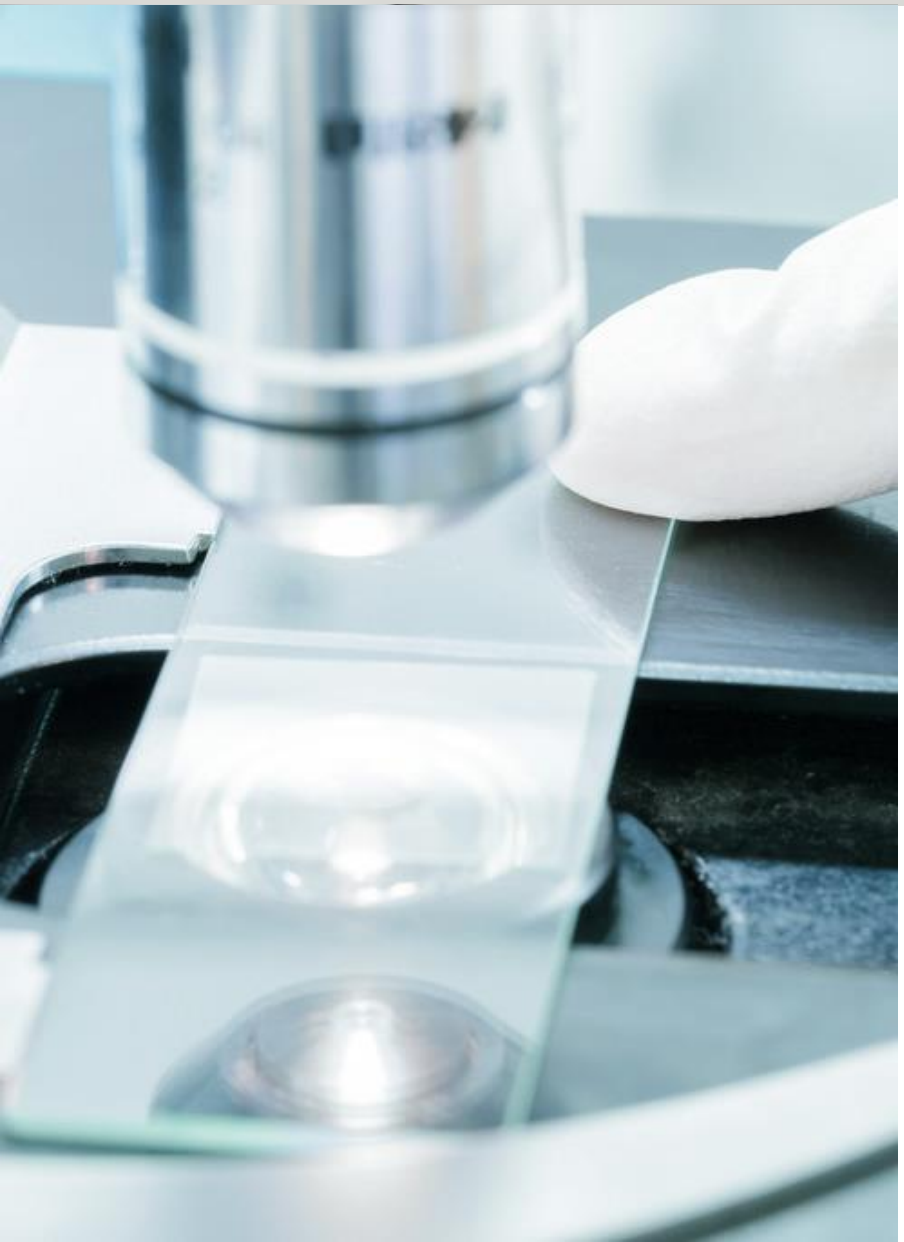
まとめ

- HER3-DXdは、多数の前治療歴を有するHER3発現乳がんの患者に対して臨床的に意義があり、かつ持続的な抗腫瘍効果を示した。
  - 様々な乳がんのサブタイプで持続的な抗腫瘍効果を示した：HR+/HER2− （ORR, 30%; mDOR, 7.2ヶ月）、TNBC （ORR, 23%; mDOR, 5.9ヶ月）、HER2+ （ORR, 43%; mDOR, 8.3ヶ月)
  - また、HER3高発現および低発現において抗腫瘍効果を示した。
- 管理可能な安全性プロファイルを示し、有害事象による治験薬投与の中止率は低かった（10%）
  - 治験薬に関連するILDと判定された割合は7%；ほとんどの症例はグレード１および２
  - グレード３以上の血液毒性は管理可能；治療の中止に繋がるグレード３以上の血小板減少症およびグレード３以上の出血は認められなかった。
- 4.8 mg/kgおよび6.4 mg/kgで同様の安全性プロファイルが確認されたことから、NSCLCで使用されている5.6 mg/kgの用量について、乳がんにおいても用量最適化のため評価中 。
- これらのデータにより、有望な抗腫瘍効果と管理可能な安全性プロファイルが認められたため、臨床学的および組織病理学的な乳がんの様々なサブタイプに対してHER3-DXdを評価する妥当性が得られた。

乳がんのさらなるニーズに対応する　Key Takeaways

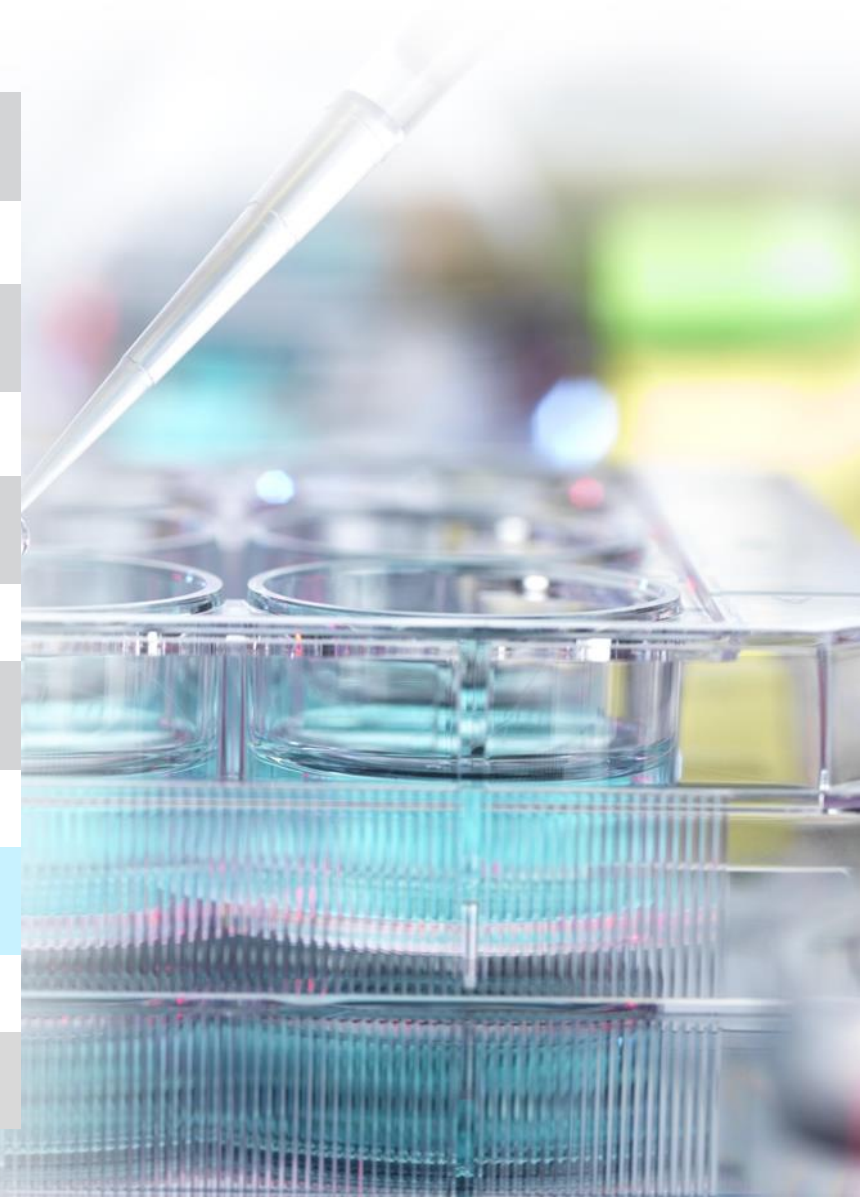


- DXd-ADCのサイエンスについて理解を深める
  – 作用/耐性機序
- 併用および早期がんでの可能性を追求する
- 複数の治療オプションにより疾患の克服を目指す

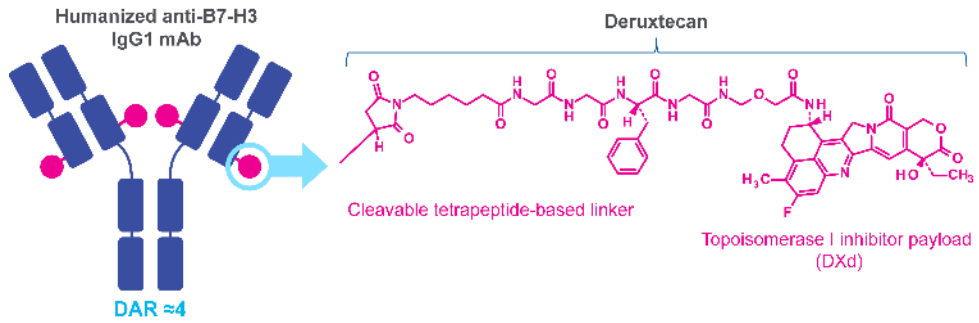
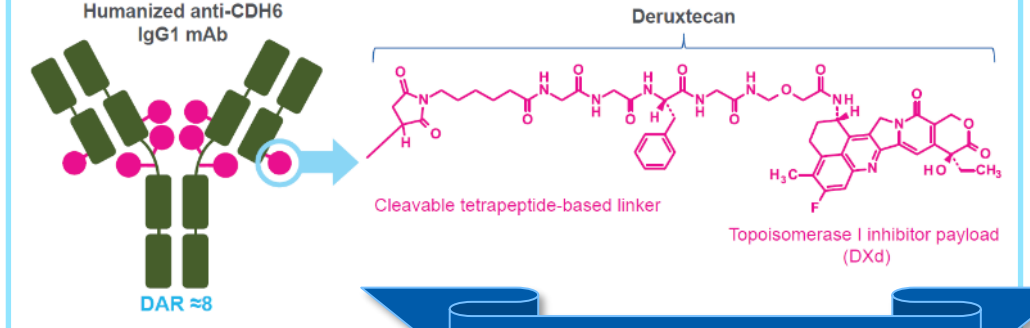
我々は乳がんにおけるアンメットニーズへの対応を継続していく

本日お話しする内容

1. イントロダクション
2. HER2低発現乳がん治療のパラダイムをシフトする
3. HER2陽性乳がんにおける信頼を構築する
4. 乳がんのさらなるニーズに対応する
5. **Rising Stars**
6. 今後のニュースフロー



Rising Stars: DS-7300 & DS-6000

	DS-7300	DS-6000
構造		
開発ステージ & 適応症	**Ph1/2** 用量漸増パート: 固形がん 用量展開パート: 食道扁平上皮がん, 去勢抵抗性前立腺がん, 扁平上皮NSCLC **Ph2 (SCLC)** 2022年度上半期の開始を目指し準備中	**Ph1** 用量漸増& 用量展開パート: 腎細胞がん & 卵巣がん 現在用量展開パートを実施中

ASCO 2022にて初めてデータ開示

DAR: 薬物抗体比、mAb: モノクローナル抗体、NSCLC: 非小細胞肺がん、SCLC: 小細胞肺がん

Rising Starsは3ADCに次ぐ成長ドライバーとなる可能性を有しており、開発を加速化している

Phase I, Two-Part, Multi-Center, First-in-Human Study of DS-6000a in Subjects with Advanced Renal Cell Carcinoma and Ovarian Cancer

Erika P. Hamilton, MD[1,2]; Shekeab Jauhari, MD[1,3]; Kathleen Moore, MD[4]; Brian Rini, MD[5]; Robert McLeod, MD[6]; Jie Lin, MD[6]; Nanae Izumi[6]; Madan G. Kundu, PhD[6]; Yusuke Myobatake[6]; Abderrahmane Laadem, MD[6]; Yutaka Noguchi[7]; Julius Kirui[1]; David R. Spigel, MD[1,2]

[1]Sarah Cannon Research Institute, Nashville, TN; [2]Tennessee Oncology, PLLC, Nashville, TN; [3]Florida Cancer Specialists and Research Institute, Lake Mary, FL; [4]University of Oklahoma College of Medicine, Oklahoma City, OK; [5]Vanderbilt-Ingram Cancer Center, Nashville, TN; [6]Daiichi Sankyo, Inc, Basking Ridge, NJ; [7]Daiichi Sankyo Co, Ltd, Tokyo, Japan

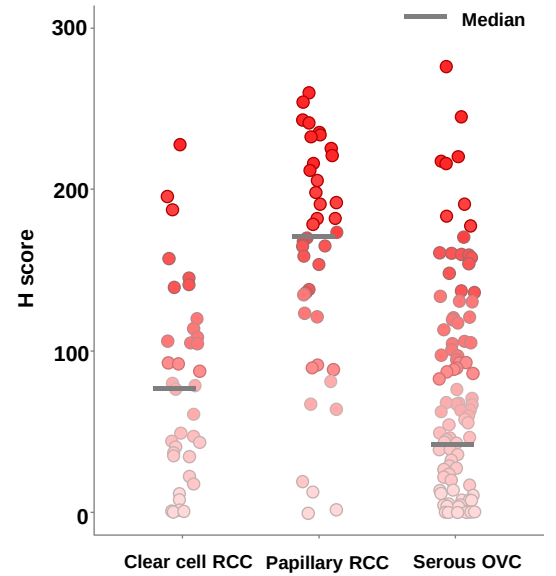
ASCO 2022 #3002 Oral

On behalf of the investigators

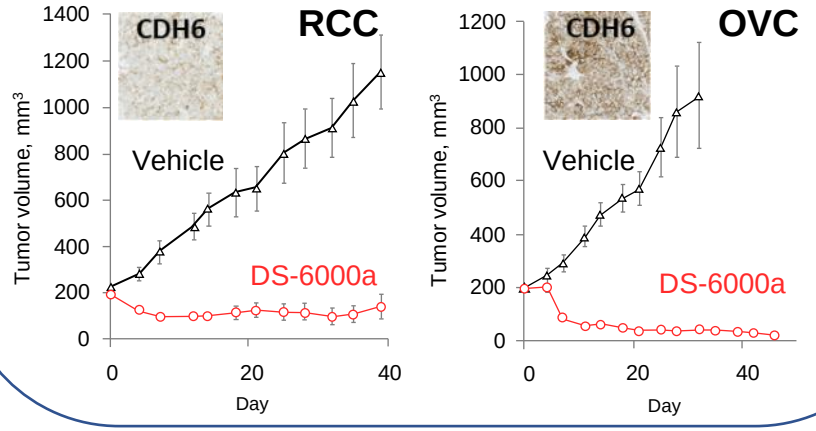
背景

- Cadherin 6 (CDH6) is part of the cadherin family, which is involved with cell-cell adhesion, organ development, and epithelial-mesenchymal transition
- CDH6 is found to be overexpressed in various cancers, particularly ovarian cancer (OVC) and renal cell carcinoma (RCC)[1]
- In preclinical studies, DS-6000a inhibited tumor growth and induced tumor regression in CDH6-expressing OVC and RCC[1]
- Here, we report initial results from the dose-escalation portion of a first-in-human trial in patients with advanced OVC and RCC (NCT04707248)

CDH6 Expression in RCC/Serous OVC[1]



Antitumor Activity of DS-6000a in RCC and OVC PDX Model[1]



PDX, patient-derived xenograft.

1. Hirokazu S, et al. ESMO 2021. Abstract 10P.

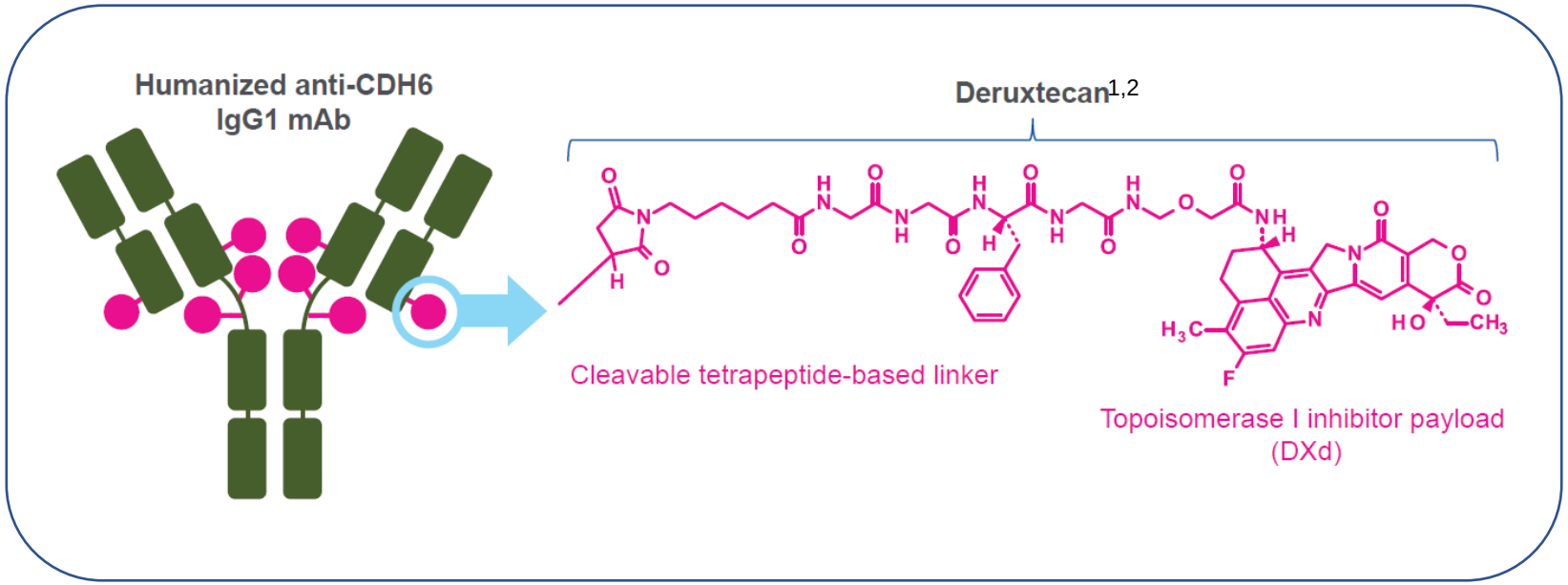
DS-6000: 主要な7つの特性

DS-6000a is a cadherin 6 (CDH6) directed ADC composed of 3 components:[1-3]

A humanized anti-CDH6 IgG1 monoclonal antibody covalently linked to:

A topoisomerase I inhibitor payload, an exatecan derivative, via

A tetrapeptide-based cleavable linker

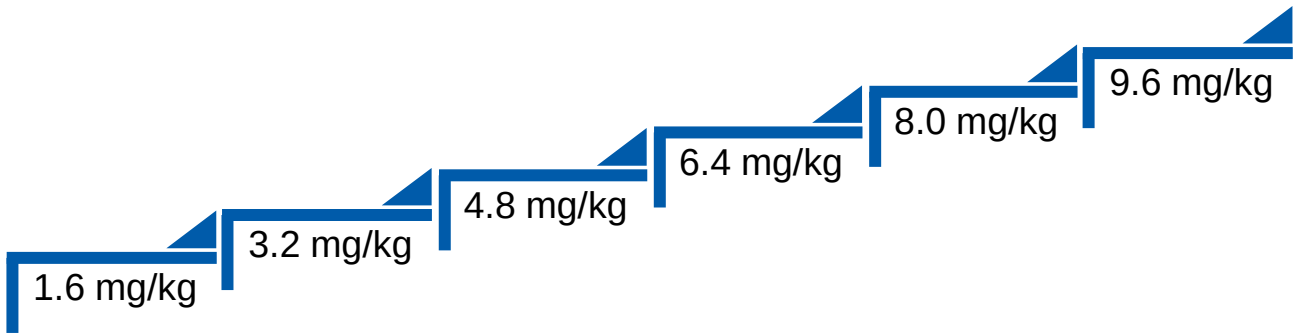


- Payload mechanism of action: topoisomerase I inhibitor [a,1,2]
- High potency of payload [a,1,2]
- High drug-to-antibody ratio ≈8 [a,1,2]
- Payload with short systemic half-life [a,b,1,2]
- Stable linker-payload [a,1,2]
- Tumor-selective cleavable linker [a,1,2]
- Bystander antitumor effect [a,1,2]

ADC, antibody-drug conjugate; DXd, a novel topoisomerase 1 inhibitor that is a derivative of exatecan; IgG1, immunoglobulin G1; mAb, monoclonal antibody.
[a] The clinical relevance of these features is under investigation. [b] Based on animal data.
1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. **2.** Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. **3.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

試験デザイン

Dose Escalation (Part A)
DS-6000a IV q3w
RCC and serous OVC



RDE

Dose Expansion (Part B)
DS-6000a IV q3w at RDE

- Cohort B-1 → RCC
- Cohort B-2 → Serous OVC

Enrollment criteria

- Advanced/metastatic RCC or OVC not amenable to SOC therapy[a]
- ECOG PS 0 to 1
- Ability to provide archived tissue for correlative testing
- No previous treatment with CDH6-targeting agents or ADCs with a linked topoisomerase I inhibitor

Primary objectives

- Safety and tolerability
- Determine MTD and RDE

Secondary objectives

- PK of DS-6000a, total anti-CDH6 antibody, and the DXd payload
- Antitumor activity per RECIST 1.1
- Immunogenicity

ADC, antibody drug conjugate; CDH6, cadherin 6; DXd, topoisomerase I inhibitor payload; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; MTD, maximum tolerated dose; OVC, ovarian cancer; PK, pharmacokinetics; q3w, every 3 weeks; RCC, renal cell carcinoma, RDE, recommended dose for expansion; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SOC, standard of care.
[a] Patients with OVC must have also had prior treatment with platinum and taxane therapy.

患者背景

DS-6000a Dose Escalation	OVC (N=20)	RCC (N=9)	Total (N=30)[a]
Age, median (range), years	65.5 (51-78)	60.0 (41-72)	64.5 (41-78)
Sex, n (%)			
Female	20 (100)	4 (44.4)	25 (83.3)
Male	0	5 (55.6)	5 (16.7)
Baseline ECOG PS, n (%)			
0	10 (50)	6 (66.7)	16 (53.3)
1	10 (50)	3 (33.3)	14 (46.7)
Tumor type, n (%)			
Renal cell carcinoma			
Clear cell RCC	–	8 (88.9)	8 (26.7)
Non–clear cell RCC	–	1 (11.1)	1 (3.3)
Serous ovarian cancer	20 (100)	–	20 (66.7)
Platinum-resistant disease	17 (85)	–	17 (56.7)
No. of prior systemic regimens			
Median (range)	4.0 (1-12)	2.0 (1-6)	3.0 (1-12)
Baseline CDH6 expression H score, range	0-250	17-218	0-250[b]

Data cutoff: February 25, 2022.
CDH6, cadherin 6; ECOG PS, Eastern Cooperative Oncology Group performance status; OVC, ovarian cancer; RCC, renal cell carcinoma.
[a] One missing primary diagnosis of OVC.
[b] Membrane CDH6 expression of 23 evaluable archival tissues.

患者および治療 概要

- As of data cutoff, 30 patients enrolled in part A (dose escalation) had received DS-6000a (OVC, n=21; RCC, n=9)
  - 17 patients (56.7%) were receiving ongoing treatment with DS-6000a (OVC, n=12; RCC, n=5)
  - 13 patients (43.3%) discontinued treatment
    - 9 of 13 patients discontinued due to disease progression
    - 1 patient (3.3%) discontinued due to TEAE
- Median treatment duration was 12.1 weeks (range, 3.0-54.1 weeks)

- Data cutoff: February 25, 2022.
- OVC, ovarian cancer; RCC, renal cell carcinoma; TEAE, treatment-emergent adverse event.

患者の10%以上に発現した有害事象 （すべてのグレード）

	1.6 mg/kg (n=1)	3.2 mg/kg (n=6)	4.8 mg/kg (n=6)	6.4 mg/kg (n=8)	8.0 mg/kg (n=6)	9.6 mg/kg (n=3)	Total (N=30)
Any treatment-related TEAE, n (%)	1 (100)	4 (66.7)	4 (66.7)	7 (87.5)	6 (100.0)	3 (100.0)	25 (83.3)
Nausea	0	3 (50.0)	3 (50.0)	5 (62.5)	5 (83.3)	2 (66.7)	18 (60.0)
Fatigue	0	2 (33.3)	3 (50.0)	4 (50.0)	6 (100.0)	2 (66.7)	17 (56.7)
Vomiting	0	2 (33.3)	1 (16.7)	2 (25.0)	2 (33.3)	2 (66.7)	9 (30.0)
Neutrophil count decreased	0	0	0	1 (12.5)	3 (50.0)	3 (100.0)	7 (23.3)
Decreased appetite	1 (100)	0	0	4 (50.0)	1 (16.7)	0	6 (20.0)
Diarrhea	0	0	0	2 (25.0)	1 (16.7)	1 (33.3)	4 (13.3)

- Treatment-related TEAEs occurred in 25 patients (83.3%)
- The most common treatment-related TEAEs of any grade were nausea, fatigue, and vomiting
- One patient in the 9.6-mg/kg arm experienced grade 2 pneumonitis, which led to treatment discontinuation

Data cutoff: February 25, 2022.
TEAE, treatment-emergent adverse event.

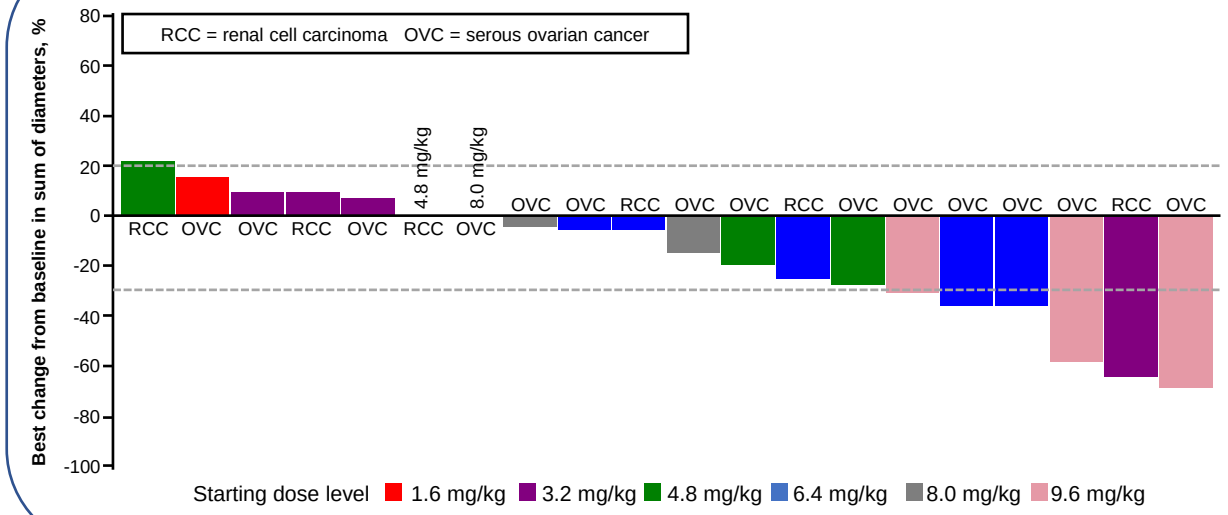
有害事象 （グレード3以上)

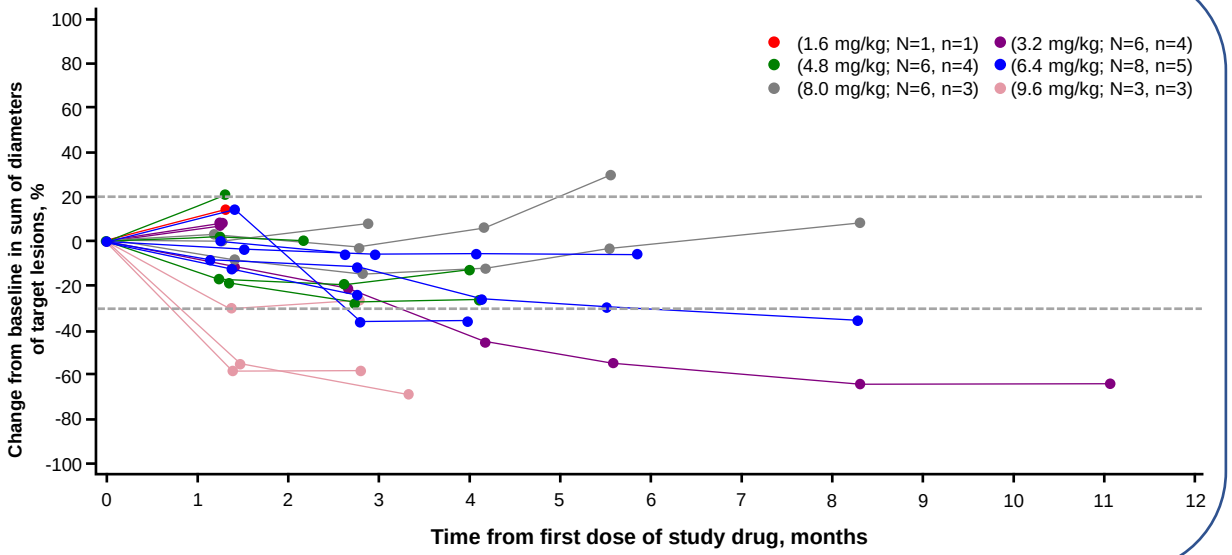
	1.6 mg/kg (n=1)	3.2 mg/kg (n=6)	4.8 mg/kg (n=6)	6.4 mg/kg (n=8)	8.0 mg/kg (n=6)	9.6 mg/kg (n=3)	Total (N=30)
Any grade ≥3 treatment-related TEAE, n (%)	0	0	0	2 (25.0)	2 (33.3)	3 (100)	7 (23.3)
Neutrophil count decreased	0	0	0	0	2 (33.3)	3 (100)	5 (16.7)
Anemia	0	0	0	1 (12.5)	0	1 (33.3)	2 (6.7)
Febrile neutropenia	0	0	0	1 (12.5)	0	1 (33.3)	2 (6.7)
Decreased appetite	0	0	0	0	1 (16.7)	0	1 (3.3)
Platelet count decreased	0	0	0	0	0	1 (33.3)	1 (3.3)

- Grade ≥3 treatment-related TEAEs occurred in 7 patients (23.3%)
- The most common treatment-related TEAEs (nausea, fatigue, and vomiting) had no grade ≥3 events
- Two patients experienced DLTs in the 9.6-mg/kg arm (grade 3 febrile neutropenia and grade 4 platelet count decreased)
- Two patients experienced grade 3 treatment-related SAEs (anemia and febrile neutropenia)

Data cutoff: February 25, 2022.
DLT, dose-limiting toxicity; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

対象病変におけるベースラインからの変化: 卵巣がん、腎細胞がんの評価可能な患者層[a]



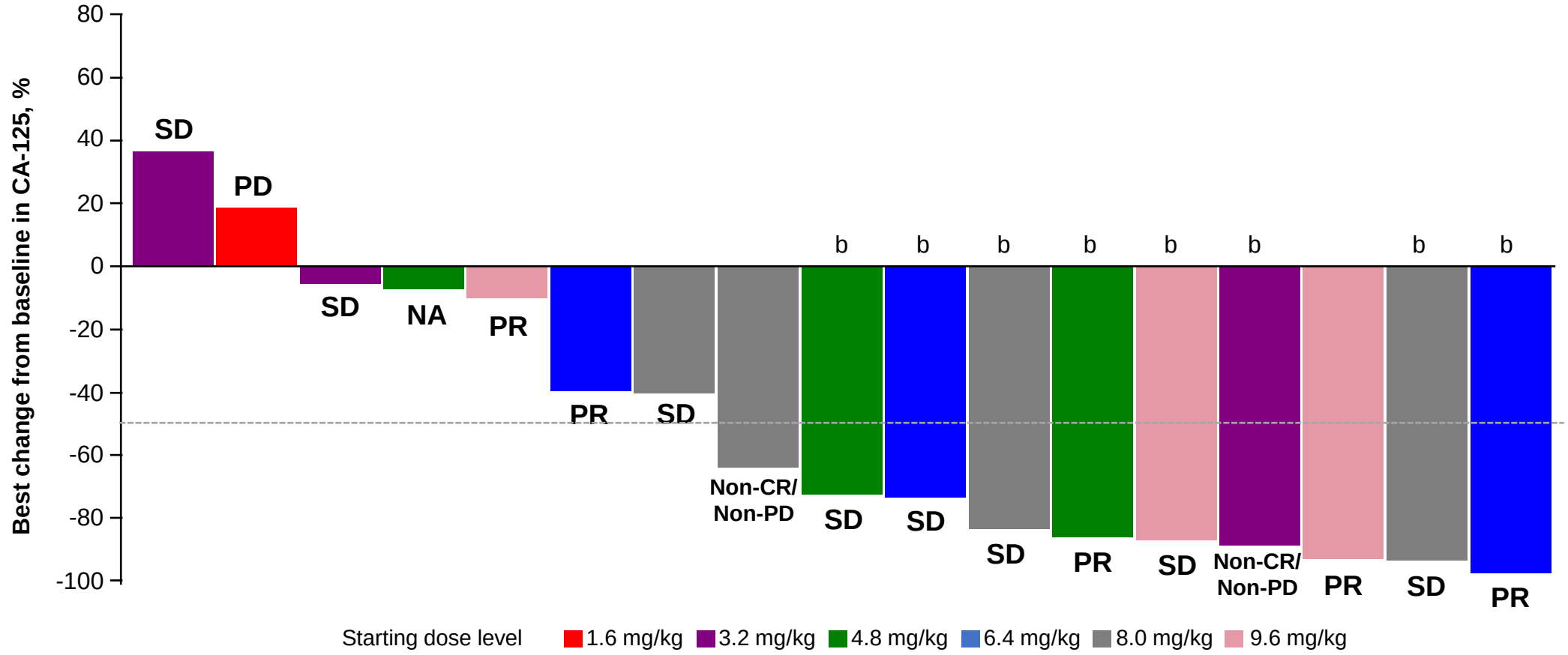


- Among 20 evaluable patients with measurable disease, there were 6 PRs (platinum-resistant OVC, n=5; RCC, n=1)
  - 4 confirmed PRs (platinum-resistant OVC, n=3; RCC, n=1)
  - 2 unconfirmed PRs (1 patient still in the trial)
- 12 patients had stable disease

Data cutoff: February 25, 2022.
OVC, ovarian cancer; PR, partial response; RCC, renal cell carcinoma.
[a] Patients who received ≥1 dose of study treatment and have completed ≥1 postbaseline tumor assessment or discontinued treatment for any reason.

CA-125レベルのベースラインからの変化

- Among 17 evaluable patients with OVC,[a] 8 CA-125 responses[b] were observed



Data cutoff: February 25, 2022.

CA-125, cancer antigen 125; CR, complete response; GCIG, Gynecologic Cancer InterGroup; NA, not available; OVC, ovarian cancer; PD, progressive disease; PR, partial response; SD, stable disease.

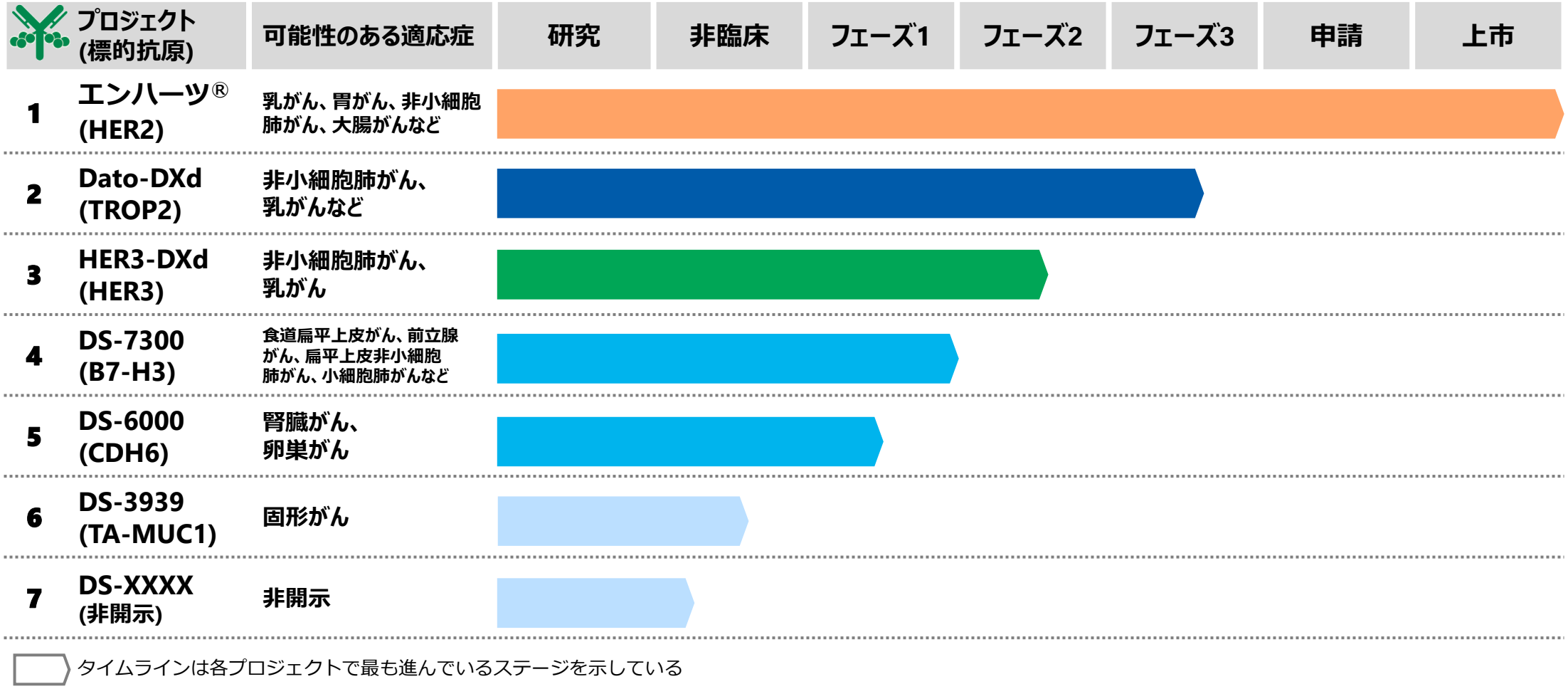
[a] Patients with baseline CA-125 value and ≥1 postbaseline CA-125 value were included.

[b] According to the GCIG criteria, patients can be evaluated for response only if they have a baseline sample that is ≥2 × the upper limit of normal obtained within 2 weeks prior to starting treatment. CA-125 response is defined as a ≥50% reduction in CA-125 levels from a pretreatment sample. The response must be confirmed and maintained for ≥28 days.

まとめ

- DS-6000aの忍容性は概ね良好であり、用量展開パートの推奨用量を8.0mg/kgに決定した。
- DS-6000aは、多数の前治療を受けた進行性白金製剤抵抗性の卵巣がんおよび腎細胞がんの患者において早期の臨床シグナル（RECISTおよびCA-125の反応）を示した。
- 用量展開パート（パートB）において、卵巣がんおよび腎細胞がんの患者登録を開始し、8.0mg/kgの用量を投与している。

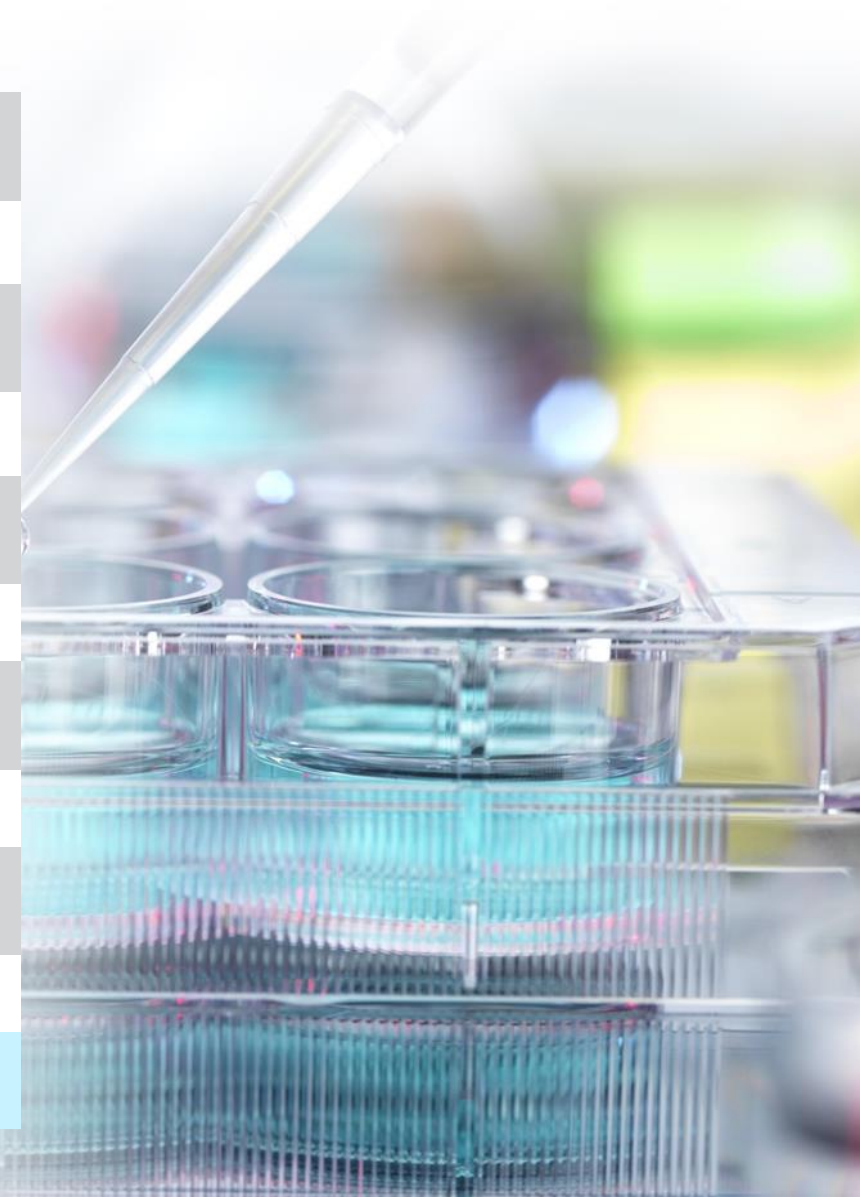
DXd-ADCパイプライン



DXd-ADCプラットフォームによるさらなるアンメットニーズへの展開

本日お話しする内容

1. イントロダクション
2. HER2低発現乳がん治療のパラダイムをシフトする
3. HER2陽性乳がんにおける信頼を構築する
4. 乳がんのさらなるニーズに対応する
5. Rising Stars
6. **今後のニュースフロー**



FY2022 今後のニュースフロー

2022年6月現在

学会発表予定

Coming Soon

2022年6月11日（土）
欧州血液学会（EHA 2022）“Presidential Symposium”において
QuANTUM-First* 試験結果を発表予定

*FLT3-ITD変異を有する急性骨髄性白血病患者への一次治療を対象としたキザルチニブのPh3試験

FY2022 今後のニュースフロー

2022年6月現在

承認見込み

エンハーツ®	DESTINY-Breast03: HER2陽性 乳がん, 2L, Ph3 • 欧州: 2022年度 上半期、 日: 2022年度 下半期 DESTINY-Breast04: HER2低発現 乳がん, 化学療法既治療, Ph3 • 米: 2022年度 下半期 DESTINY-Gastric02: HER2陽性 胃がん, 2L, Ph2 • 欧州: 2022年度 下半期 DESTINY-Lung01: HER2変異NSCLC, 2L, Ph2 • 米: 2022年度 上半期
キザルチニブ	QuANTUM-First: AML, 1L, Ph3 • 日米: 2022年度 下半期
バレメトスタット	申請用Ph2: 再発・難治性ATL/L • 日: 2022年度 上半期

主要データの入手見込み

エンハーツ®	DESTINY-Breast02: HER2陽性 乳がん, 3L, Ph3 • 2022年度 上半期
Dato-DXd	TROPION-Lung01: NSCLC, 2/3L, Ph3 • 2022年度 下半期
DS-5670	Ph1/2/3: COVID-19 mRNAワクチン, 追加投与 • 2022年度 下半期

承認申請予定

エンハーツ®	DESTINY-Breast04: HER2低発現 乳がん, 化学療法既治療, Ph3 • 日米欧中: 2022年度 上半期
キザルチニブ	QuANTUM-First: AML, 1L, Ph3 • 日米欧: 2022年度 上半期
DS-5670	Ph1/2/3: COVID-19 mRNAワクチン, 追加投与 • 日: 2022年度 下半期

ピボタル試験開始見込み

Dato-DXd	TROPION-Breast02: TNBC, 1L, Ph3 • 2022年度 上半期
HER3-DXd	HERTHENA-Lung02: EGFR変異 NSCLC, 2L, Ph3 • 2022年度 上半期

AML: 急性骨髄性白血病、ATL/L: ,成人T細胞白血病/リンパ腫、NSCLC: 非小細胞肺がん

表示されているタイムラインは現時点の予測であり、今後変更する場合があります。

Appendix

エンハーツ®: 臨床開発計画 | 乳がん

As of Jun 2022			FY2021	FY2022	FY2023
HER2 Positive		Metastatic 3L+	DESTINY-Breast01 completed		
			DESTINY-Breast02 monotherapy vs PC		
		Metastatic 2L	DESTINY-Breast03		
			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	DESTINY-Breast11 T-DXd vs T-DXd / THP vs AC / THP		
		Adjuvant			
HER2 Low	HR+ HR-	Metastatic Post Chemo	DESTINY-Breast04 mono vs PC		
			DESTINY-Breast08 combination		
		Post-neoadjuvant			
	HR+	Metastatic Chemo Naive	DESTINY-Breast06 monotherapy vs PC		
	HR-	Metastatic 1L	BEGONIA durvalumab combination Ph1b/2 (Arm 6)		
		Neoadjuvant			

Ph 1 ongoing　Ph 2 ongoing　Ph 3 ongoing　New　Completed

試験の開始と終了は一律上期または下期の初めより表示

AC: アドリアマイシン+シクロフォスファミド、THP: タキサン+ハーセプチン+ペルツズマブ、PC: 医師選択治療

エンハーツ®: 臨床開発計画 | 胃がん & NSCLC

As of Jun 2022			FY2021	FY2022	FY2023
Gastric	HER2 Positive	Metastatic 3L+	DESTINY-Gastric01 completed	DESTINY-Gastric06 monotherapy China Ph2	
		Metastatic 2L	DESTINY-Gastric02 West		
			DESTINY-Gastric04 mono vs ramucirumab+paclitaxel		
		Metastatic 1L	DESTINY-Gastric03 combination (2L/1L) Ph1b/2		
NSCLC	HER2 Expressing	Metastatic 2L+	DESTINY-Lung01		
			HUDSON durvalumab combination		
		Metastatic 2L			
		Metastatic 1L	DESTINY-Lung03 combination		
	HER2 Mutated	Metastatic 2L+	DESTINY-Lung01		
			DESTINY-Lung02 monotherapy		
				DESTINY-Lung05 China Ph2	
		Metastatic 1L	DESTINY-Lung04 mono vs SOC		

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

試験の開始と終了は一律上期または下期の初めより表示

NSCLC: 非小細胞肺がん、SOC: 標準治療

エンハーツ®: 臨床開発計画 | 大腸がん & その他がん

As of Jun 2022			FY2021	FY2022	FY2023
CRC	HER2 Expressing	Metastatic 3L	DESTINY-CRC01 completed	DESTINY-CRC02 monotherapy	
Other Tumors/ multiple tumors	HER2 Expressing	Metastatic 2L	Nivolumab combo (breast, bladder)		
			Pembrolizumab combination (breast, NSCLC)		
			DESTINY-PanTumor02		
	HER2 Mutated	Metastatic 2L	DESTINY-PanTumor01		

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

試験の開始と終了は一律上期または下期の初めより表示

CRC: 大腸がん、NSCLC: 非小細胞肺がん

Dato-DXd: 臨床開発計画 | NSCLC

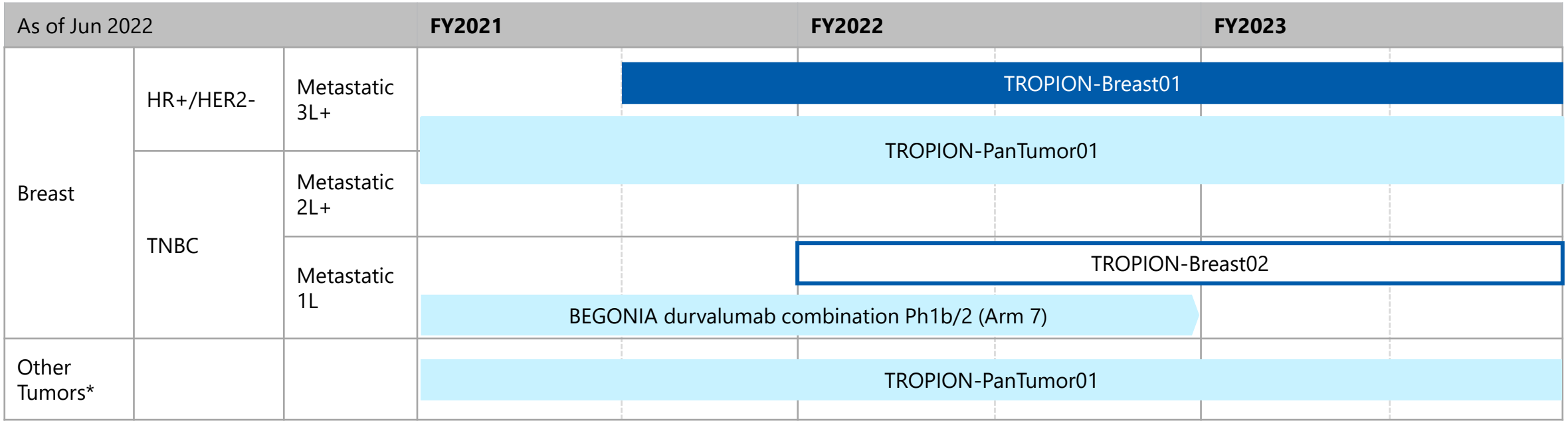
As of Jun 2022			FY2021	FY2022	FY2023
NSCLC	All comers	Metastatic 2L/3L	TROPION-Lung01 monotherapy		
	ICI combination Without actionable mutations	Metastatic 1L/2L	TROPION-Lung02 pembrolizumab combination		
			TROPION-Lung04 durvalumab combination		
		Metastatic 1L		TROPION-Lung08 pembrolizumab combination	
	With actionable mutations	Metastatic 2L+	TROPION-Lung05 monotherapy		

Ph 1 ongoing　Ph 2 ongoing　Ph 3 ongoing　New　Completed

試験の開始と終了は一律上半期または下期の初めより表示

ICI: 免疫チェックポイント阻害剤、NSCLC: 非小細胞肺がん

Dato-DXd: 臨床開発計画 | 乳がん & その他のがん



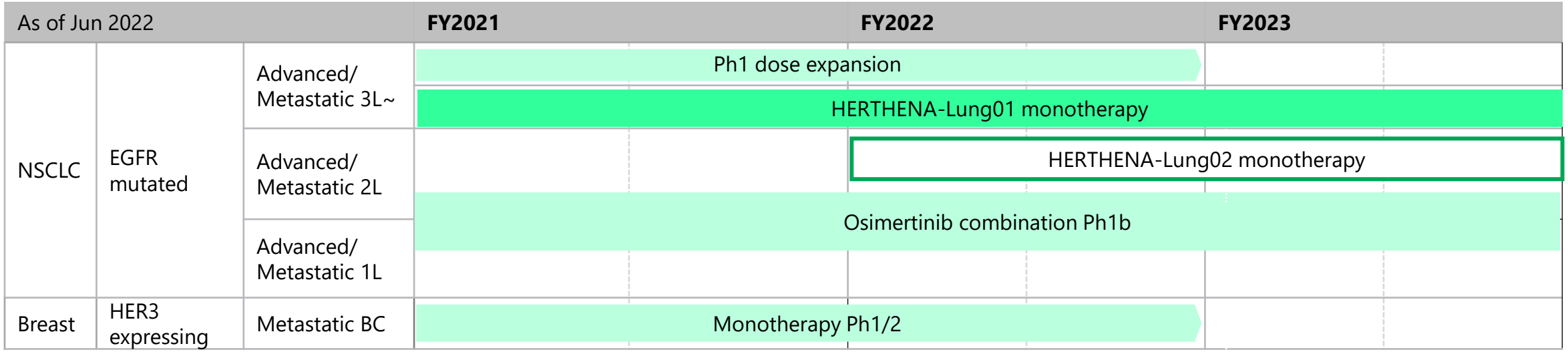
*その他のがん：胃がん、食道がん、尿路上皮がん、小細胞肺がん
TROP2発現量および非臨床データやDato-DXdが有効であることが示唆されるその他のエビデンスに基づきがん種を選択

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

試験の開始と終了は一律上期または下期の初めより表示

TNBC: トリプルネガティブ乳がん

HER3-DXd: 臨床開発計画 | NSCLC & その他のがん



試験の開始と終了は一律上期または下期の初めより表示

BC: 乳がん、 NSCLC: 非小細胞肺がん

本資料に関するお問い合わせ先

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