Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

ASCO 2021 ハイライト

第一三共株式会社

代表取締役社長 兼 CEO
眞鍋　淳

2021年 6月 8日

将来の見通しに関する注意事項

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ASCO 2020からの1年

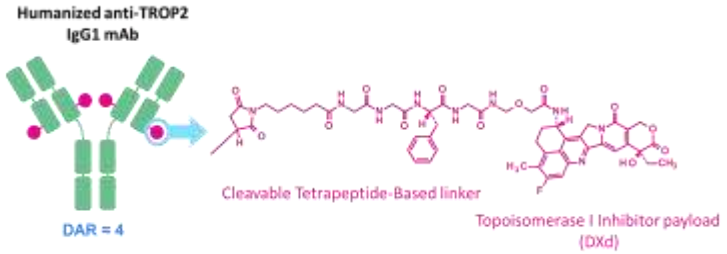
エンハーツ®

ENHERTU
trastuzumab deruxtecan

AZとの戦略的提携を通じた

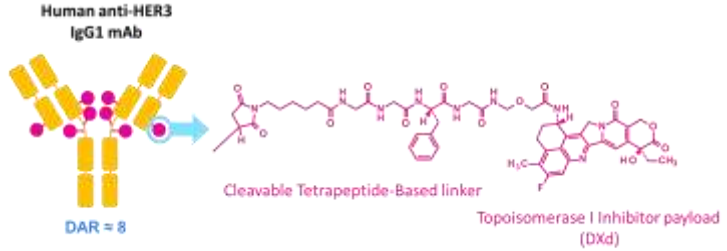
- 順調な市場浸透
  - HER2陽性乳がん3L 販売国拡大
- 順調な新適応の追加
  - HER2陽性胃がん
    3L（日）、2L（米）
- 順調な開発
  - 幅広いがん種で9本の試験開始

Dato-DXd



- AZとの戦略的提携の締結
- AZと提携を通じた開発の加速化
  - NSCLC 2/3L
    ピボタル試験開始
  - Ph1 TNBCコホート
    中間データ取得
  - その他NSCLCで3本試験開始

HER3-DXd



- 自社開発による最速上市を目指し
  NSCLC 3L ピボタル試験開始
- その他NSCLC/大腸がんで試験開始

NSCLC：非小細胞肺がん、TNBC：トリプルネガティブ乳がん

持続的成長に向けた第5期中期経営計画

ESG経営のもと、第5期中計期間は2025年ビジョン
がんに強みを持つ先進的グローバル創薬企業を実現し、
2030年ビジョン達成に向けた成長ステージに移行

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

2025年ビジョンを実現し成長ステージへ

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

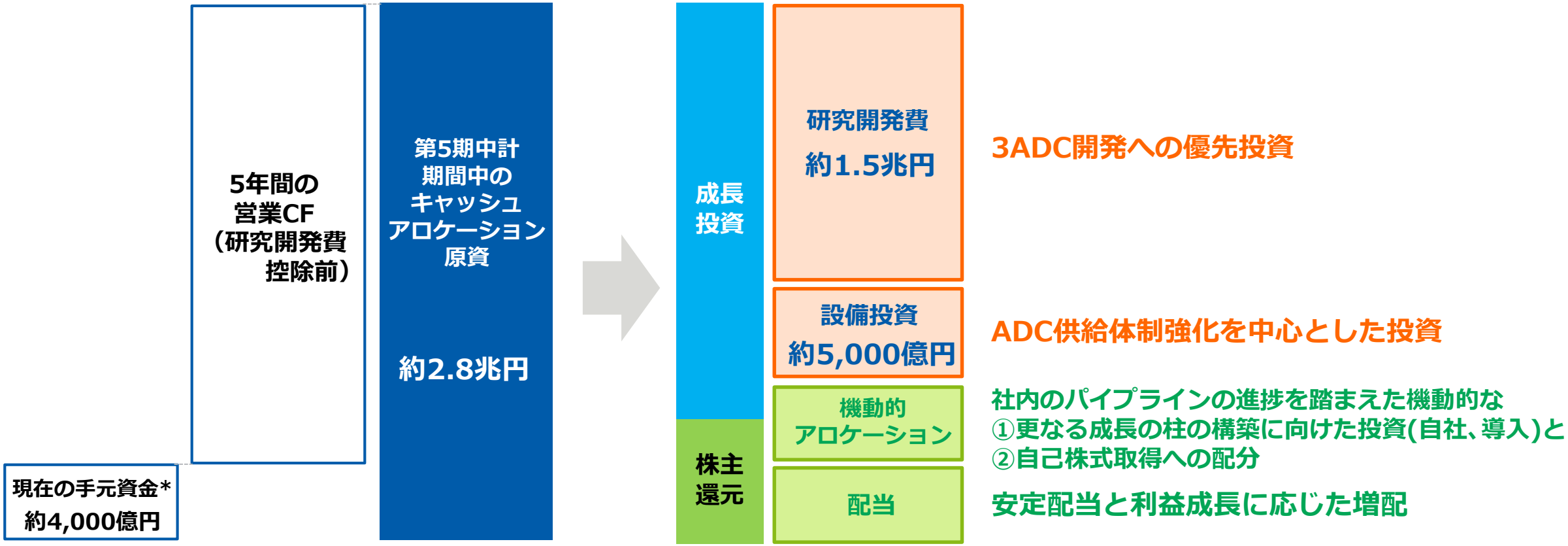
- DX推進によるデータ駆動型経営の実現と先進デジタル技術による全社の変革
- 新たなグローバルマネジメント体制による迅速な意思決定の実現

*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）

第５期中計　キャッシュ・アロケーション

3ADCの研究開発・設備投資を第一優先とし、利益成長に応じた配当を行う

キャッシュ・アロケーションの規模イメージ

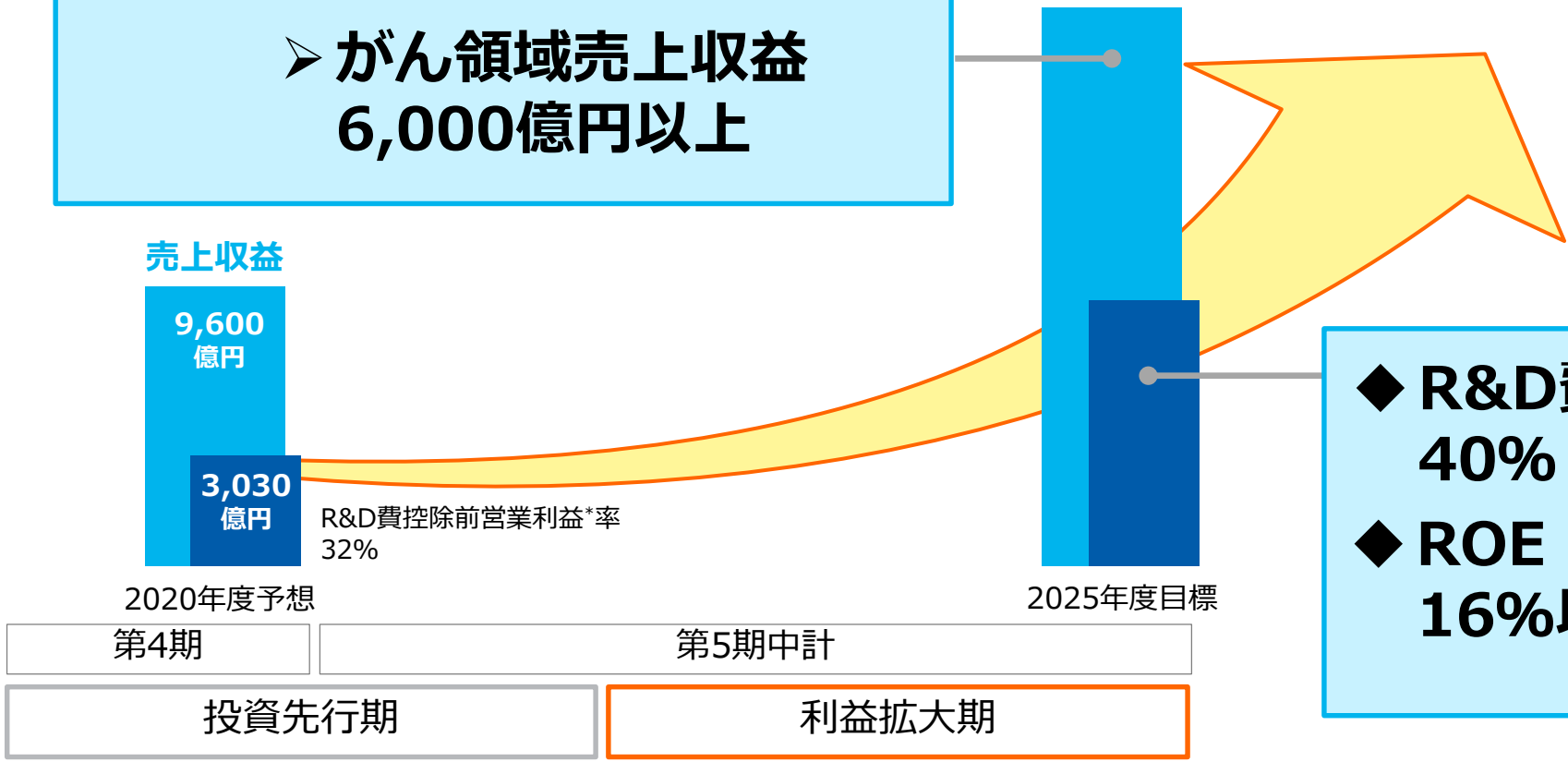


*運転資本を除く手元資金

第５期中計　計数目標

◆ 売上収益
1兆 6,000億円
➢ がん領域売上収益
6,000億円以上

3ADCの投資先行期を乗り越え、
大幅な売上・利益成長を実現し
2030年ビジョン実現に向けた新たなステージへ



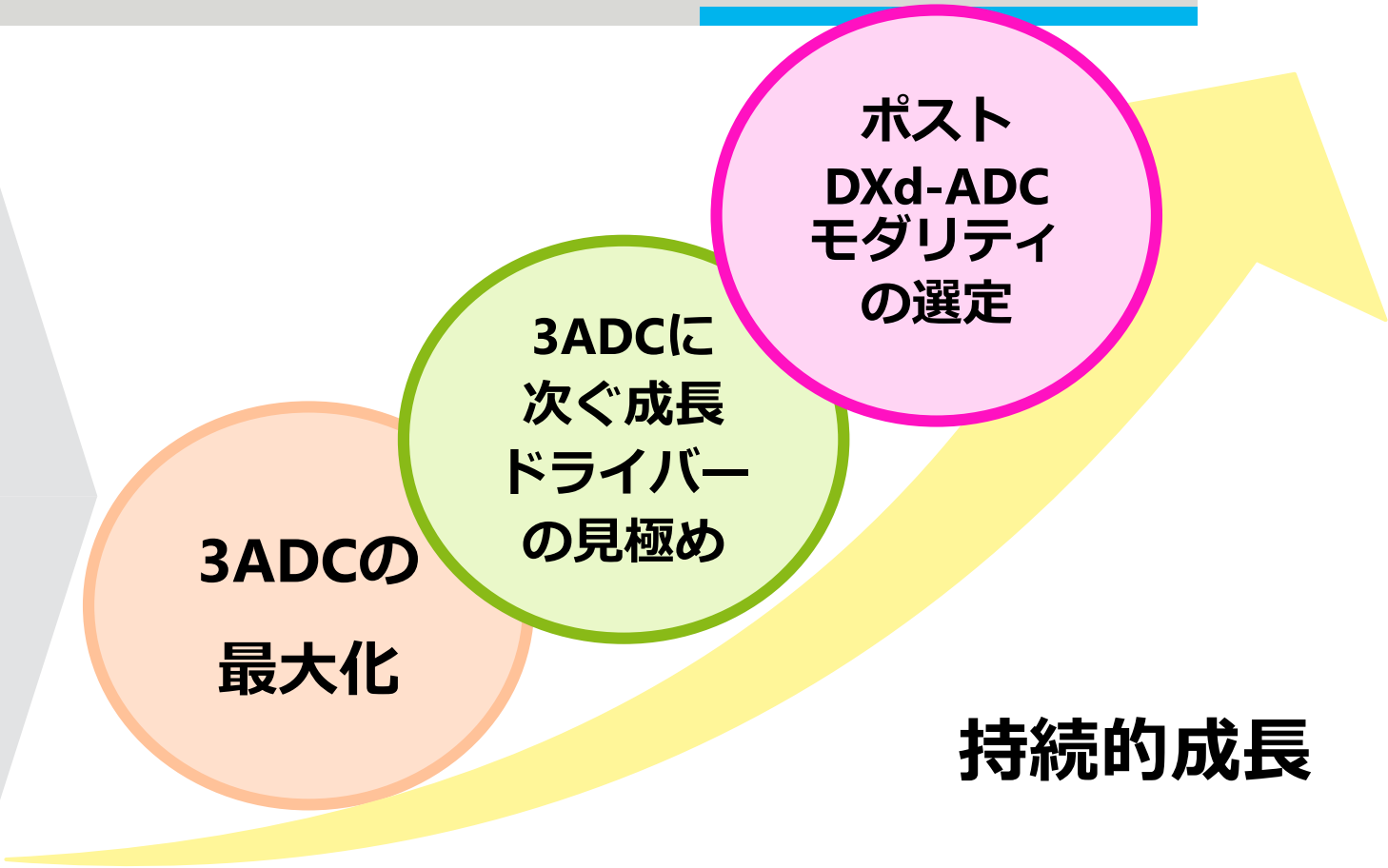
◆ R&D費控除前営業利益*率
40%
◆ ROE
16%以上
◆ DOE
8%以上

*固定資産売却、事業再編、減損、訴訟等に関連する特殊要因を除く
2025年度為替レートの前提：1USD=105円、1EUR=120円

2030年ビジョンを見据えて

先進的な
サイエンス＆テクノロジー
を強みにした研究

研究成果を製品に導く
着実なグローバル開発



研究と開発を一元的にリードし、
次の成長ドライバーを見極める目利きのあるリーダーシップが**持続的成長の鍵**

第一三共の新たなフェーズへ

Passion for Innovation.
Compassion for Patients.™

Daiichi-Sankyo

ASCO 2021 ハイライト

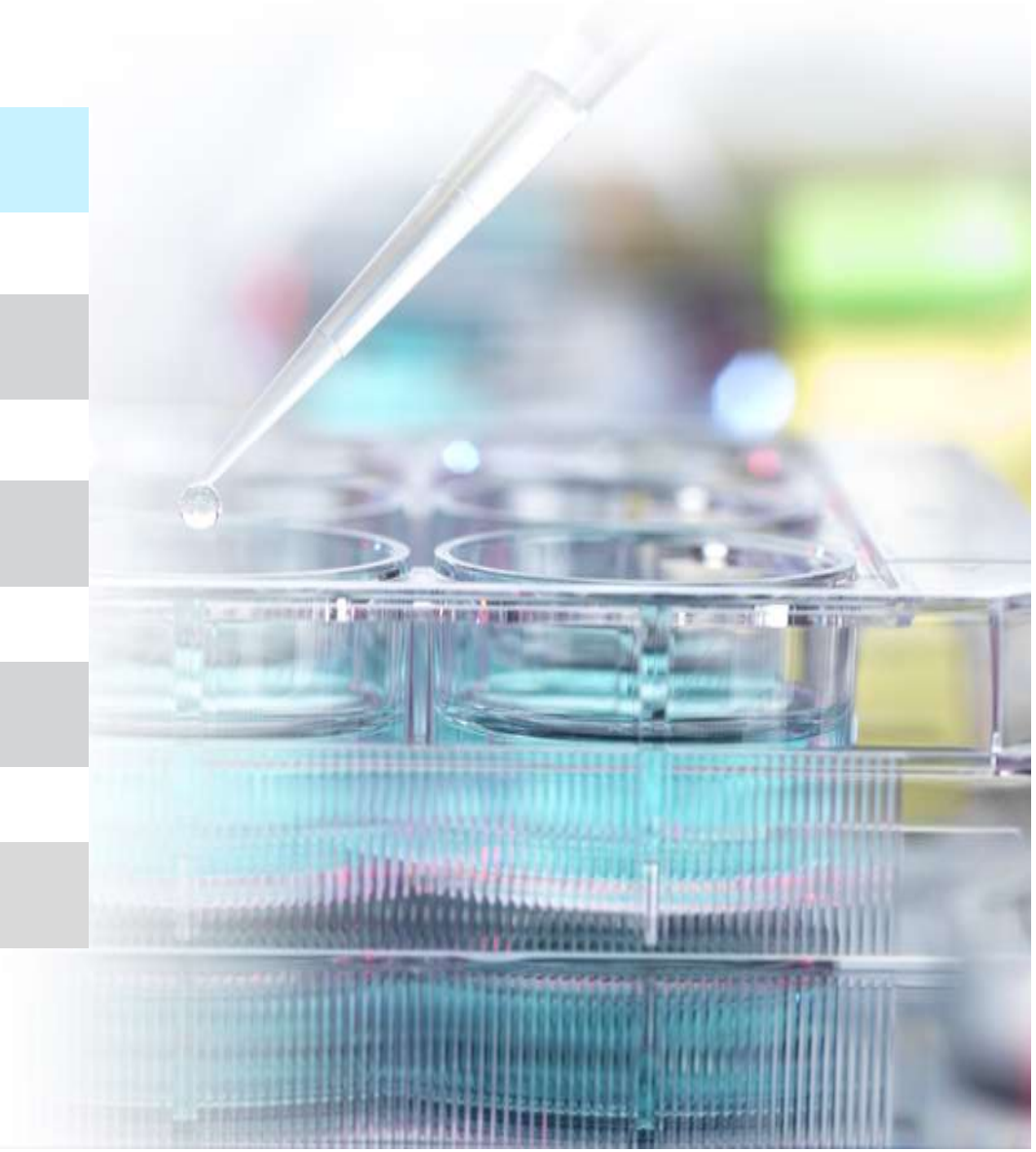
第一三共株式会社

グローバル研究開発ヘッド
竹下　健一

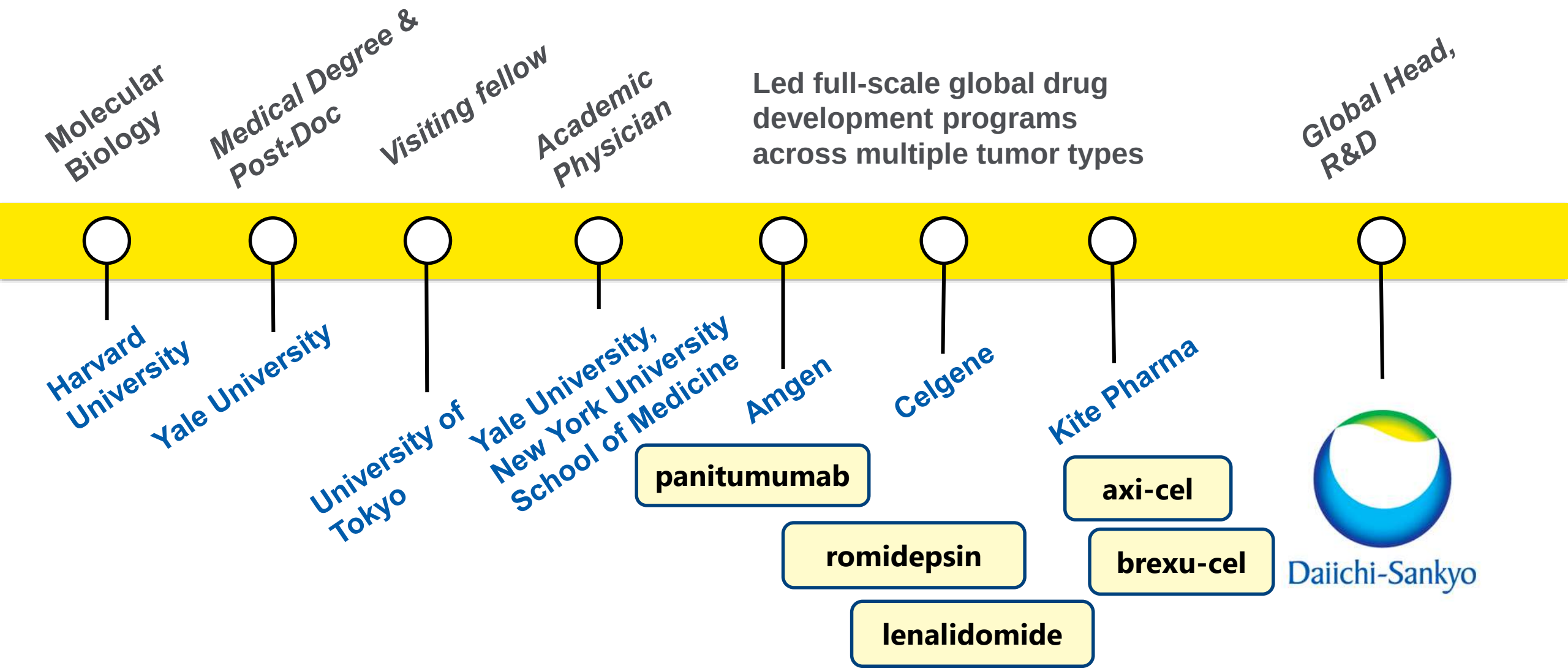
2021年 6月 8日

本日の内容

1. イントロダクション
2. エンハーツ®: 新規データおよび開発計画
3. Dato-DXd: 新規データおよび開発計画
4. HER3-DXd: 新規データおよび開発計画
5. 今後のニュースフロー



学歴および職歴


Molecular Biology
Harvard University
Medical Degree & Post-Doc
Yale University
Visiting fellow
University of Tokyo
Academic Physician
Yale University, New York University School of Medicine
Led full-scale global drug development programs across multiple tumor types
Amgen
panitumumab
romidepsin
lenalidomide
Celgene
Kite Pharma
axi-cel
brexu-cel
Global Head, R&D
Daiichi-Sankyo

第一三共に入社した理由

外から見た第一三共...

- 非常に強力な自社研究力
- 意欲的な変革姿勢
  - 循環器からがんへ
  - 日本から世界へ
- 承認取得の進むパイプライン

第一三共のR&Dに対する考え方とビジョン

真のグローバル製薬企業となるため…

グローバルレベルで組織を最適化し、人材を育成

◆ 競争力

- 3ADCに次ぐ成長ドライバーを生み出すサイエンス＆テクノロジーの継続強化
  - 最先端のサイエンス： 次世代ADC、mRNA、AAV 等
- 独自のモダリティ戦略の展開

◆ 研究開発の一元化

- 適切な臨床的洞察に基づく研究活動および開発機能との強力な連携
- 研究から開発への円滑な移行の強化

◆ グローバル開発

- グローバルな臨床開発の強化による開発スピードの加速
- グローバル人材の育成・採用

第一三共のR&D戦略

◆ **3 and Alpha戦略**

- 3つのADCに研究開発費、人的リソースを集中
- AlphaではSOCを変革し得る製品に注力

3ADC & **Alpha**

エンハーツ®	Dato-DXd	HER3-DXd	オンコロジー	スペシャルティ メディスン	ワクチン

幅広いがん種と治療ラインの適応を迅速に取得

確かな目利き力により有望なアセットを見極め、適切にリソースを配分

エンハーツ®の開発目標

HER2を標的とし得るがんの治療法を変革

HER2陽性乳がん	**転移性および早期乳がん治療の新たなSOCを確立** - HER2陽性乳がんの既存治療薬を上回るデータに基づき確立 -
HER2低発現乳がん	**乳がん治療のパラダイムを再定義** - HER2低発現のコンセプトを定着させ、既存の乳がん治療パラダイムを変革 -
その他がん	**HER2を標的とするがんの治療選択肢を拡大** - 幅広いHER2発現がんの治療法を変革（胃がん,NSCLC,大腸がん,その他） -

ASCO 2021データ

BEGONIA 試験
エンハーツ®+デュルバルマブの初期データ
***HER2*低発現/*HR*陰性乳がんの適応取得に向けた探索**

DESTINY-CRC01 試験
最終データ
大腸がんの適応症の探索

AACR 2021データ

治験薬に関連したILDの統合解析
8つのシングルアーム試験の解析
多様ながん種に対するエンハーツ®の良好なリスク・ベネフィットを示唆

HR: ホルモン受容体, NSCLC: 非小細胞肺がん, SOC: standard of care

Dato-DXdの開発目標

ベストインクラスの抗TROP2 ADCの地位を確立

NSCLC	**NSCLC治療におけるファーストインクラス、ベストインクラスのTROP2 ADCの地位を確立** - 再発・難治性NSCLCの単剤療法で上市後、免疫チェックポイント阻害剤との併用療法で転移性NSCLCの１次治療の適応取得を目指す -
乳がん	**乳がん治療における最適なADCの地位を確立** - 乳がん治療において前例のないレベルの有効性の確立を目指す -

ASCO 2021 データ

TROPION-PanTumor01 試験
NSCLCコホートにおける至適用量の解析
***TROPION-Lung01*試験（ピボタル試験）を後押しするデータ**

ESMO BC 2021 データ

TROPION-PanTumor01 試験
TNBCコホートの初期結果
今後の開発を後押しするデータ

NSCLC: 非小細胞肺がん, TNBC: トリプルネガティブ乳がん

HER3-DXdの開発目標

ファーストインクラスの抗HER3 ADCの地位を確立

NSCLC	**EGFR TKIに対する多様な耐性機序を持つEGFR変異NSCLCにおけるファーストインクラスの抗HER3 ADCとしての地位を確立** - 単剤療法での早期上市とオシメルチニブとの併用での適応拡大を目指す -
その他がん	**HER3発現がんに適応を拡大** - 幅広いHER3発現がんの治療法を変革（大腸がん, 乳がん,その他） -

ASCO 2021 データ

Ph1 試験
フォローアップ期間が延長されたEGFR変異NSCLCコホートの更新データ
***HERTHENA-Lung01* 試験（ピボタル試験）を後押しするデータ**

NSCLC: 非小細胞肺がん,, TKI:チロシンキナーゼ阻害剤

本日の内容

1. イントロダクション
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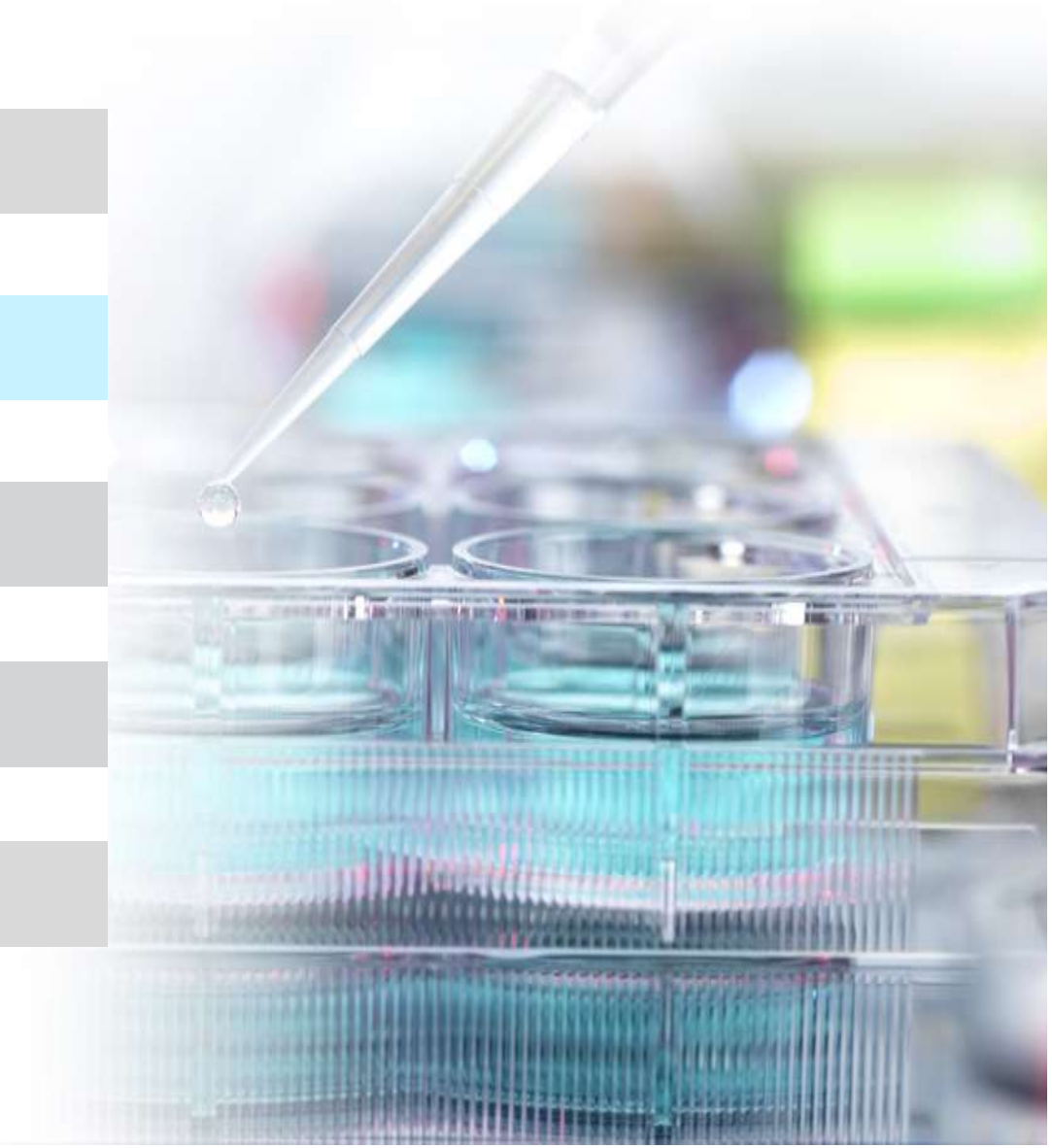

HER2発現を有する転移性大腸がん患者における トラスツズマブ デルクステカン (T-DXd; DS-8201) : 多施設共同、非盲検、第Ⅱ相試験 (DESTINY-CRC01)の最終結果

Takayuki Yoshino; National Cancer Center Hospital East, Kashiwa, Japan

June 7, 2021

Additional authors: Maria Di Bartolomeo, Kanwal Raghav, Toshiki Masuishi, Fotios Loupakis, Hisato Kawakami, Kensei Yamaguchi, Tomohiro Nishina, Zev Wainberg, Elena Elez, Javier Rodriguez, Marwan Fakih, Fortunato Ciardiello, Kapil Saxena, Kojiro Kobayashi, Emarjola Bako, Yasuyuki Okuda, Gerold Meinhardt, Axel Grothey, Salvatore Siena

On behalf of the DESTINY-CRC01 investigators

DESTINY-CRC01 試験デザイン

An open-label, multicenter, phase 2 study (NCT03384940)

6.4 mg/kg dose of T-DXd administered Q3W (all cohorts)

Patients
- Unresectable and/or metastatic CRC
- HER2 expressing (central confirmation)
- *RAS/BRAF*^{V600E} wild type
- ≥2 prior regimens
- Prior anti-HER2 treatment was allowed
- Excluded patients with a history of or current/suspected interstitial lung disease

Cohort A:
HER2 Positive
(IHC3+ or IHC2+/ISH+)
n = 53

Cohort B[a]:
HER2 IHC2+/ISH−
n = 15

Cohort C[a]:
HER2 IHC1+
n = 18

Primary endpoint
- ORR[b] (cohort A)

Secondary endpoints
- ORR[b] (cohorts B and C)
- PFS
- OS
- DOR
- DCR
- Safety and tolerability

Primary analysis (Data cutoff: August 9, 2019)

Final analysis (Data base lock: December 28, 2020)

Primary analysis of cohort A[1]
- Results yielded promising antitumor activity and a manageable safety profile
- The median follow-up was 27.1 weeks at data cutoff

Patient disposition at final analysis[c]
- No patients remain on treatment
- At the end of the study, median follow-up was 62.4 weeks for cohort A, 27.0 weeks for cohort B and 16.9 weeks for cohort C

CRC, colorectal cancer; DCR, disease control rate; DOR, duration of response; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; q3w, every three weeks; RECIST, Response Evaluation Criteria in Solid Tumors; T-DXd, trastuzumab deruxtecan.
[a]A futility monitoring analysis was done after ≥20 patients in Cohort A had 12 weeks of follow-up to inform opening of Cohorts B and C. [b]ORR was based on RECIST version 1.1 in all cohorts. [c]Data presented are from the full analysis set.
1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

有効性結果

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
Confirmed ORR by ICR, n (%) [95% CI]	**24 (45.3)** [31.6-59.6]	0 [0.0-21.8]	0 [0.0-18.5]
CR	0	0	0
PR	24 (45.3)	0	0
SD	20 (37.7)	9 (60.0)	4 (22.2)
PD	5 (9.4)	5 (33.3)	10 (55.6)
Not evaluable[a]	4 (7.5)	1 (6.7)	4 (22.2)
Disease control rate, % (95% CI)	83.0 (70.2-91.9)	60.0 (32.3-83.7)	22.2 (6.4-47.6)
Median duration of response, (95% CI) months	7.0 (5.8-9.5)	NE (NE-NE)	NE (NE-NE)
Median treatment duration, (95% CI) months	5.1 (3.9-7.6)	2.1 (1.4-2.6)	1.4 (1.3-1.5)

CR, complete response; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; NE, non-evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Patients were missing postbaseline scans.

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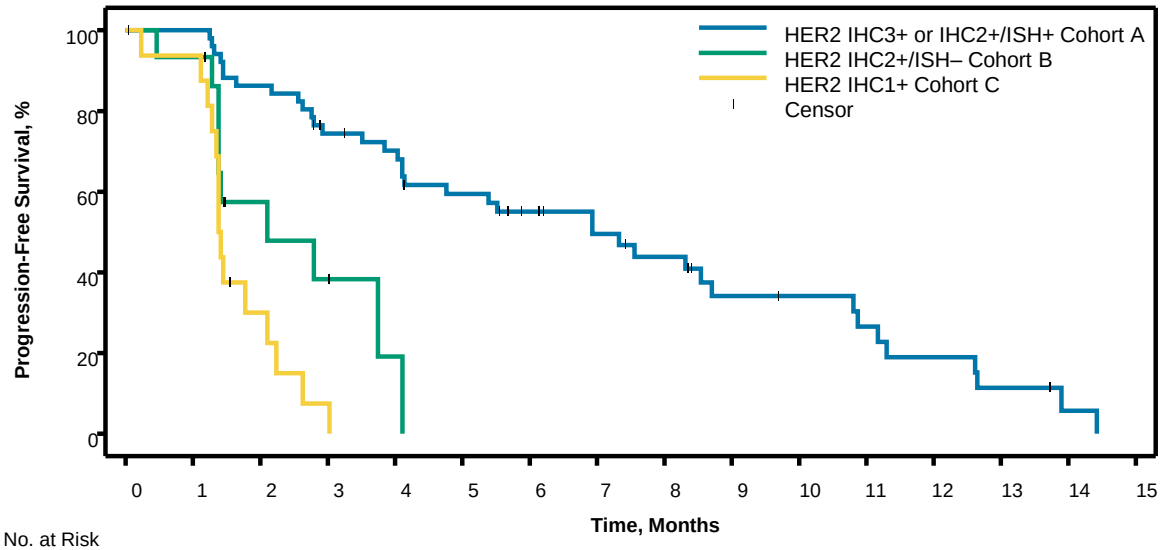
無増悪生存期間および全生存期間

Progression-Free Survival

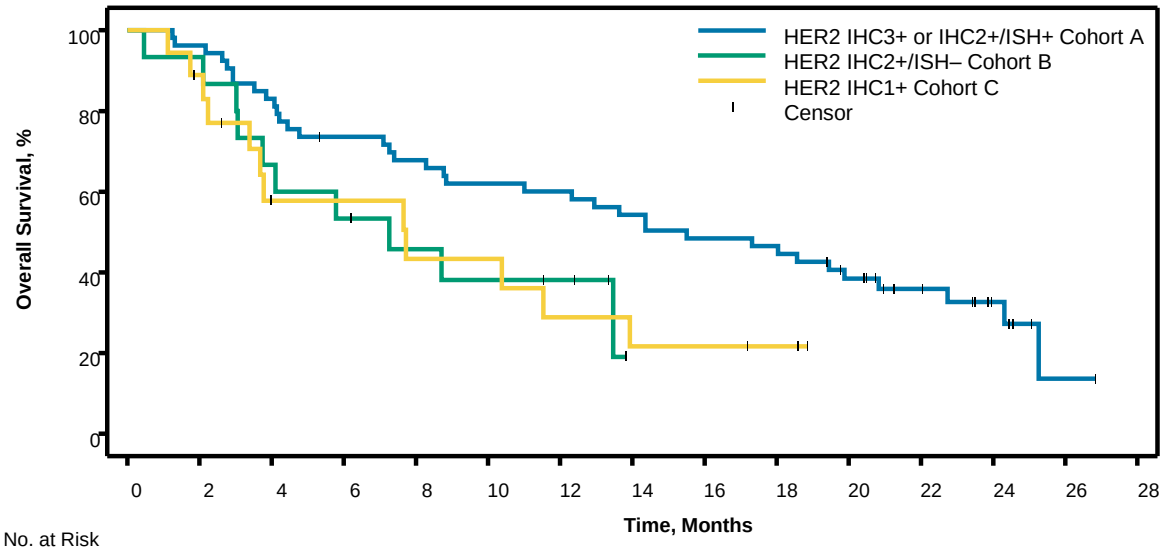


No. at Risk

Cohort A	53	51	44	36	33	27	22	18	15	10	9	7	5	3	1	0
Cohort B	15	14	6	4	1	0	0	0	0	0	0	0	0	0	0	0
Cohort C	18	15	4	1	0	0	0	0	0	0	0	0	0	0	0	0

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mPFS (95% CI), months	6.9 (4.1-8.7)	2.1 (1.4-4.1)	1.4 (1.3-2.1)

Overall Survival



No. at Risk

Cohort A	53	51	44	38	35	32	31	28	25	24	18	12	6	1	0	
Cohort B	15	14	10	8	6	5	4	0	0	0	0	0	0	0	0	
Cohort C	18	15	8	8	6	6	4	3	3	2	0	0	0	0	0	

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)
mOS (95% CI), months	15.5 (8.8-20.8)	7.3 (3.0-NE)	7.7 (2.2-13.9)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mOS, median overall survival; mPFS, median progression-free survival; NE, not-evaluable.

20%以上の患者に発現した有害事象

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)	
n (%)	Any Grade	Any Grade	Any Grade	Any Grade	Grade ≥3
Patients with any TEAE	**53 (100)**	**15 (100)**	**18 (100)**	**86 (100)**	**56 (65.1)**
Nausea	37 (69.8)	9 (60.0)	7 (38.9)	53 (61.6)	5 (5.8)
Anemia	21 (39.6)	4 (26.7)	6 (33.3)	31 (36.0)	12 (14.0)
Fatigue	21 (39.6)	7 (46.7)	3 (16.7)	31 (36.0)	1 (1.2)
Decreased appetite	18 (34.0)	5 (33.3)	7 (38.9)	30 (34.9)	0
Platelet count decreased	17 (32.1)	4 (26.7)	7 (38.9)	28 (32.6)	8 (9.3)
Vomiting	23 (43.4)	3 (20.0)	1 (5.6)	27 (31.4)	1 (1.2)
Neutrophil count decreased	20 (37.7)	2 (13.3)	4 (22.2)	26 (30.2)	19 (22.1)
Diarrhea	19 (35.8)	0	4 (22.2)	23 (26.7)	1 (1.2)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; TEAE, treatment-emergent adverse events.

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特記すべき有害事象: 間質性肺疾患（ILD）

All Patients (N=86)	n (%)
Grade 1	0
Grade 2	4 (4.7)
Grade 3	1 (1.2)
Grade 4	0
Grade 5	3 (3.5)[a]
Any Grade/Total	8 (9.3)[b,c]

薬剤と関連があると判定されたILD:

- 発症までの期間中央値は61日 (範囲 9-165日)
- 8例中8例にコルチコステロイドを投与
- グレード2の4例が回復、グレード3の1例が回復せず (後に病勢進行により死亡)
- 8例のILD患者において、発症と判定された日からステロイド治療開始までの期間中央値は3.5日（範囲 0-50）

グレード5 ILD:

- 薬剤と関連があると判定された3例の死亡例について、ILDの発症は9日後から120日後（中央値：22日）であり、診断後6～19日で死亡 (中央値：6日)

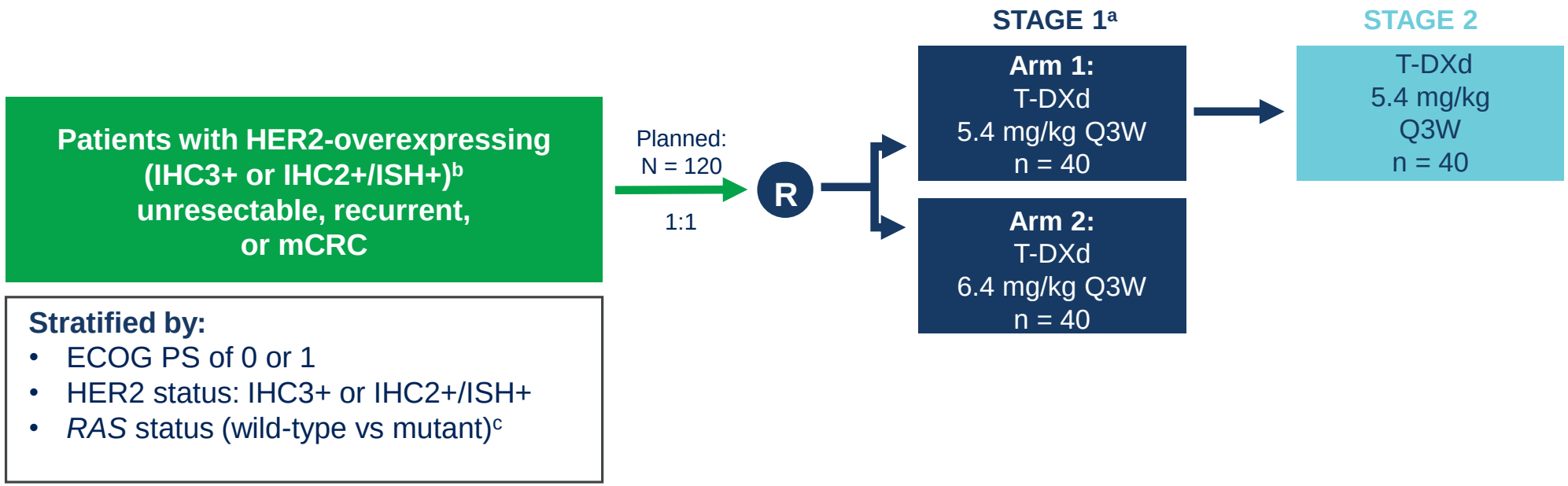
ILDが疑われた場合、直ちに症状のモニタリングを行い、治療を中断あるいは中止し、臨床的に必要な場合はイメージングを実施してステロイド治療を行うことが、改訂されたILD/肺炎のガイドラインで推奨されている。

AE, adverse events; ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.
[a]2 patients were from cohort A, 1 from cohort B. [b]4 patients were from cohort A, 3 from cohort B and 1 from cohort C. [c]ILD grades are the highest/most severe grade recorded in a patient.

ASCO2021

DESTINY-CRC02 試験デザイン

A randomized, 2-arm, 2-stage, phase 2, multicenter global study (NCT04744831)



HER2発現を有する大腸がん患者において
至適用量(6.4 もしくは 5.4 mg/kg) を確認するためのDESTINY-CRC02試験を開始した

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mCRC, metastatic colorectal cancer; Q3W, every 3 weeks; R, randomization; T-DXd, trastuzumab deruxtecan.
[a]Enrollment will not be interrupted between stages 1 and 2; it is not the intent to modify the study design based on the interim analysis results. Study will be blinded to investigators and patients.
[b]Maximum number of patients with HER2 IHC 2+/ISH+ will be n = 30.
[c]Maximum and minimum number of patients with *RAS* mutant status will be n = 30 and n = 20, respectively.

BEGONIA: 局所進行性/転移性トリプルネガティブ乳がんにおける デュルバルマブ併用フェーズ1B/2試験: アーム6の初期結果、デュルバルマブ + トラスツズマブ デルクステカン (T-DXD)

Peter Schmid, Seock-Ah Im, Anne Armstrong, Yeon Hee Park, Wei-Pang Chung, Zbigniew Nowecki, Simon Lord, Piotr Wysocki, Yen-Shen Lu, Hannah Dry, Vatsala Karwe, Ross Stewart, Pia Herbolsheimer, Ana Nunes, Kyung Hae Jung

On behalf of the investigators

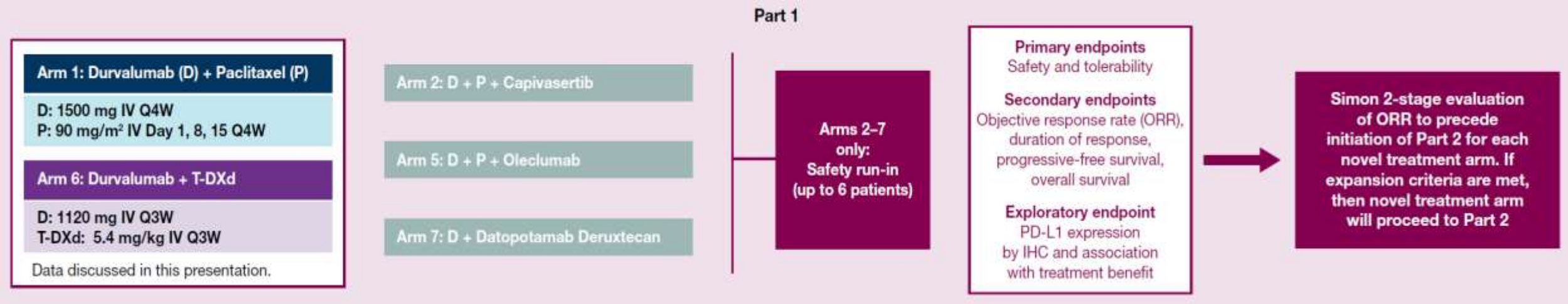
BEGONIA 試験デザイン

Eligibility Criteria:

- Unresectable locally advanced or metastatic Stage IV TNBC
- No prior treatment for Stage IV TNBC
- ≥12 months since taxane therapy for early-stage disease
- ECOG performance status of 0-1
- Measurable disease per RECIST 1.1
- No autoimmune, inflammatory illnesses

Additional Arm 6 Criteria:

- HER2-low-expressing (IHC 2+/ISH-, IHC 1+/ISH-, or IHC 1+/ISH untested, per local testing), estrogen receptor (ER)-negative, and progesterone receptor (PR)-negative tumors
- No ongoing pulmonary disorders



- **2021年3月のデータカットオフ時点において、21例がD+T-DXdの治療を受け、そのうち19例は治療を継続中**
- **フォローアップ期間の中央値 (範囲) : 3.6 (0–9) カ月**

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アーム6: 安全性の概要 (N=21)

- 2例で肺炎 (グレード2およびグレード3)が観察され 、2例ともステロイド治療を行った
  - グレード3の肺炎によりD+T-DXd の治療が中止
  - グレード2の肺炎によりT-DXdの治療のみが中止
- さらに1例が呼吸困難(T-DXdの中止)および病勢進行(デュルバルマブの中止)によりD+T-DXdの治療を中止
- さらに1例が血小板減少症によりT-DXd単独の中止
- 1例で発生したトロポニンの上昇は非重篤であり、心室の駆出率に変化なし

	n (%)
Any AE	21 (100)
Common AEs (≥20% patients, any grade)	
Nausea	16 (76.2)
Fatigue	11 (52.4)
Alopecia, neutropenia, anemia, constipation	6 (28.6) each
Decreased appetite, hypothyroidism, hypokalemia	5 (23.8) each
Any Grade 3/4 AE	8 (38.1)
Any SAE	5 (23.8)
Any treatment-related AE	20 (95.2)
Any AESI for durvalumab	11 (52.4)
Any AESI for T-DXd	2 (9.5)
AE leading to death	0
AE leading to dose interruption	7 (33.3)
Any durvalumab dose delay	9 (42.9)
Any T-DXd dose delay	9 (42.9)
T-DXd dose reduction	5 (23.8)

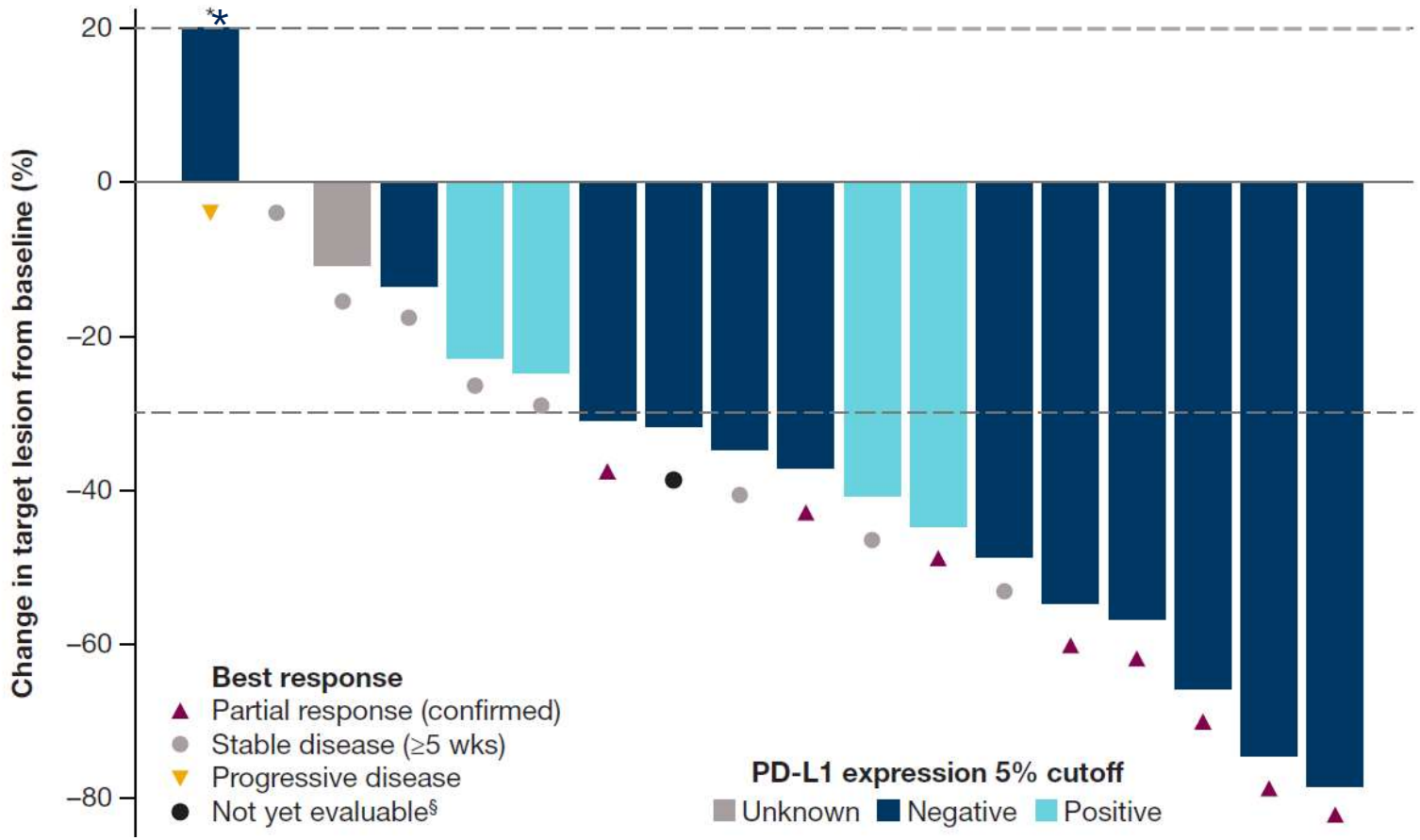
AESIs for T-DXd include pneumonitis/interstitial lung disease and left ventricular ejection fraction decrease.

ASCO2021

アーム6: 腫瘍サイズの最大変化率

- HER2発現の診断テストにより、この併用治療でベネフィットが得られると考えられるHER2 IHC1+ および HER2 IHC2+/ISH−のがん患者を特定することができた 。
- この少数の患者群において、PD-L1陽性群（確定ORR 1/1 [100%]）およびPD-L1陰性群（確定ORR 7/10 [70.0%]）の双方で奏効が認められた。

Parameter	D+T-DXd
Patients who completed at least 1 on-treatment assessment, n	18
Response evaluable analysis set, n‡	12
Confirmed ORR, n (%)‡ 95% CI Complete response, n Partial response, n	8/12 (66.7) 41.0, 86.7 0 8
Stable disease, n	8
Progressive disease, n	1



* 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%

‡ Number of subjects that had the opportunity to complete at least two on-treatment disease assessments or have PD or death

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アーム6の結論: デュルバルマブ + T-DXd

- 転移性HER2低発現/ER陰性/PR陰性 乳がんの1次治療において、有望な早期の有効性シグナルが見られている：有効性の評価が可能な患者のうち確定ORRが 8/12 (66.7%)
  - PD-L1の発現（5% カットオフ）に関わらず奏効が認められた。
  - HER2発現の診断テストにより、HER2 1+ およびHER2 2+/ISH−群の双方におけるベネフィットを示している。
  - 効果は持続しており、87.5%がデータカットオフ時に有効性を持続していた。
- それぞれの薬剤の既知のプロファイルと同様であり、忍容性のある安全性プロファイルを示している。
  - グレード3/4の有害事象の割合は8/21 (38.1%)と低く、2例の肺炎（グレード2, グレード3）が確認された。
  - 現在までのフォローアップ期間および治療期間が短いため、全体的な安全性評価は限定的。

併用の有効性と持続性を引き続きBEGONIA試験で評価した上で、次の計画を決定する

ASCO2021

* Optimal scoring algorithms and cutoffs for PD-L1 expression that are relevant to durvalumab treatment for metastatic TNBC have not yet been established.

Daiichi-Sankyo

トラスツズマブ デルクステカン：8つのシングルアーム試験における治験薬と関連のある間質性肺疾患に関する統合解析

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On behalf of the investigators

ILDの発症率

Daiichi-Sankyo

薬剤に関連するILD：がん種およびグレード別

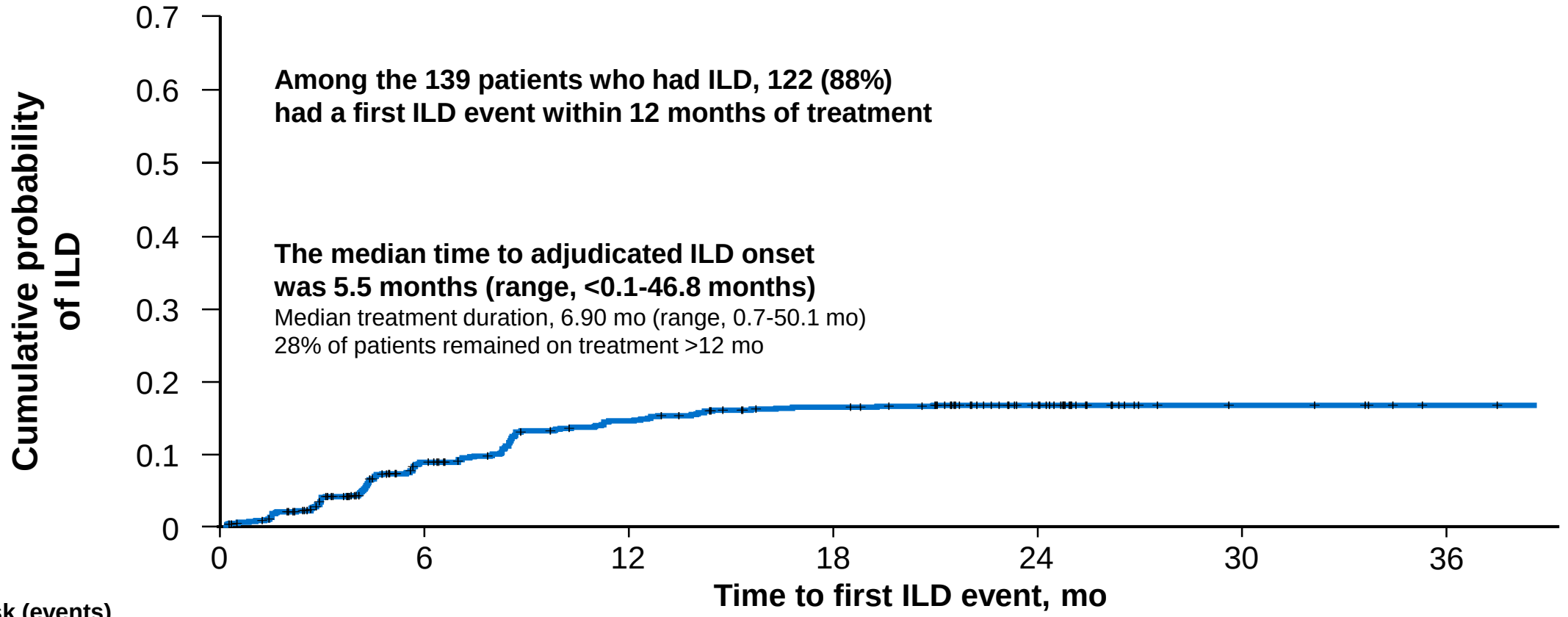
n (%)	All patients (N=879)	HER2+ Breast Cancer, 5.4 mg/kg (n=245)	Gastric cancer (n=78)	Lung cancer (n=148)	Colorectal cancer (n=107)
Grade 1	40 (4.6)	9 (3.7)	0	4 (2.7)	1 (0.9)
Grade 2	68 (7.7)	21 (8.6)	4 (5.1)	8 (5.4)	5 (4.7)
Grade 3	9 (1.0)	1 (0.4)	0	1 (0.7)	1 (0.9)
Grade 4	1 (0.1)	1 (0.4)[a]	0	0	0
Grade 5	21 (2.4)	6 (2.4)	0	4 (2.7)	3 (2.8)
Total	**139 (15.8)**	**38 (15.5)**	**4 (5.1)**	**17 (11.5)**	**10 (9.3)**

ILDを発症した患者のうち、ほとんどがグレード1もしくは2のイベントを発症
(108/139 例がILDを発症 - 78%)

[a] The severity was updated from Grade 4 to Grade 5 following ILD AC re-adjudication of the event after the database lock.

Kaplan-Meier解析：初回ILDイベント発症までの時間

12カ月後にすべてのグレードのILD発生リスクは低減、薬剤に関連するILDと判定される累積確率がこの時点で横ばい状態になり始める



No. at risk (events)							
All-Tumor	879 (0)	480 (75)	242 (122)	136 (136)	53 (138)	15 (138)	8 (138)
ILD rate	0	8.9%	14.8%	16.5%	16.8%	16.8%	16.8%

Treatment discontinuations due to reasons other than ILD were included as competing event.

治験におけるILDのモニタリングと管理に関するガイドラインの改訂版(2019)

Daiichi-Sankyo

STEP 1: Monitor

Suspected ILD

Interrupt drug

Rule out ILD if a patient develops radiographic changes potentially consistent with ILD or develops an acute onset of new or worsening pulmonary or other related signs/symptoms, such as dyspnea, cough, or fever.

STEP 2: Confirm

Evaluations should include:

- 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
- PFTs and pulse oximetry
- Arterial blood gasses, if clinically indicated
- One blood sample collection for PK analysis as soon as ILD is suspected, if feasible

All events of ILD, regardless of severity or seriousness, should be followed until resolution including after drug discontinuation.

STEP 3: Manage

Drug must be interrupted for any ILD events regardless of grade

- **Grade 1**: **Interrupt until fully resolved**, then:
  - if resolved in 28 days or less from date of onset, maintain dose
  - if resolved in greater than 28 days from date of onset, reduce dose one level
  - however, if the event Grade 1 ILD occurs beyond cycle day 22 and has not resolved within 49 days from the last infusion, the drug should be discontinued
- **Grades 2-4**: **Permanently discontinue treatment.** Refer to toxicity management guidelines for trastuzumab deruxtecan

Modi S, et al. *N Engl J Med*. 2020;382(7):610-21.

治験におけるILDのモニタリングと管理に関するガイドラインの改訂版(2019)

Daiichi-Sankyo

ステロイドの投与量、投与期間については、ガイドラインを改訂し、より具体的なガイドラインを作成した。

	Grade 1	Grade 2	Grade 3/4

Toxicity management	• Monitor and closely follow-up in 2 to 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** (e.g. at least 0.5 mg/kg/day prednisone or equivalent) until improvement, followed by **gradual taper over at least 4 weeks**
	• If worsening of diagnostic observations despite initiation of corticosteroids, then follow Grade 2 guidelines
	  • **If patient is asymptomatic, then patient should still be considered as grade 1 even if steroid treatment is given**
		• Promptly start and **treat with systemic steroids** (e.g., at least 1mg/kg/day prednisone or equivalent) for at **least 14 days** or until complete resolution of clinical symptoms and chest CT findings, then followed by a **gradual taper over at least 4 weeks**
		• Monitor symptoms closely
		• Re-image as clinically indicated
		• If worsening or no improvement in clinical or diagnostic observations in 5 days,
		  • **Consider increasing dose of steroids** (e.g., 2 mg/kg/day prednisone or equivalent) and administration may be switched to intravenous (e.g. methylprednisolone)
		  • Re-consider additional work-up for alternative etiologies as described above
		  • Escalate care as clinically indicated
			• Hospitalization required
			• Promptly **initiate empiric high-dose methylprednisolone IV treatment** (e.g., 500-1000 mg/day for 3 days), followed by at least 1.0 mg/kg/day of prednisone (or equivalent) **for at least 14 days** followed by a gradual taper over at least 4 weeks
			• Re-image as clinically indicated
			• If still no improvement within 3 to 5 days,
			  • Re-consider additional work-up for alternative etiologies as described above
			  • Consider other immuno-suppressants and/or treat per local practice

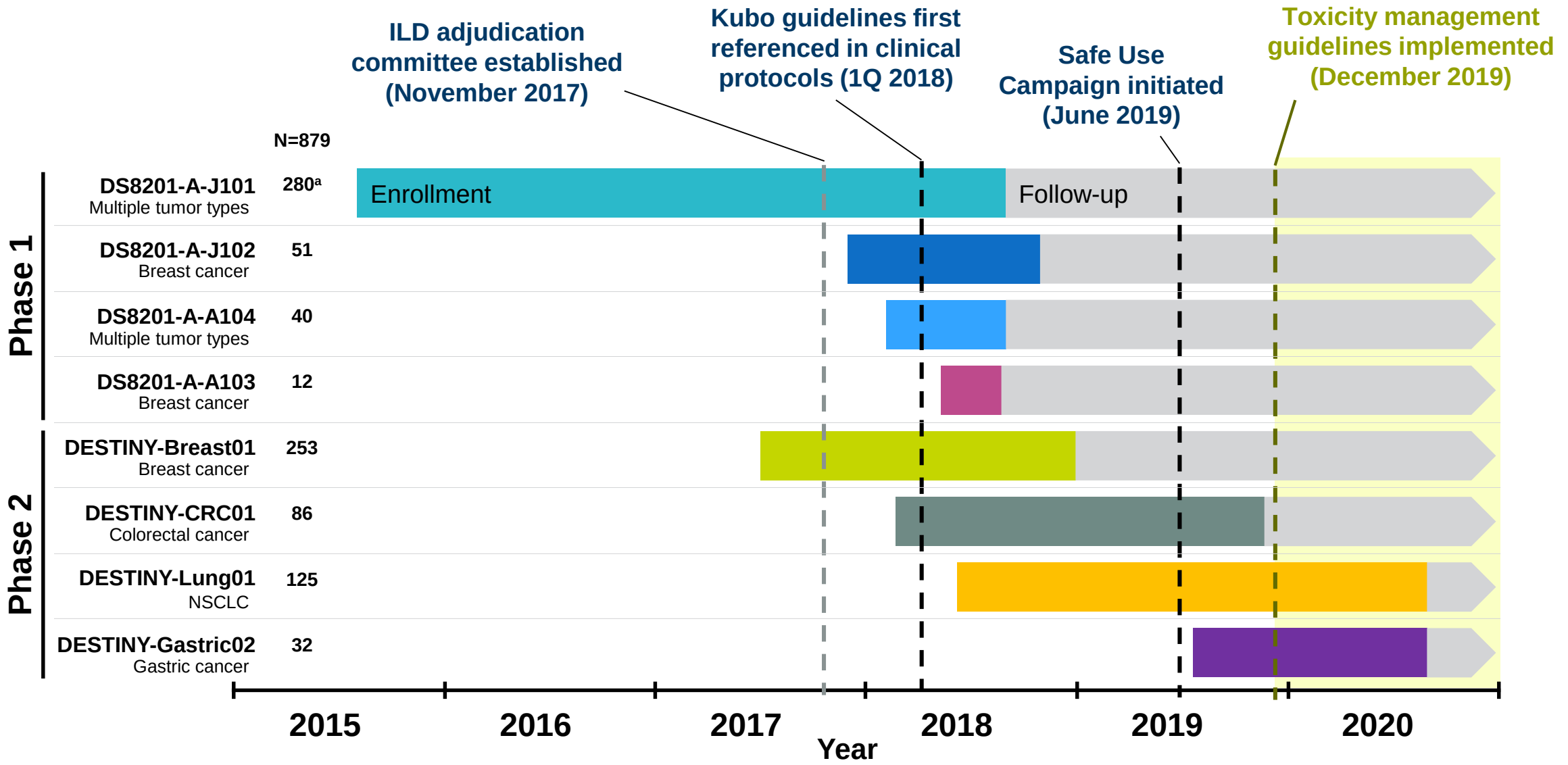
CBC, complete blood count; CT, computed tomography; ILD, interstitial lung disease; IV, intravenous; PFT, pulmonary function test; PK, pharmacokinetic.

Modi S, et al. *N Engl J Med*. 2020;382(7):610-21.

統合解析に含まれる試験と患者群

AACR 2021

Daiichi-Sankyo



[a] Only patients who received T-DXd 5.4, 6.4, 7.4, or 8.0 mg/kg are included. All studies noted here are active but no longer recruiting, except for DESTINY-CRC01, which was completed in November 2020. Note that most patients were enrolled prior to the implementation of toxicity management guidelines. The color bar on each arrow indicates the time of patient enrollment and the gray is follow-up.

安全性管理ガイドライン施行後のILD発症率

Daiichi-Sankyo

Updated toxicity management guidelines implemented (December 2019)

Incidence of ILD over time

	2016 (n=74)	2017 (n=168)	2018 (n=569)	2019 (n=179)	2020 (n=160)
Any Grade ILD, n (%)	18 (24.3)	33 (19.6)	87 (15.3)	28 (15.6)	11 (6.9)
Grade ≥3 ILD, n (%)	2 (2.7)	6 (3.6)	21 (3.7)	8 (4.5)	3 (1.9)
Grade 5 ILD, n (%)	1 (1.4)	5 (3.0)	12 (2.1)	5 (2.8)	2 (1.3)

Patients grouped by year of enrollment, based on a data snapshot from **December 2020**.

安全性管理ガイドライン施行後、2020年に治験に登録された患者は、それ以前に登録された患者と比較してすべてのグレードのILD発症率が低いように見受けられる (6.9%)、 グレード3以上 (1.9%) 、グレード5 ILD (1.3%)。ただし、治療期間の短さも要因の一つと考えられる。

エンハーツ®: 臨床開発計画 | 乳がん

2021年6月現在			FY2020	FY2021	FY2022	計画中
HER2 陽性		転移性 3L~	DESTINY-Breast01 終了			
			DESTINY-Breast02 単剤 vs 医師選択治療			
		転移性 2L	DESTINY-Breast03 単剤 vs T-DM1			
			DESTINY-Breast07 併用 (2L/1L) Ph1b/2			
		転移性 1L		DESTINY-Breast09 T-DXd ± ペルツズマブvs THP		
		ポストネオアジュバント		DESTINY-Breast05 単剤 vs T-DM1		
		ネオアジュバント				Phase 3
		アジュバント				Phase 3
HER2 低発現	HR+ HR-	転移性 ポスト化学療法	DESTINY-Breast04 単剤 vs 医師選択治療			
				DESTINY-Breast08 併用		
		ポストネオアジュバント				Phase 3
	HR+	転移性 化学療法未治療	DESTINY-Breast06 単剤 vs 医師選択治療			
		転移性 内分泌療法				Phase 3
	HR-	転移性 1L	BEGONIA デュルバルマブ 併用 Ph1b/2（アーム6）			
		ネオアジュバント				Phase 3

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 下半期 の初めより表示

エンハーツ®: 臨床開発計画 | 胃がん & NSCLC

試験の開始と終了は一律上半期 または 下半期 の初めより表示

NSCLC: 非小細胞肺がん

エンハーツ®: 臨床開発計画 | 大腸がん & その他がん

2021年6月現在			FY2020	FY2021	FY2022	計画中
大腸がん	HER2発現	転移性 3L	DESTINY-CRC01 単剤	DESTINY-CRC02 単剤		
		転移性 2L				Phase 3
		転移性 1L				Phase 3
その他がん/多発性がん	HER2発現	転移性 2L	ニボルマブ併用 (乳がん, 膀胱がん)			
			ペムブロリズマブ併用 (乳がん, NSCLC)			
			DESTINY-PanTumor02			
		卵巣がん				Phase 2
	HER2変異	転移性 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半期 または 下半期 の初めより表示

NSCLC: 非小細胞肺がん

エンハーツ®: 主要なデータの入手予想

DESTINY-Breast02 | HER2 陽性 転移性乳がん vs標準治療	• イベントドリブンの主たる解析結果、 2022年度第2四半期と予想
DESTINY-Breast03 | HER2 陽性 転移性乳がん vs T-DM1	• イベントドリブンの中間解析結果、 2021年度第2四半期と予想
DESTINY-Breast04 | HER2低発現 転移性乳がん vs 標準治療	• イベントドリブンの主たる解析結果、 2021年度第4四半期と予想
DESTINY-Lung01 | HER2 過剰発現/変異NSCLC	• 主たる解析結果 2021年度第2四半期と予想

NSCLC: 非小細胞肺がん

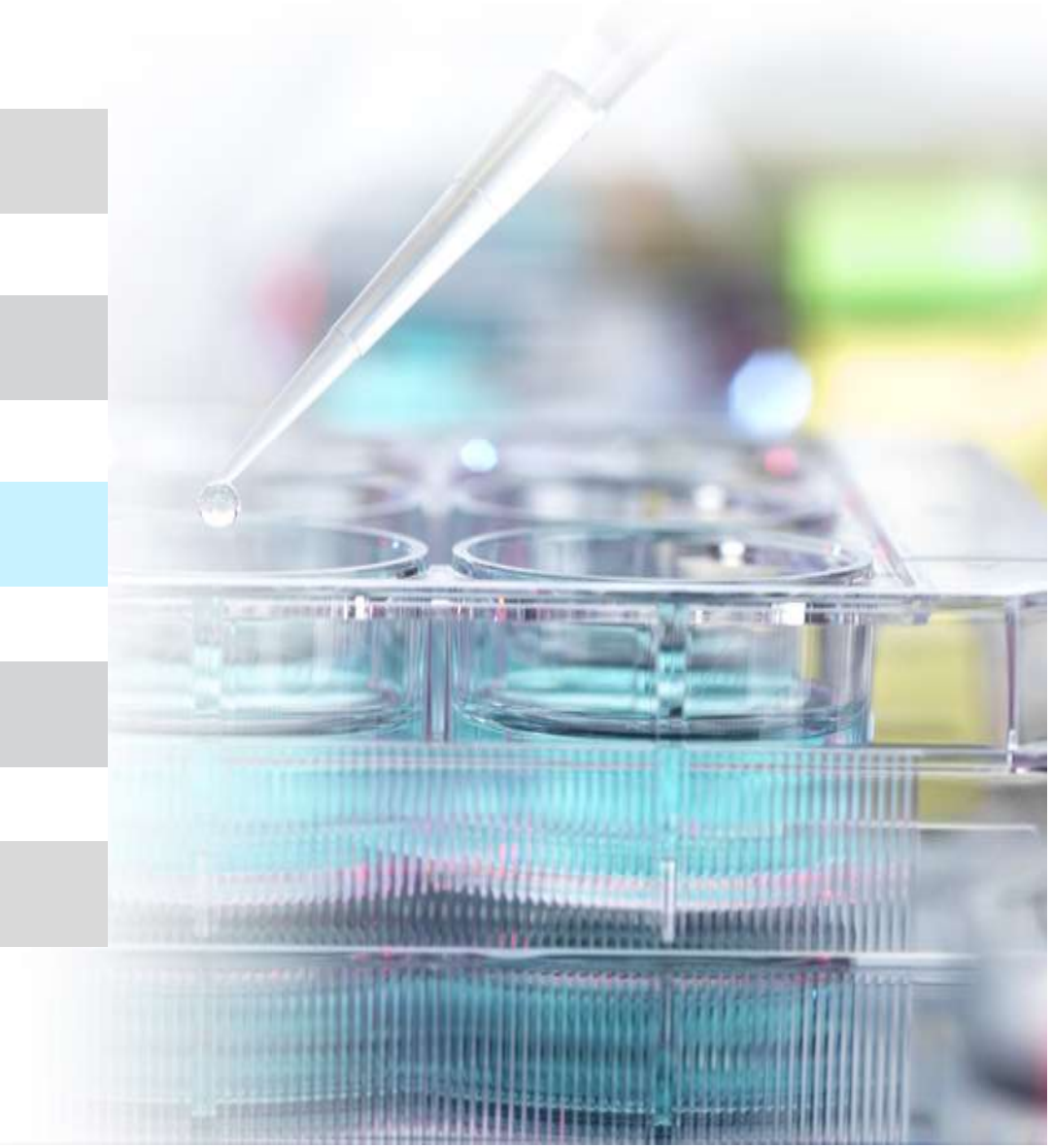
エンハーツ®: 最近開始および今後開始予定のピボタル試験

DESTINY-Breast09 | HER2陽性 転移性乳がん vs THP	• Ph3、1L 進行性/転移性 HER2陽性 乳がん	2021年6月 開始
DESTINY-Gastric04 | HER2陽性 転移性胃がん vs ラムシルマブ+パクリタキセル	• Ph3、2L 進行性/転移性 HER2陽性 胃がん	2021年度 上半期 開始予定

THP: タキサン、ハーセプチン、ペルツズマブ

本日の内容

1. イントロダクション
2. エンハーツ®: 新規データおよび開発計画
3. **Dato-DXd: 新規データおよび開発計画**
4. HER3-DXd: 新規データおよび開発計画
5. 今後のニュースフロー



TROPION-PanTumor01: TROP2抗体薬物複合体 ダトポタマブ デルクステカン (Dato-DXd; DS-1062) の進行性もしくは転移性非小細胞肺がん(NSCLC)治療における投与量の解析結果

Funda Meric-Bernstam,[1] Alexander Spira,[2] Aaron E. Lisberg,[3] Jacob M. Sands,[4] Noboru Yamamoto,[5] Melissa L. Johnson,[6] Kiyotaka Yoh,[7] Edward B. Garon,[8] Rebecca S. Heist,[9] Adam Petrich,[10] Jonathan Greenberg,[10] Naoyuki Tajima,[10] Yui Kawasaki, [11] Wen Gu,[10] Fumiaki Kobayashi,[11] Yasong Lu,[10] Ferdinand Guevara,[10] Toshio Shimizu[5]

[1]University of Texas, MD Anderson Cancer Center, Houston, TX; [2]Virginia Cancer Specialists, Fairfax, VA; [3]UCLA Jonsson Comprehensive Cancer Center, Santa Monica, CA; [4]Dana-Farber Cancer Institute, Boston, MA; [5]Department of Experimental Therapeutics, National Cancer Center Hospital, Tokyo, Japan; [6]Sarah Cannon Research Institute, Nashville, TN; [7]National Cancer Center Hospital East, Chiba, Japan; [8]University of California, Los Angeles, Los Angeles, CA; [9]Massachusetts General Hospital, Boston, MA; [10]Daiichi Sankyo, Basking Ridge, NJ; [11]Daiichi Sankyo Co, Ltd, Tokyo, Japan

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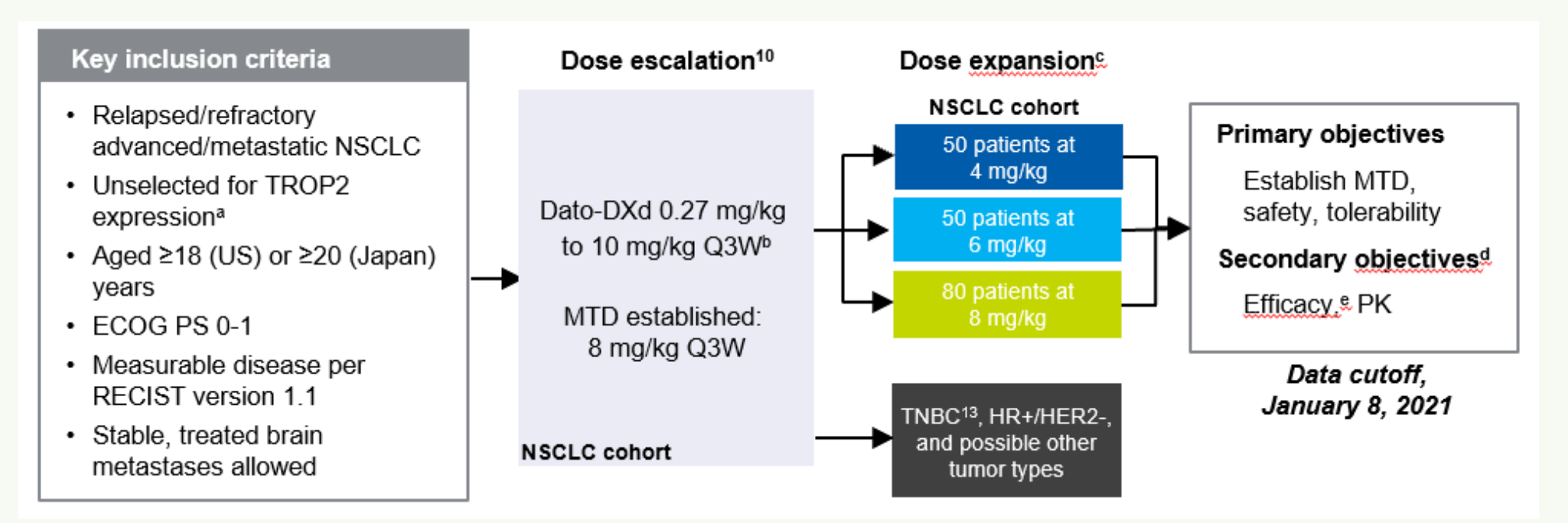
On behalf of the investigators

TROPION-PanTumor01試験デザイン



- NSCLCコホートの有効性および安全性結果のアップデート（データカットオフ：2021年1月8日）ならびにファーマコメトリクス解析結果を報告
- 今後の開発における至適用量の選択のために、すべての投与量で得られたデータを集積し、母集団薬物動態（PopPK）および曝露-反応モデル解析を含むファーマコメトリクス解析を実施

ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; TNBC, triple-negative breast cancer; TROP2, trophoblast cell-surface antigen 2.
[a] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression. [b] The 4-, 6-, and 8-mg/kg dose levels are being further evaluated for safety and efficacy. [c] Includes patients treated in the dose-escalation and dose-expansion portions. [d] Additional exploratory endpoints include analyses of biomarkers associated with response. [e] Response assessments are based on RECIST v1.1.

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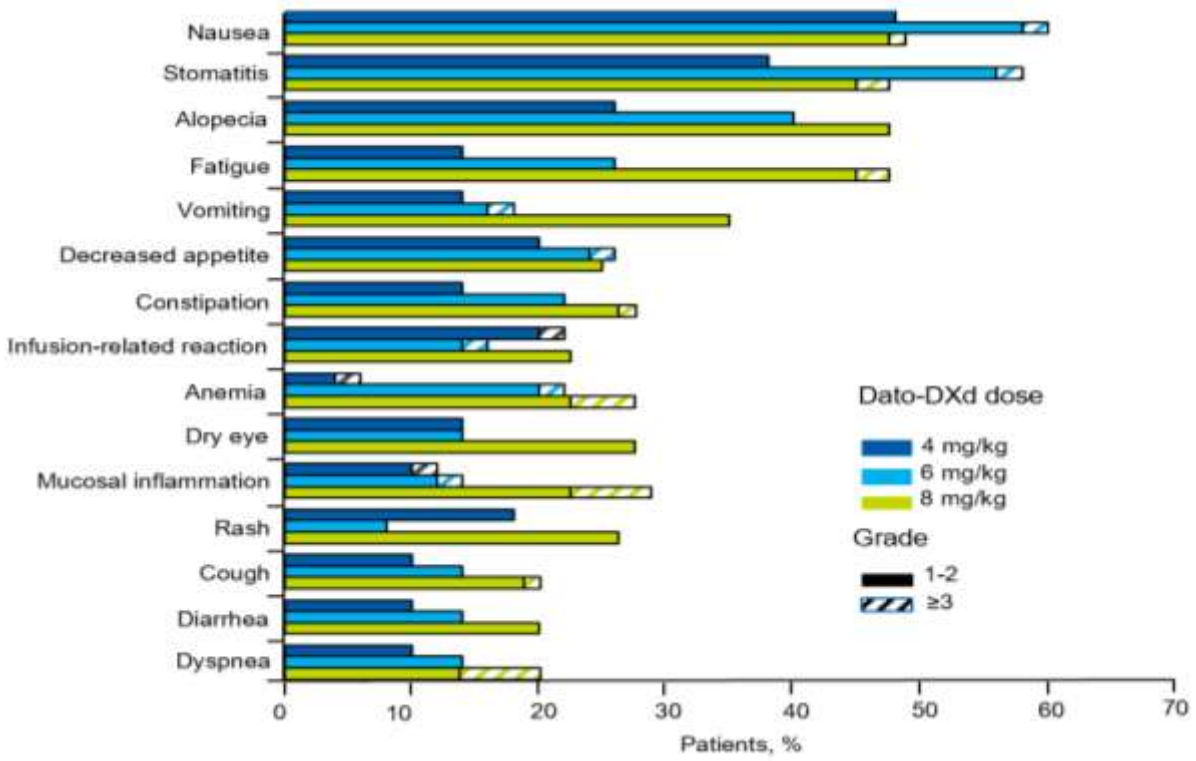
安全性結果

Overall Safety Summary

Patients, n (%)	Dato-DXd dose 4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
TEAE	49 (98)	48 (96)	80 (100)
Grade ≥3	15 (30)	24 (48)	46 (58)
Drug-related TEAE	46 (92)	41 (82)	77 (96)
Grade ≥3	7 (14)	8 (16)	28 (35)
Serious TEAE	11 (22)	24 (48)	39 (49)
Grade ≥3	10 (20)	18 (36)	36 (45)
Dose adjustments			
TEAEs associated with discontinuation	7 (14)	5 (10)	15 (19)
TEAEs associated with dose interruption	7 (14)	9 (18)	17 (21)
TEAEs associated with dose reduction	1 (2)	4 (8)	24 (30)
Interstitial lung disease	5 (10)	2 (4)	12 (15)
Grade ≤2	4 (8)	2 (4)	8 (10)
Grade 3	1 (2)	0	1 (1)
Grade 4	0	0	0
Grade 5	0	0	3 (4)
Deaths			
Drug-related fatal ILD/pneumonitis[a]	0	0	3 (4)

ILD, interstitial lung disease; TEAE, treatment-emergent adverse event.
[a] All fatal TEAEs reported as drug-related were pulmonary events and therefore were adjudicated for ILD/pneumonitis by an independent, external committee.

Treatment-Emergent Adverse Events in ≥15% of Patients



[a] Of 180 patients (4 mg/kg [n=50]; 6 mg/kg [n=50]; 8 mg/kg [n=80]).
[b] Grade ≥3 neutropenia occurred in 1 patient at the 8-mg/kg dose; no cases of febrile neutropenia were reported.

- 全体的にDato-DXdは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観察されなかった
- 今回得られた予備的な結果により、有害事象の中で可逆的なもの（消化器毒性と貧血）が判明し、今後より成熟した試験結果をもとに有害事象の経過を解析する

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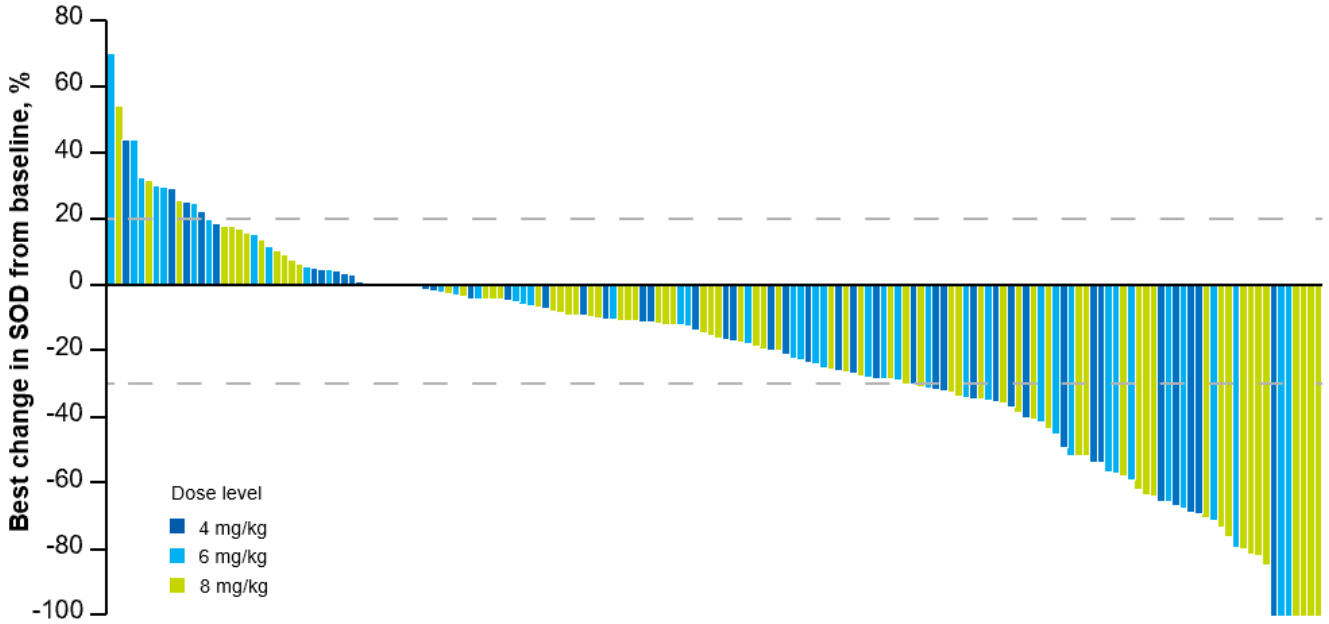
有効性結果

Best Overall Response (BICR)

Patients[a]	Dato-DXd Dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
ORR, n (%)	12 (24)	13 (26)	19 (24)
CR/PR	10 (20)	11 (22)	19 (24)
CR/PR (too early to be confirmed)	2 (4)	2 (4)	0
DCR, n (%)	38 (76)	35 (70)	64 (80)
PD, n (%)	7 (14)	10 (20)	7 (9)
DOR, median (95% CI), mo	NE (2.8-NE)	10.5 (4.1-NE)	9.0 (5.8-NE)
PFS, median (95% CI), mo[b]	4.3 (3.5-8.4)	6.9 (2.7-8.8)	5.2 (4.1-7.1)

BICR, blinded independent central review; CR, complete response; DCR, disease control rate; DOR, duration of response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response.
[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. [b] Median PFS was limited by immature duration of follow-up in the 4- and 6-mg/kg dosing cohorts.

Best Change in Sum of Diameters (BICR)



BICR, blinded independent central review; SOD, sum of diameters.

4, 6, and 8 mg/kg においてDato-DXdの抗腫瘍効果が確認された

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ファーマコメトリクス解析: バーチャル集団における予測確率

Endpoint for model projection	Dato-DXd dose		
	4 mg/kg	6 mg/kg	8 mg/kg
Probability of response, mean (90% CI)	18.7 (14.4-23.6)	23.4 (18.4-29.1)	26.3 (19.9-33.6)
Probability of dose reductions, mean (90% CI)	4.9 (2.6-8.1)	15.6 (11.9-19.7)	27.4 (21.7-33.1)
Probability of grade ≥2 stomatitis/mucosal inflammation, mean (90% CI)	17.3 (12.1-23.9)	35.0 (29.4-40.7)	47.7 (41-53.9)

A virtual population of N=200 patients per dose was created by random sampling of the patients in the TROPION-PanTumor01 study. The factors that affect pharmacokinetics (weight, baseline albumin, sex) were well balanced across doses. No dose reductions were considered for the simulation.

- モデルシミュレーションにより、用量減量およびグレード2以上の口内炎/粘膜炎症の発生確率は、4もしくは 6 mg/kgと比較して8 mg/kgの方が高いことが示唆された
- さらに、4 mg/kgと比較して6 mg/kgの方が有効性を示す確率が高いことが示唆された

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サマリー/結論

- Dato-DXdは、進行性または転移性NSCLC患者において、有望な抗腫瘍効果と管理可能な安全性プロファイルを示すが、フォローアップ期間が短く、用量間のフォローアップ期間が同等でないため結果が限られている
- 腫瘍縮小効果はいずれの用量でも持続的であり、 6 mg/kgの用量でPFSが長くなる傾向が認められた。
- ファーマコメトリクス解析から予備的に示唆されるものは以下の通りである。
  - 曝露量の増加は有効性の改善と関連していた。
  - 曝露量の増加は用量の減量率及びTEAEの発現率の増加と関連していた。
- これらの解析は、無作為化第3相TROPION-Lung01試験 (NCT04656652) で6 mg/kgを用量として選択したことを支持している。
- 間質性肺疾患、消化管毒性などの有害事象の発現頻度および重症度は、T-DXdと同様の傾向が認められたが、Dato-DXdでは口内炎の発現率が高く、骨髄抑制の発現率が低いことから、DAR、ADCの標的、またはその他の要因が毒性プロファイルに影響を与えることが示唆された。

この試験の結果をもとにピボタル試験であるTROPION-Lung01試験が進行中

TROP2抗体薬物複合体 ダトポタマブ デルクステカン（Dato-DXd）：進行中のPh1試験よりトリプルネガティブ乳がんコホートの予備的結果

Aditya Bardia,[1] Dejan Juric,[1] Toshio Shimizu,[2] Anthony Tolcher,[3] Raghad Karim,[3] Alexander Spira,[4] Toru Mukohara,[5] Aaron E. Lisberg,[6] Takahiro Kogawa,[7] Ian Krop,[8] Kyriakos P Papadopoulos,[9] Erika Hamilton,[10] Senthil Damodaran,[11] Jonathan Greenberg,[12] Wen Gu,[12] Fumiaki Kobayashi,[13] Ferdinand Guevara,[12] Takahiro Jikoh,[13] Yui Kawasaki,[13] Funda Meric-Bernstam[11]

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On behalf of the investigators

TROPION-PanTumor01 (NCT03401385) – TNBCコホート

Phase 1, First-in-human, Dose Escalation and Expansion Study

- Advanced/metastatic HR-/HER2-negative breast cancer (TNBC)[a]
- Relapsed/progressed on standard treatment
- Unselected for TROP2 expression[b]
- Measurable disease (per RECIST version 1.1)

→

Dato-DXd 6mg/kg IV Q3W

N≈40

2 patients received 8 mg/kg prior to selection of the 6-mg/kg dose for dose expansion

→

Primary objectives include:

- Safety, Tolerability

Secondary objectives include:

- Efficacy, Pharmacokinetics

Data cutoff January 8, 2021

- 現時点の解析は24例の症例を含む： 6 mg/kg (n=22) および 8 mg/kg (n=2)[c]
- 18例 (75%)で治療継続中； 病勢進行により6例 (25%)が治療を中止[d]

HER2, human epidermal growth factor receptor 2; HR, hormone receptor; IV, intravenous; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors.
[a] Estrogen receptor positivity <1%; [b] Pretreatment tumor tissue was required for retrospective analysis of TROP2 expression; [c] An HR+ cohort is currently open for enrollment at 6 mg/kg; [d] Progression includes progressive disease per RECIST 1.1 and clinical progression.

大半の患者が多数の前治療歴を有する

Patient characteristics	N=24
Age, median (range), y	57.0 (32-82)
Country, n (%)	
US	18 (75)
Japan	6 (25)
ECOG PS, n (%)	
0	8 (33)
1	16 (67)
De-novo metastatic disease, n (%)	
Yes	9 (38)
No	15 (63)

Patient characteristics	N=24
Brain metastases, n (%)	2 (8)
Prior therapies, median (range), n[a]	4 (1-9)
≥2 prior lines of therapy, n (%)[a]	21 (88)
Previous systemic treatment, n (%)[a]	
Taxanes	20 (83)
Platinum-based chemotherapy	12 (50)
Immunotherapy	8 (33)
Sacituzumab govitecan	2 (8)
PARPi	1 (4)

ECOG PS, Eastern Cooperative Oncology Group performance status; PARPi, Poly (ADP-ribose) polymerase inhibitor; US, United States.
[a] Includes prior lines of therapy in the (neo)adjuvant and/or metastatic setting.

Data cutoff: January 8, 2021

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Dato-DXdは管理可能な安全性プロファイルを示した

Patients, n (%)	N=24	
	Any grade	Grade ≥3
TEAEs	24 (100)	8 (33)
Treatment related	24 (100)	4 (17)
Serious TEAEs[a]	3 (13)	3 (13)
Treatment related	0	0
Fatal TEAEs	0	–
Treatment related	0	–

- 有害事象による用量減量が6例 (25%)で発生し、ほとんどが口内炎（3 例 [13%]) および粘膜炎症 (2例 [8%]）によるものであった。
- 有害事象によって投与を中止した患者はいなかった。

TEAE, treatment-emergent adverse event.
[a] A serious TEAE was defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, or results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect or is an important medical event.

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Data cutoff: January 8, 2021

管理可能かつ主に非血液関連の有害事象

- 主にグレード1もしくは2 (67%) で非血液関連
- グレード3以上の下痢と好中球減少は見られなかった
- 薬剤に関連すると判定されたILDは発症せず

Preferred Term, n (%)[a]	N=24	
	Any grade	Grade ≥3
TEAEs	**24 (100)**	**8 (33)**
Stomatitis	15 (63)	3 (13)
Nausea	15 (63)	0
Fatigue	10 (42)	1 (4)
Vomiting	10 (42)	0
Alopecia	6 (25)	–
Cough	5 (21)	0
Pruritus	5 (21)	0
Anemia	4 (17)	1 (4)
Headache	4 (17)	0
Constipation	4 (17)	0

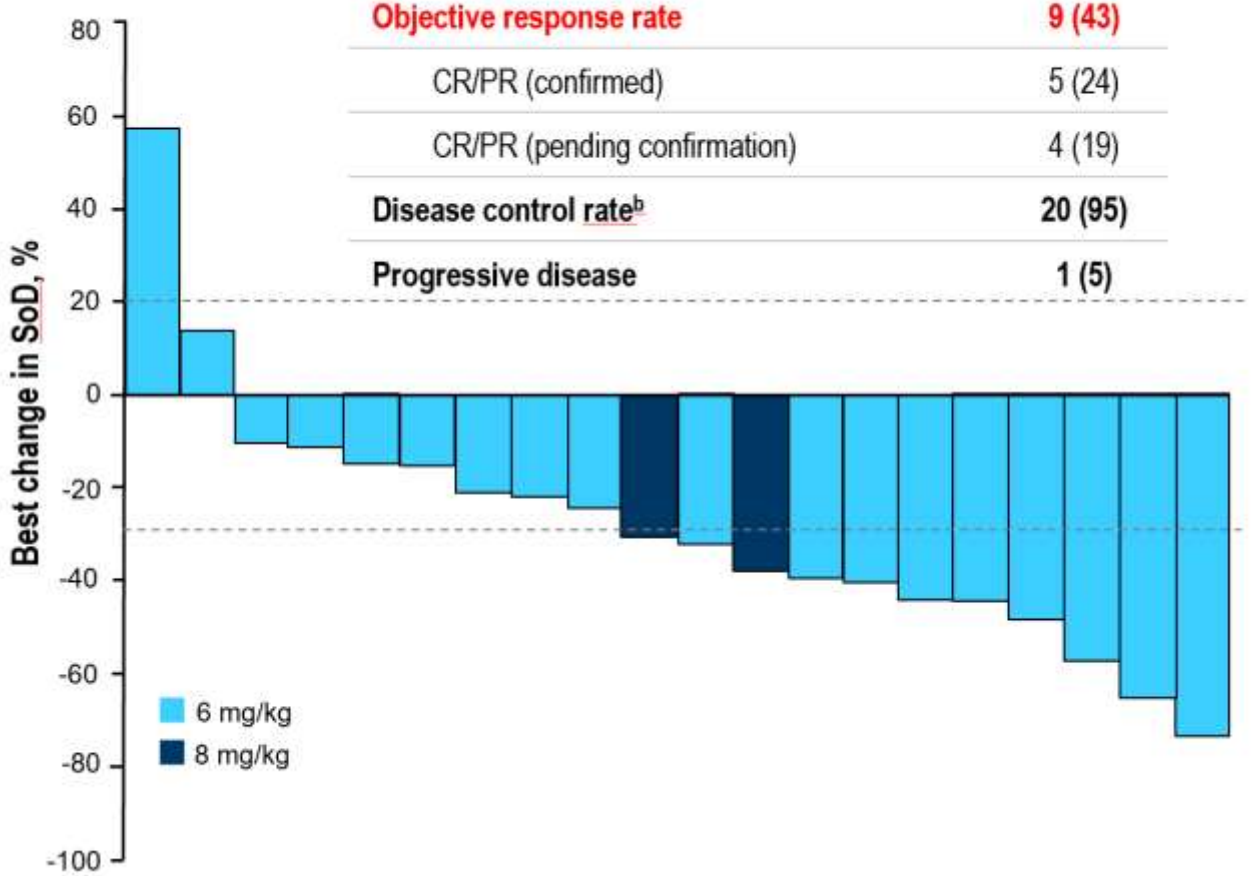
ILD, interstitial lung disease.
[a] TEAEs observed in ≥15% of patients.

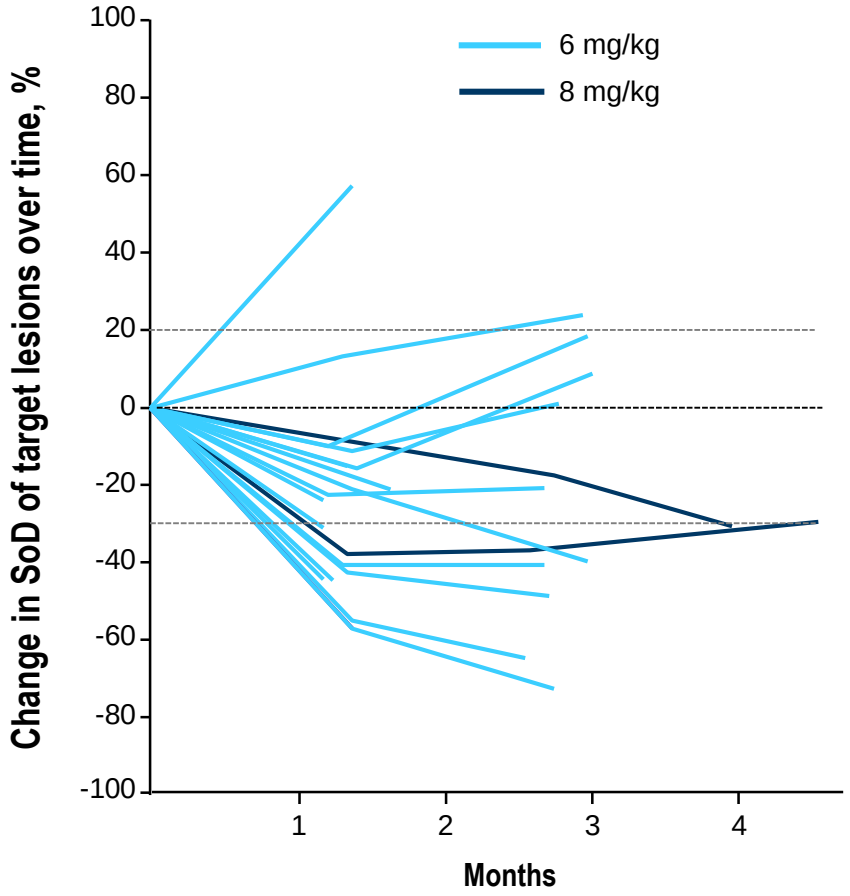
ESMO2021

Data cutoff: January 8, 2021

抗腫瘍効果 (盲検下独立中央評価)

Patients, n (%)[a]	N=21
Objective response rate	9 (43)
CR/PR (confirmed)	5 (24)
CR/PR (pending confirmation)	4 (19)
Disease control rate[b]	20 (95)
Progressive disease	1 (5)





BICR, blinded independent central review; CR, complete response; PD, progressive disease; PR, partial response; SoD, sum of diameters.
[a] Includes response evaluable patients who had ≥1 postbaseline tumor assessment or discontinued treatment. Postbaseline tumor assessments were not yet available for 3 patients at the data cutoff. One patient was not confirmed to have a target lesion per BICR and therefore had a best overall response of non-CR/non-PD; [b] Includes patients with a best overall response of CR, PR, stable disease, or non-CR/non-PD.

Data cutoff: January 8, 2021

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結論

- Dato-DXdは管理可能な安全性プロファイルを示し、有害事象によって治療を中止した患者はいなかった
- 多数の前治療歴を有する転移性TNBC患者に対して抗腫瘍効果を示した
  - 盲検下独立中央評価によるORRは43%、病勢コントロール率は95%
- 乳がんを対象とした更なる臨床試験が必要
  - HR陽性乳がんコホートで患者を登録中

今回得られた結果をもとに、TNBCを対象としたピボタル試験を現在計画中

ESMO2021

Dato-DXd: 臨床開発計画 | NSCLC & 乳がん

2021年6月現在			FY2020	FY2021	FY2022	検討中
NSCLC	オールカマー	進行/転移性 2L~	TROPION-PanTumor01			
	actionable 遺伝子 変異なし	進行/転移性 2L~		TROPION-Lung01 単剤 vs ドセタキセル		
		進行/転移性 2L		TROPION-Lung02 & 04 免疫チェックポイント阻害剤 併用		
		進行/転移性 1L				Ph3
	actionable 遺伝子 変異あり	進行/転移性 2L~		TROPION-Lung05 単剤		
		進行/転移性 1L				
乳がん	TNBC	転移性 2L~	TROPION-PanTumor01			Ph3
		転移性1L		BEGONIA デュルバルマブ 併用 Ph1b/2（アーム7）		
	HR陽性/ HER2陰性	転移性2L~		TROPION-PanTumor01		Ph3
		転移性1L				

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 下半期 の初めより表示

Dato-DXd: 直近のアップデート

TROPION-PanTumor01 | HR陽性 乳がん コホート	• HR陽性 乳がん コホートを Ph1に追加 • 2021年3月に臨床試験を開始
BEGONIA | TNBC デュルバルマブ 併用	• アストラゼネカ主導 Ph1b/2 試験, 1L TNBC • Arm 7 (Dato-DXd+デュルバルマブ) 新規追加 • 2021年5月に臨床試験を開始

本日の内容

1. イントロダクション
2. エンハーツ®: 新規データおよび開発計画
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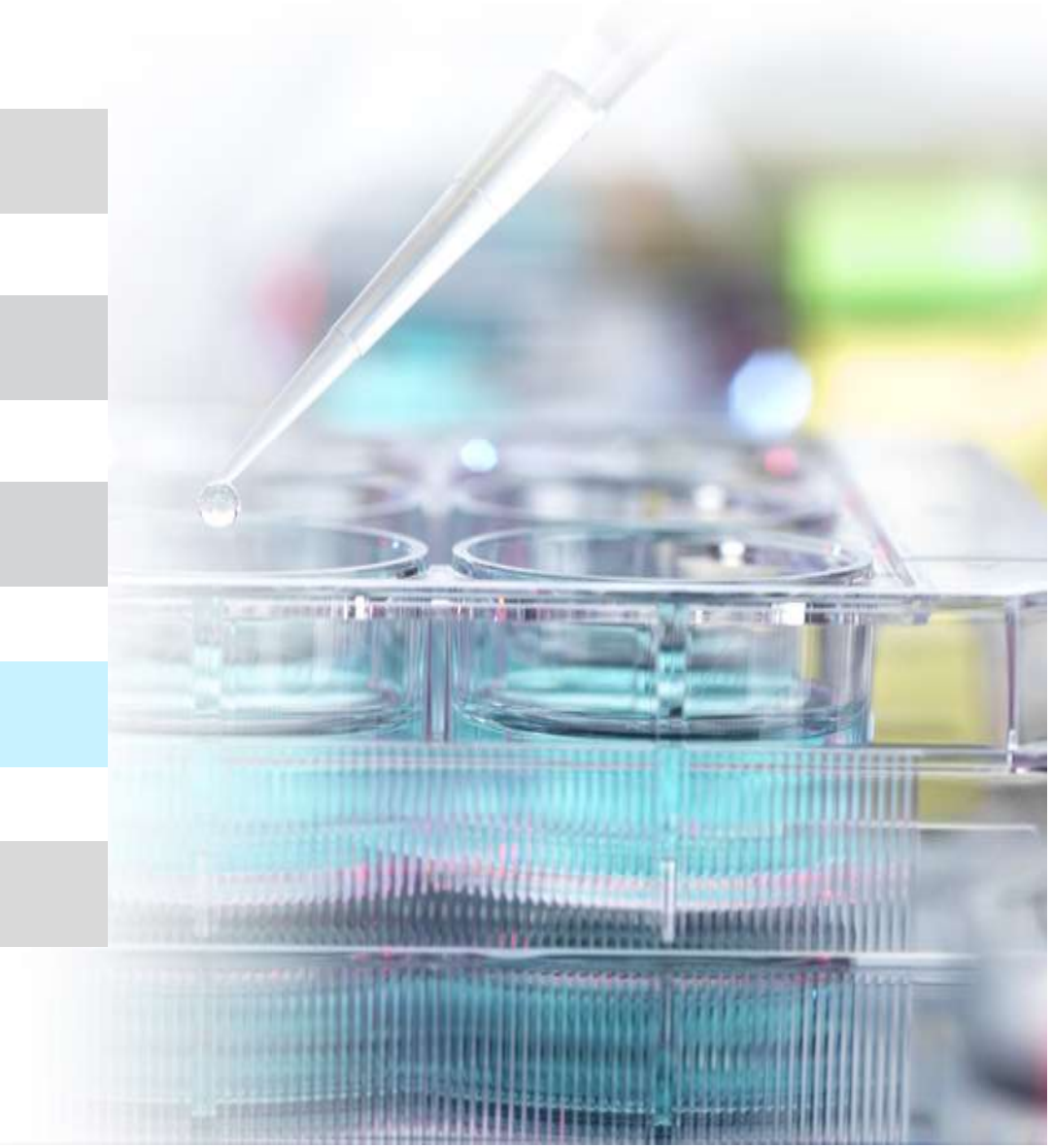

EGFR阻害剤抵抗性、EGFR変異 (*EGFR*m)非小細胞肺がん (NSCLC)における パトリツマブ デルクステカン (HER3-DXd)の有効性および安全性

Pasi A. Jänne,[1] Christina Baik,[2] Wu-Chou Su,[3] Melissa L. Johnson,[4] Hidetoshi Hayashi,[5] Makoto Nishio,[6] Dong-Wan Kim,[7] Marianna Koczywas,[8] Kathryn Gold,[9] Conor Steuer,[10] Haruyasu Murakami,[11] James C. H. Yang,[12] Sang-We Kim,[13] Michele Vigliotti,[14] Zhenhao Qi,[14] Yang Qiu,[14] Lihui Zhao,[14] David Sternberg,[14] Channing Yu,[14] Helena A. Yu[15]

04 June 2021

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On behalf of the investigators

HER3-DXd: 進行性EGFR変異NSCLCのPh1試験

Daiichi-Sankyo

Dose escalation[a]

HER3-DXd IV Q3W (21-day cycles)

Locally advanced/metastatic NSCLC with *EGFR* mutations

Progression on prior EGFR TKI treatment

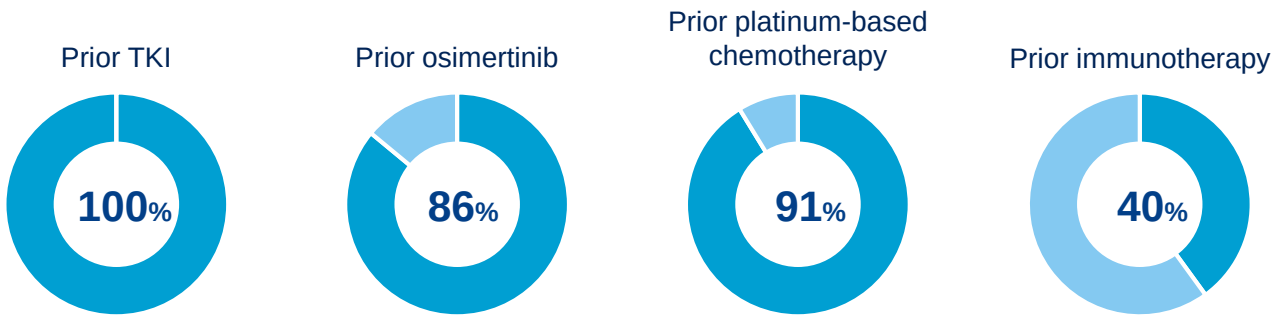
- 6.4 mg/kg (N=5)
- 5.6 mg/kg (N=12)
- 4.8 mg/kg (N=15)
- 3.2 mg/kg (N=4)

Recommended dose for expansion: HER3-DXd 5.6 mg/kg IV Q3W

Dose expansion[a]

1	Adenocarcinoma NSCLC with *EGFR* mutations; prior EGFR TKI and platinum-based chemotherapy	5.6 mg/kg (N=45)
2	Squamous or nonsquamous NSCLC without *EGFR*-activating mutations	
3	NSCLC with *EGFR* mutations including any histology other than combined small and nonsmall cell	

Baseline Patient Characteristics



この試験に登録された患者は
多数の前治療歴を有し、
中央値として4種類の前治療を
受けている

Data cutoff: September 24, 2020

Clinicaltrials.gov, NCT03260491; EudraCT, 2017-000543-41; JapicCTI, 194868.

[a] Patients with stable brain metastases were permitted to enroll; A tumor biopsy was required prior to study entry but patients were not selected for inclusion based on measurement of HER3.

HER3-DXdはEGFR TKI及びプラチナ製剤併用化学療法(PBC)が無効となった患者に持続的な抗腫瘍効果を示した

Outcomes (BICR per RECIST 1.1) Median Follow Up: 10.2 (range, 5.2-19.9) mo[a]	HER3-DXd 5.6 mg/kg Prior TKI, ± PBC (N=57)	HER3-DXd 5.6 mg/kg Prior OSI, PBC (N=44)
Confirmed ORR, % (95% CI)	39 (26-52)	39 (24-55)
Best overall response, n (%)		
CR	1 (2)	1 (2)
PR	21 (37)	16 (36)
SD, Non-CR/Non-PD	19 (33)	13 (30)
PD	9 (16)	8 (18)
Not evaluable	7 (12)	6 (14)
Disease control rate, % (95% CI)	72 (59-83)	68 (52-81)
Time to response, median (range), mo	2.6 (1.2-5.4)	2.7 (1.2-5.4)
Duration of response, median (95% CI), mo	6.9 (3.1-NE)	7.0 (3.1-NE)
PFS, median (95% CI), mo	8.2 (4.4-8.3)	8.2 (4.0-NE)

The subgroup of patients treated with prior **osimertinib (OSI)** and **platinum-based chemotherapy** demonstrated similar efficacy to the overall efficacy population

BICR, blinded independent central review; CR, complete response; NE, not evaluable; ORR, objective response rate; OSI, osimertinib; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Data cutoff: September 24, 2020.
[a] For patients treated with the recommended dose for expansion of HER3-DXd (N=57)

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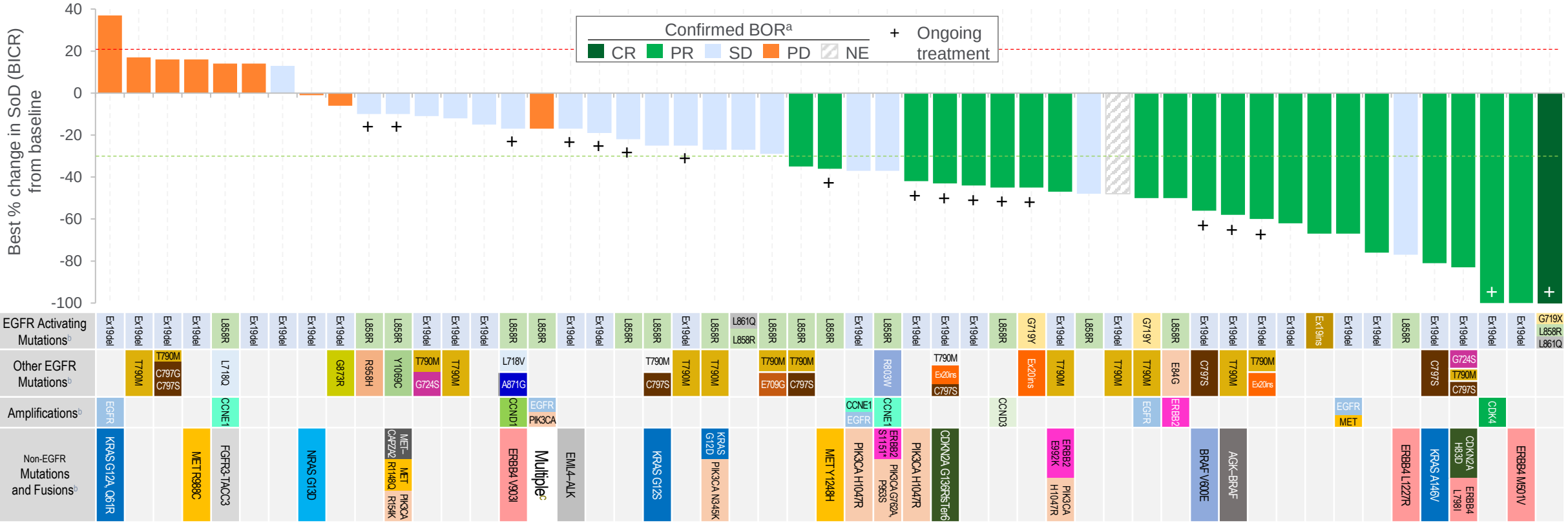
HER3-DXdはEGFR TKIに対して多様な耐性メカニズムを有する患者に対して有効性を示した

Confirmed ORR 39%

Median Duration of Response 6.9 months

Median PFS 8.2 months



Data cutoff: September 24, 2020.

[a] Six patients had BORs of NE due to no adequate post-baseline tumor assessment and are not shown; 1 had BOR of NE due to SD too early (< 5 weeks) and is shown with hatched markings [b] Genomic alterations known to be associated with EGFR TKI resistance identified in assays of tumor tissue/ctDNA in blood, collected prior to treatment with HER3-DXd. [c] CDKN2A A143V; PIK3CA E542K, E545K, E726K; ERBB2 K200N; ERBB3 Q847*, Q849*.

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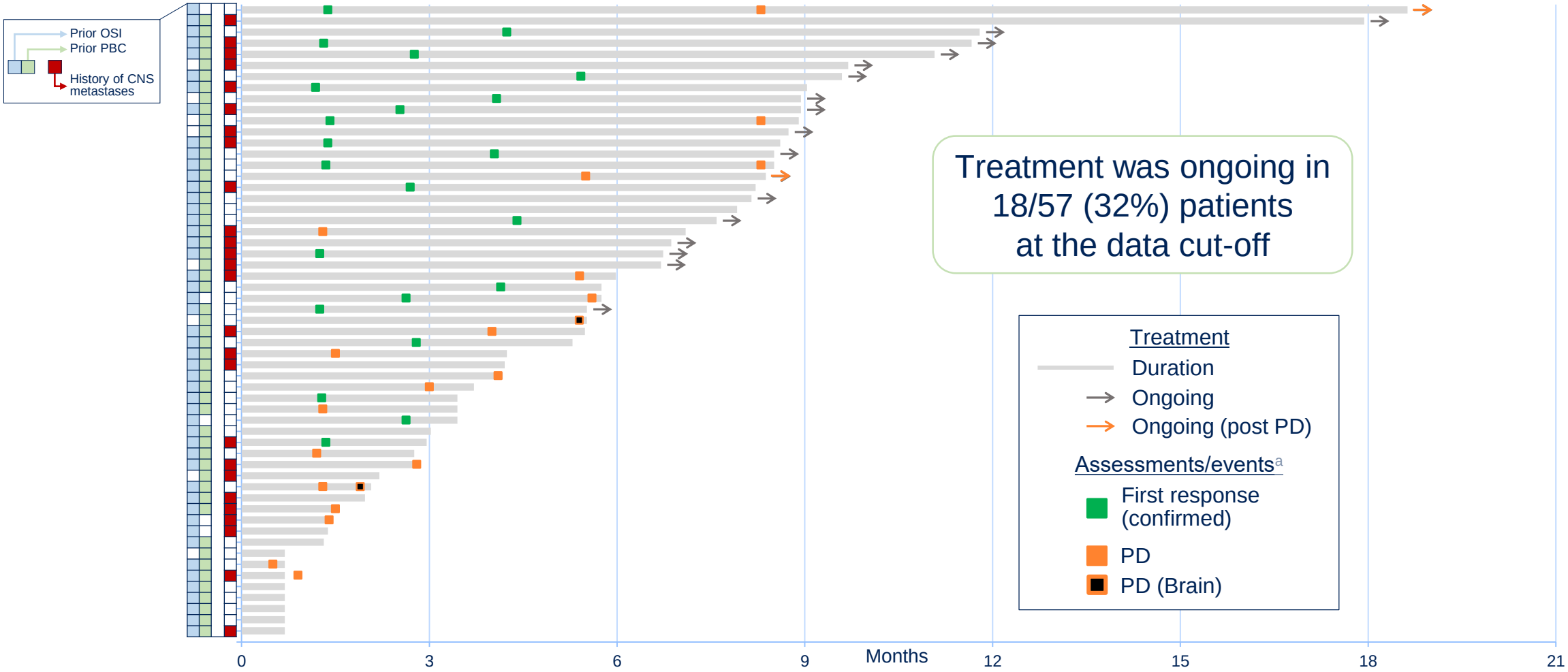
前治療の種類や脳転移歴の有無に関わらず持続的な有効性が確認された



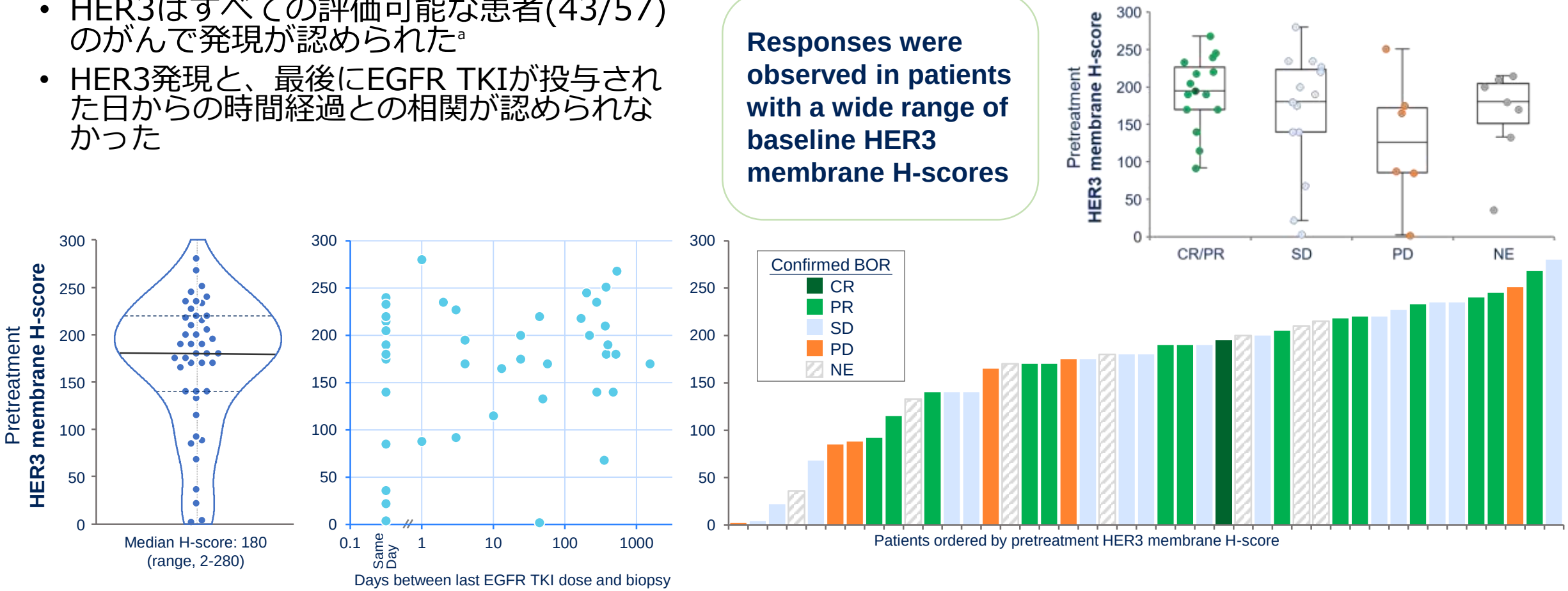
CR/PR, complete response/partial response; NE, not evaluable; OSI, osimertinib; PBC, platinum-based chemotherapy; PD, progressive disease; SD stable disease
Data cutoff: September 24, 2020; By blinded independent central review.
[a] First sign of confirmed response or PD.

ASCO2021

広範なベースラインでのHER3発現に対して奏効が観察された

- HER3はすべての評価可能な患者(43/57)のがんで発現が認められた[a]
- HER3発現と、最後にEGFR TKIが投与された日からの時間経過との相関が認められなかった

Responses were observed in patients with a wide range of baseline HER3 membrane H-scores



BOR, best overall response; CR/PR, complete response/partial response; NE, not evaluable; PD, progressive disease; SD stable disease.
Data cutoff: September 24, 2020; BOR by blinded independent central review.
[a] Immunohistochemistry analysis of membrane HER3 in pre-treatment biopsy tissue from patients subsequently receiving HER3-DXd 5.6 mg/kg (N=43; taken since progression on last treatment and within the 6 months prior to enrollment).

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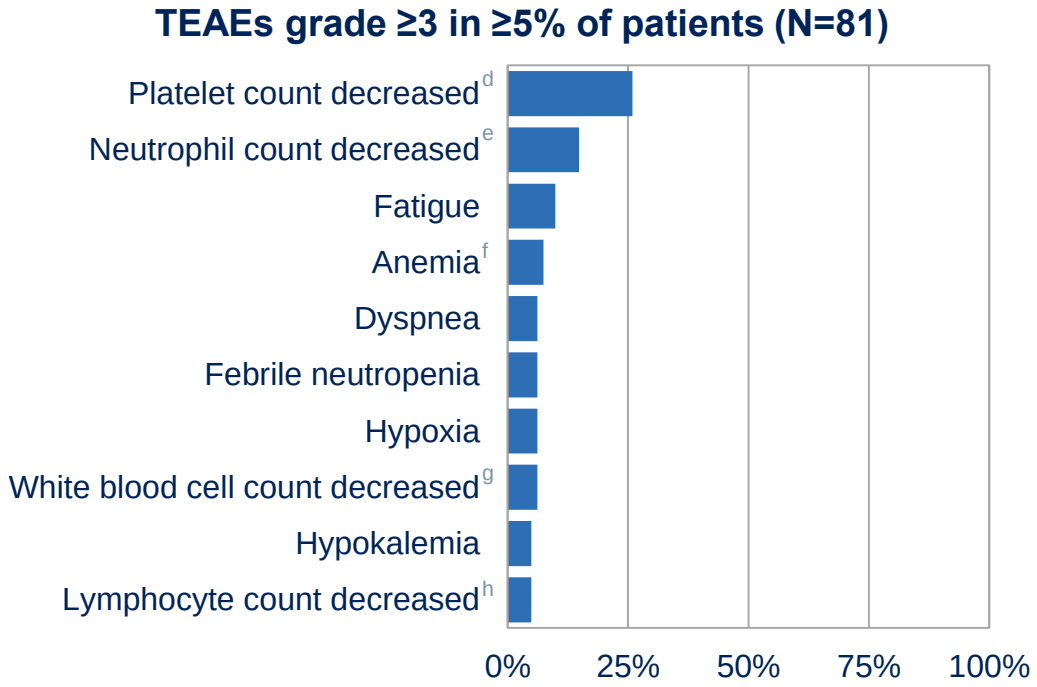
HER3-DXdは管理可能な安全性プロファイルを示し、有害事象による中止率が低かった

TEAEs, n (%) Median treatment duration: 5.7 (range, 0.7-28.3) mo	5.6 mg/kg (N=57)	All Doses (N=81)
Any TEAE	57(100)	81 (100)
Associated with treatment discontinuation[a]	6 (11)	7 (9)
Associated with treatment dose reduction	12 (21)	18 (22)
Associated with treatment dose interruption	21 (37)	30 (37)
Associated with death[b]	4 (7)	5 (6)
Grade ≥3 TEAE	42 (74)	52 (64)
Treatment-related TEAE:	55 (96)	78 (96)
Associated with death	0	0
Grade ≥3	31 (54)	38 (47)
Serious TEAE	12 (21)	15 (19)
Interstitial lung disease[c]	4 (7)	4 (5)
Grade 1	2 (4)	2 (2)
Grade 2	1 (2)	1 (1)
Grade 3	1 (2)	1 (1)
Grade 4/5	0	0



- The rate of adjudicated treatment-related interstitial lung disease was 5%; none were grade 4/5
- Median time to adjudicated onset of treatment-related interstitial lung disease was 53 (range, 13-130) days

Data cutoff: September 24, 2020.

[a] TEAEs associated with treatment discontinuation were fatigue (2); nausea, decreased appetite, interstitial lung disease, neutrophil count decreased, pneumonitis, and upper respiratory tract infection; none were for thrombocytopenia (1 each). [b] TEAEs associated with death were: disease progression (2), respiratory failure (2), and shock (1). [c] One additional occurrence of Grade 5 ILD was determined by adjudication to be unrelated to study treatment. [d] Includes thrombocytopenia. [e] Includes neutropenia. [f] Includes hemoglobin decreased. [g] Includes leukopenia. [h] Includes lymphopenia.

HER3-DXd: EGFR-TKI耐性EGFR変異 NSCLCにおけるアンメットメディカルニーズの充足

抗腫瘍効果	**臨床的意義のある持続的な有効性** (ORR, 39%; PFS中央値, 8.2か月) • 様々なEGFR TKI耐性機序を有する、治療困難な患者に対して有効性を示した • ベースラインのHER3発現量に関わらず抗腫瘍効果が認められた
安全性	**忍容性があり、管理可能な安全性プロファイル** • 有害事象による中止率が低い (7/81; 血小板減少による中止はなし) • 薬剤に関連するILDの発症率が低い (4/81; グレード4/5はなし)

この試験結果をもとにピボタル試験であるHERTHENA-Lung01を実施中

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HER3-DXd: 臨床開発計画 | NSCLC & その他がん

2021年6月現在			FY2020	FY2021	FY2022	計画中
NSCLC	EGFR変異	進行/転移性 3L~	Ph1 用量展開			
				HERTHENA-Lung01 単剤		
		進行/転移性 2L				
		進行/転移性 1L		オシメルチニブ併用 Ph1b		
大腸がん	ｵｰﾙｶﾏｰ	転移性 3L~	単剤			
乳がん	ｵｰﾙｶﾏｰ	転移性 3L~	単剤 Ph1/2			

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 下半期 の初めより表示

NSCLC: 非小細胞肺がん

本日の内容

1. 自己紹介
2. エンハーツ®: 新規データおよび開発計画
3. Dato-DXd: 新規データおよび開発計画
4. HER3-DXd: 新規データおよび開発計画
5. 今後のニュースフロー

FY2021 News Flow

2021年6月現在

学会発表予定

欧州血液学会(6月9日-17日)	
DS-3201	非ホジキンリンパ腫, Ph1 • 成人T細胞白血病/リンパ腫, 末梢性T細胞リンパ腫 データ (オーラル発表)
WCLC (Sep 8-14)	
Dato-DXd	TROPION-PanTumor01: Ph1 NSCLCコホート • 最新データ
ESMO (Sep 16-21)	
エンハーツ®	DESTINY-Lung01: HER2陽性/変異NSCLC, 2L, Ph2 • HER2変異コホート データ
DS-7300	固形がん Ph1 • Ph1 用量漸増 データ
DS-6000	非臨床薬理試験データ

上記アブストラクトのESMOでの採択は未定

承認見込み

DS-1647/G47Δ	悪性神経膠腫 • 日本: 2021年度 第1四半期
リクシアナ®	超高齢者心房細動 • 日本: 2021年度 第2四半期
エフィエント®	虚血性脳血管障害 • 日本: 2021年度 第3四半期

主要データの入手見込み

エンハーツ®	DESTINY-Breast03: HER2陽性乳がん, 2L, Ph3 • 2021年度 第2四半期 DESTINY-Lung01: HER2陽性/変異NSCLC, 2L, Ph2 • 2021年度 第2四半期 DESTINY-Breast04: HER2低発現乳がん, ポスト化学療法, Ph3 • 2021年度 第4四半期
キザルチニブ	QuANTUM-First: 急性骨髄性白血病, 1L, Ph3 • 2021年度 第3四半期

ピボタル試験の開始予定

エンハーツ®	DESTINY-Breast09: HER2陽性乳がん, 1L, Ph3 • 2021年6月（すでに開始） DESTINY-Gastric04: HER2陽性胃がん, 2L, Ph3 • 2021年度 上半期
DS-3201	末梢性T細胞リンパ腫, Ph2 • 2021年度 第1四半期

下線部: 2020年度 第4四半期からの追加またはアップデート

NSCLC: 非小細胞肺がん


第一三共グループは世界中の人々の
健康で豊かな生活に貢献してまいります



Appendix

Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with human epidermal growth factor receptor 2–positive advanced gastric cancer or gastroesophageal junction adenocarcinoma: final overall survival results from a randomized, multicenter, open-label, phase 2 study (DESTINY-Gastric01)

Kensei Yamaguchi

The Cancer Institute Hospital of JFCR, Tokyo, Japan June 2021

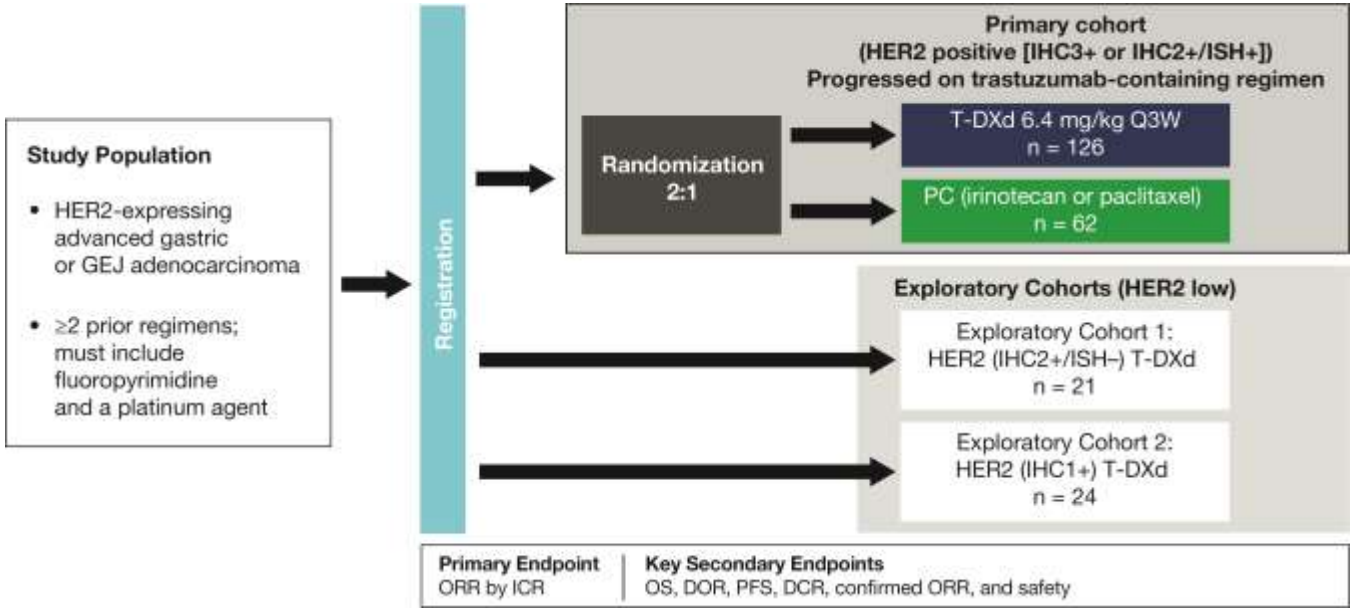
ON BEHALF OF THE DESTINY-Gastric01 INVESTIGATORS

Additional authors: Yung-Jue Bang, Satoru Iwasa, Naotoshi Sugimoto, Min-Hee Ryu, Daisuke Sakai, Hyun Cheol Chung, Hisato Kawakami, Hiroshi Yabusaki, Jeeyun Lee, Kaku Saito Yoshinori Kawaguchi, Takahiro Kamio, Akihito Kojima, Masahiro Sugihara, Kohei Shitara

Background and Study Design

- T-DXd is an antibody–drug conjugate comprising an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor payload (DXd)[1] approved in the United States and Japan for adult patients with advanced HER2+ gastric or GEJ adenocarcinoma[2,3]
- In the primary DESTINY-Gastric01 analysis, T-DXd exhibited statistically significant ORR and OS benefit vs standard chemotherapy
- Here, we present final OS results as well as updated efficacy and safety data
- Patients had a median of 2 prior lines of therapy (range, 2-9); 44.4% of patients had ≥3 previous lines
- As of June 3, 2020, 10 patients (8%) receiving T-DXd and no patients receiving PC remained on treatment

DESTINY-Gastric01 Study Design



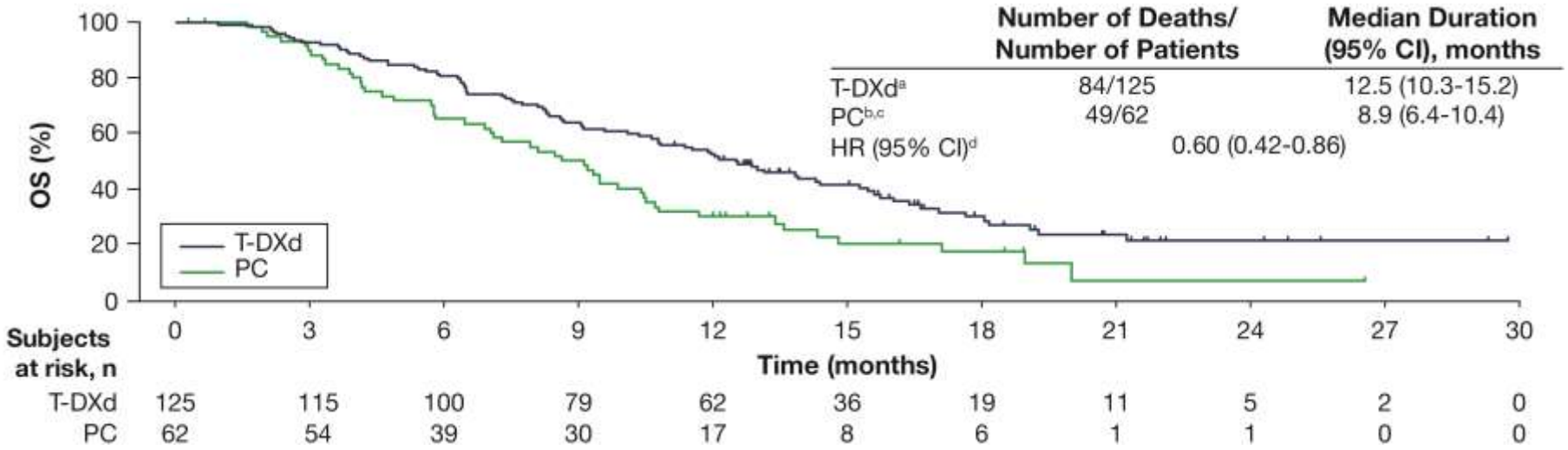
Key secondary endpoint of OS was to be statistically evaluated hierarchically if the primary endpoint was statistically significant

DCR, disease control rate; DOR, duration of response; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; ORR, objective response rate; OS, overall survival; PC, physician's choice; PFS, progression-free survival; Q3W, every three weeks; T-DXd, trastuzumab deruxtecan.

1. Shitara K et al. Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer. *N Engl J Med*. 2020;382:2419-2430. 2. Enhertu. Prescribing information. Daiichi Sankyo Inc.; 01/2021. 3. Enhertu. Summary of product characteristics. Daiichi Sankyo Co. LTD.; 2020.

Results: Overall Survival

Kaplan-Meier Analysis of Overall Survival



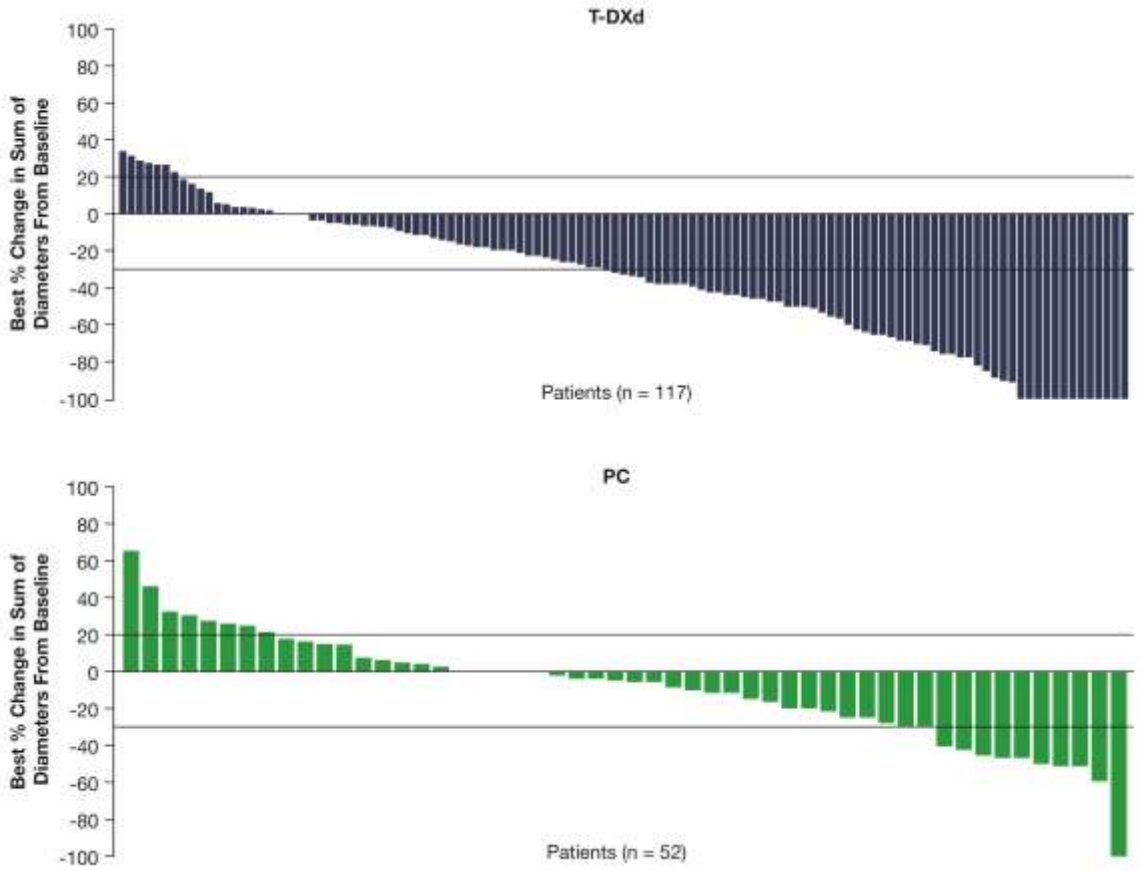
As in the primary analysis (101 OS events; 54.0% maturity), in this updated analysis (133 OS events; 71.1% maturity), T-DXd showed superior antitumor activity compared to PC

HR, hazard ratio; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.

Results: ORR and Other Efficacy Endpoints

	T-DXd n = 119	PC Overall n = 56
ORR (CR + PR) by ICR, n (%)[a]	61 (51.3) 95% CI, 41.9-60.5	8 (14.3) 95% CI, 6.4-26.2
	P < 0.0001[b]	
CR	11 (9.2)	0
PR	50 (42.0)	8 (14.3)
SD	42 (35.3)	27 (48.2)
PD	14 (11.8)	17 (30.4)
Not evaluable	2 (1.7)	4 (7.1)
Confirmed ORR (CR + PR) by ICR, n (%)[a]	50 (42.0) 95% CI, 33.0-51.4	7 (12.5) 95% CI, 5.2-24.1
CR	10 (8.4)	0
PR	40 (33.6)	7 (12.5)
SD	52 (43.7)	28 (50.0)
PD	14 (11.8)	17 (30.4)
Not evaluable	3 (2.5)	4 (7.1)
Confirmed DCR (CR + PR + SD), n (%)[a]	102 (85.7) 95% CI, 78.1-91.5	35 (62.5) 95% CI, 48.5-75.1
Confirmed DOR, median, months	12.5 95% CI, 5.6-NE	3.9 95% CI, 3.0-4.9
PFS, median, months	5.6 95% CI, 4.3-6.9	3.5 95% CI, 2.0-4.3
	P = 0.0003[c]	
TTR, median, months	1.5 95% CI, 1.4-1.7	1.6 95% CI, 1.3-1.7

Best Percentage Change from Baseline in Tumor Size for Individual



CR, complete response; DCR, disease control rate; DOR, duration of response; ICR, independent central review; NE, not estimable; ORR, objective response rate; PC, physician's choice; PD, progressive disease; PFS, progression-free response; PR, partial response; SD, stable disease; T-DXd, trastuzumab deruxtecan; TTR, time to response. [a]Includes data for the response-evaluable set: all randomized patients who received ≥1 dose of study drug and had measurable tumors based on ICR at baseline. [b]Comparison between T-DXd and PC overall using Cochran-Mantel-Haenszel test stratified by region. [c]Comparison between T-DXd and PC overall using stratified Log-rank test stratified by region.

Safety

- Grade ≥3 AEs occurred in 85.6% of T-DXd patients vs 56.5% with PC
  - The most common were decreased neutrophil count (51.2%, 24.2%), anemia (38.4%, 22.6%), and decreased white blood cell count (20.8%, 11.3%)
- 16 patients (12.8%) had T-DXd–related ILD, as determined by an independent adjudication committee
  - There were 13 grade 1 or 2, two grade 3, one grade 4, and no grade 5 events
  - There were four ILD events since the primary analysis; one grade 1 and three grade 2
  - Among the 16 total ILD events, the median time to first onset was 102.5 days (range, 36-638 days)
  - There were no ILD events in the PC arm
- There was one T-DXd-related death from pneumonia (non-ILD), as reported in the primary analysis
- There were no AE-related deaths in the PC arm

TEAEs in ≥20% of Patients Treated with T-DXd

	T-DXd n = 125			PC Overall n = 62		
	Grade			Grade		
Preferred Term, %	Any	3	4	Any	3	4
Neutrophil count decreased[b]	64.8	38.4	12.8	35.5	16.1	8.1
Nausea	63.2	5.6	0	46.8	1.6	0
Decreased appetite	60.8	16.8	0	45.2	12.9	0
Anemia[c]	57.6	38.4	0	30.6	21.0	1.6
Platelet count decreased[d]	40.0	9.6	1.6	6.5	1.6	1.6
White blood cell count decreased[e]	38.4	20.8	0	35.5	8.1	3.2
Malaise	34.4	0.8	0	16.1	0	0
Diarrhea	32.8	2.4	0	32.3	1.6	0
Vomiting	26.4	0	0	8.1	0	0
Pyrexia	24.8	0	0	16.1	0	0
Constipation	24.8	0	0	24.2	0	0
Lymphocyte count decreased[f]	23.2	7.2	4.8	3.2	0	1.6
Alopecia	22.4	0	0	14.5	0	0
Fatigue	21.6	7.2	0	24.2	3.2	0

AE, adverse event; ILD, interstitial lung disease; PC, physician's choice; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent AE.
No additional TEAEs were observed in ≥20% of patients receiving PC. [a]There were no grade 5 events. [b]Includes preferred terms "neutrophil count decreased" and "neutropenia." [c]Includes preferred terms "hemoglobin decreased," "red blood cell count decreased," "anemia," and "hematocrit decreased." [d]Includes preferred terms "platelet count decreased" and "thrombocytopenia." [e]Includes preferred terms "leukopenia" and "white blood cell count decreased." [f]Includes preferred terms "lymphocyte count decreased" and "lymphopenia."

Conclusions

- With continued follow-up after the primary analysis, T-DXd demonstrated clinically meaningful OS benefit (~40% reduced risk of death) and clinically relevant improvement in ORR compared with PC standard chemotherapy in HER2+ advanced gastric or GEJ cancer
- The overall safety profile of T-DXd was manageable and consistent with that of the primary analysis
  - The most common AEs were gastrointestinal or hematologic in nature
  - 16 patients (12.8%) had T-DXd-related ILD as determined by an independent adjudication committee. Most were grade 1 or 2
- Additional follow-up provides continued evidence that T-DXd is an effective treatment option for patients with HER2+ advanced gastric or GEJ adenocarcinoma who have progressed after ≥2 previous lines of therapy, including trastuzumab, fluoropyrimidine, and a platinum agent

AE, adverse event; GEJ, gastroesophageal junction; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; ORR, objective response rate; OS, overall survival; PC, physician's choice; T-DXd, trastuzumab deruxtecan.

Unmet Clinical Need for Approved Targeted Therapies in HER2-Positive Metastatic CRC

- **HER2 overexpression in mCRC**
  - CRC is the 3rd most common type of cancer and ≈25% of patients have metastatic CRC, of which around 2-3% of patients have HER2-amplified tumors
  - Current treatment options are fluoropyrimidine with oxaliplatin and/or irinotecan with an anti-VEGF compound or anti-EGFR monoclonal antibody (depending on the *RAS* mutational status)
  - Other therapies including regorafenib and trifluridine/tipiracil are recommended in the third-line or subsequent settings
    - Median OS was 6.4 months for regorafenib compared to 5.0 months for placebo and 7.1 months for trifluridine/tipiracil compared to 5.3 months for placebo
  - There are currently no approved HER2-targeted therapies for CRC

CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; mCRC, metatstatic colorectal cancer; OS, overall survival; VEGF, vascular endothelial growth factor.

ASCO2021 | DESTINY-CRC01

Baseline Characteristics

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Age, median (range), years	57.0 (27-79)	62.0 (37-78)	58.5 (43-79)	58.5 (27-79)
Female, %	52.8	33.3	38.9	46.5
Region, %				
Europe	52.8	60.0	50.0	53.5
Asia	28.3	20.0	44.4	30.2
North America	18.9	20.0	5.6	16.3
ECOG performance status, %				
0	69.8	53.3	50.0	62.8
1	30.2	46.7	44.4	36.0
2	0	0	5.6	1.2
Sum of target lesions, median, cm	8.1	8.1	10.2	9.0
Primary tumor site, %[a]				
Left	88.6	93.3	94.4	90.7
Right	11.4	6.7	5.6	9.3

ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
[a]Left: rectum, sigmoidal, descending; Right: cecum, ascending, transverse.

Baseline Characteristics (cont)

	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Microsatellite status, %[a]				
MSI-H	0	0	0	0
Microsatellite stable	81.1	93.3	66.7	80.2
Unknown	18.9	6.7	33.3	19.8
***RAS* wild type, %[a,b]**	98.1	93.3	100	97.7
***BRAF*^{V600E} wild type, %[a,c]**	100	100	94.4	98.8
HER2 status, %[d]				
IHC 3+	75.5	0	0	46.5
IHC 2+	24.5	100	0	32.6
IHC 1+	0	0	100	20.9
ISH+	98.1[e]	0	22.2	65.1
ISH–	0	100	77.8	33.7

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; MSI-H, microsatellite instability status-high.
[a]By local assessment. [b]1 patient cohort A had an *NRAS* mutation; 1 patient in cohort B was not examined. [c]1 patient in cohort C was not examined. [d]By central assessment. Sums may not total 100% due to rounding. [e]1 patient was non-evaluable for ISH testing.

Prior Treatments

Prior Treatment, %	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
Irinotecan	100	100	100	100
Fluorouracil / capecitabine	100 / 54.7	93.3 / 46.7	100 / 55.6	98.8 / 53.5
Oxaliplatin	100	93.3	100	98.8
Cetuximab or panitumumab	100	100	94.4	98.8
Bevacizumab	75.5	73.3	83.3	76.7
Prior anti-HER2 agents	30.2	0	0	18.6

- Median prior regimens for metastatic disease was 4 (range, 2–11)

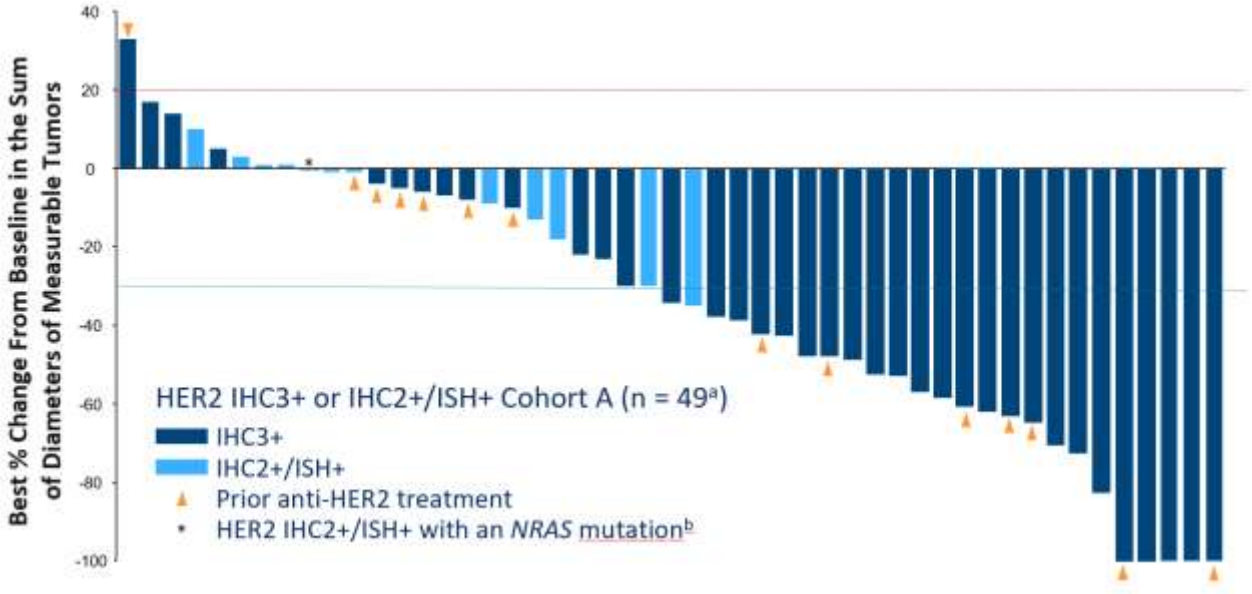
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.

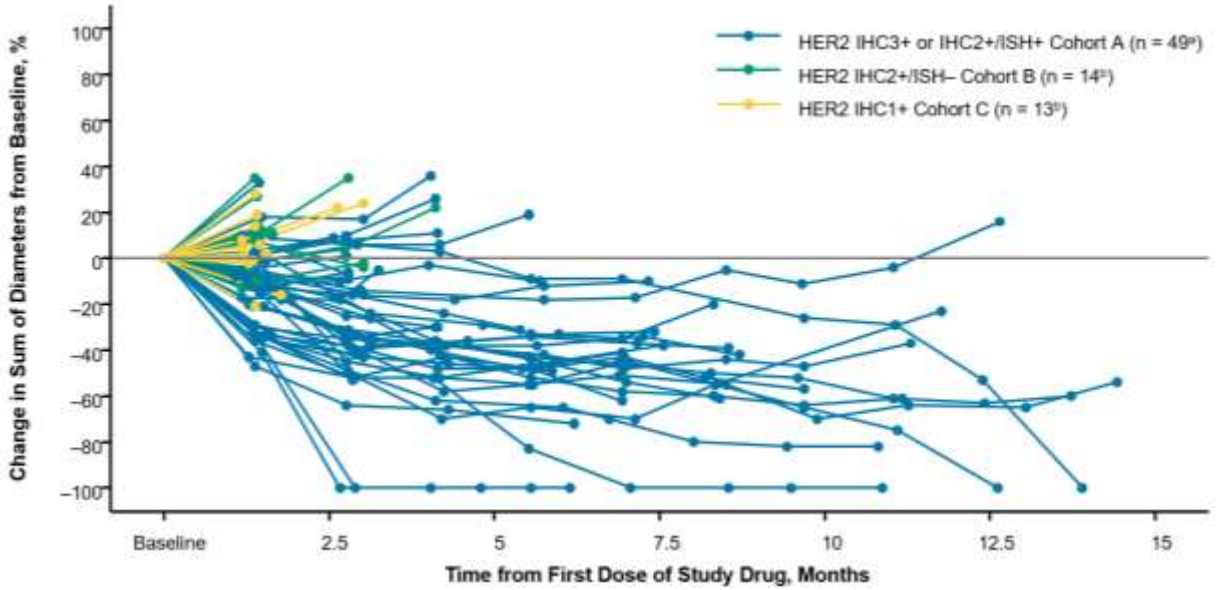
Overall Safety Summary

n (%)	HER2 IHC3+ or IHC2+/ISH+ Cohort A (n = 53)	HER2 IHC2+/ISH– Cohort B (n = 15)	HER2 IHC1+ Cohort C (n = 18)	Overall (N = 86)
TEAEs	53 (100)	15 (100)	18 (100)	86 (100)
Grade 3 or above	35 (66.0)	7 (46.7)	14 (77.8)	56 (65.1)
Drug-related TEAEs	51 (96.2)	15 (100)	15 (83.3)	81 (94.2)
Grade 3 or above	29 (54.7)	4 (26.7)	9 (50.0)	42 (48.8)
Serious TEAEs	20 (37.7)	6 (40.0)	9 (50.0)	35 (40.7)
Drug-related serious TEAEs	12 (22.6)	2 (13.3)	2 (11.1)	16 (18.6)
TEAEs leading to drug discontinuations	8 (15.1)	2 (13.3)	3 (16.7)	13 (15.1)
Drug-related TEAEs leading to drug discontinuations	4 (7.5)	2 (13.3)	1 (5.6)	7 (8.1)
TEAEs leading to dose reduction	11 (20.8)	0	4 (22.2)	15 (17.4)
Drug-related TEAEs leading to dose reduction	10 (18.9)	0	4 (22.2)	14 (16.3)
TEAEs leading to drug interruption	26 (49.1)	3 (20.0)	5 (27.8)	34 (39.5)
Drug-related TEAEs leading to drug interruption	19 (35.8)	1 (6.7)	3 (16.7)	23 (26.7)
TEAEs associated with death	5 (9.4)	2 (13.3)	2 (11.1)	9 (10.5)
Drug-related TEAEs associated with death[a]	2 (3.8)	1 (6.7)	0	3 (3.5)

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; TEAE, treatment-emergent adverse events.
[a]3 drug-related TEAEs associated with death were 3 fatal ILDs adjudicated as drug-related.

Change in Tumor Size in Cohort A





HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization.
The line at 20% indicates progressive disease. The line at -30% indicates partial response. [a]4 patients from the full analysis set were excluded since 1 patient had no measurable target lesion and 3 patients had no postbaseline data. [b]By local assessment.

[a]4 patients from the full analysis set were excluded since 1 patient had no measurable target lesion and 3 patients had no postbaseline data. [b]1 patient from cohort B and 5 patients from cohort C had missing postbaseline data.
Adapted from *The Lancet Oncology*, Siena S et al. Trastuzumab deruxtecan (DS-8201) in patients with HER2-expressing metastatic colorectal cancer (DESTINY-CRC01): a multicentre, open-label, phase 2 trial. 2021, with permission from Elsevier.

Conclusions

- **T-DXd monotherapy at the 6.4 mg/kg Q3W dose showed promising activity and durability with longer-term follow-up (additional 35.3 weeks from the primary analysis) in patients with HER2+ mCRC**
  - For cohort A, confirmed ORR was 45.3% (95% CI, 31.6–59.6), mDOR was 7.0 months (95% CI, 5.8–9.5), mPFS was 6.9 months (95% CI, 4.1-8.7), and mOS was 15.5 months (95% CI, 8.8–20.8)
- **No responses for ORR were observed in cohorts B and C**
- **The safety profile is consistent with the known safety profile of T-DXd**
  - Low grade gastrointestinal and hematologic AEs were most common[1]
  - ILD/pneumonitis (9.3% of patients; 3.5% grade 5) is an important risk and requires careful monitoring and prompt intervention
- **These promising results support continued exploration of T-DXd in patients with HER2+ mCRC**

AE, adverse events; ECOG PS, Eastern Cooperative Oncology Group performance status; HER2, human epidermal growth factor receptor 2; ILD, interstitial lung disease; mCRC, metastatic colorectal cancer; mDOR, median duration of response; mOS, median overall survival; ORR, objective response rate; q3w, every three weeks; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse events.

1. Siena S et al. *Lancet Oncol*. 2021;S1470-2045(21)00086-3.

Introduction

- BEGONIA (NCT03742102) is an ongoing 2 part, multicenter, multiarm, open-label platform study evaluating safety and efficacy of durvalumab + paclitaxel (D+P) and durvalumab with or without paclitaxel (P) combined with novel therapies as first-line (1L) treatment for metastatic TNBC.

Objectives

- Determine initial safety, tolerability, and efficacy of the combination of durvalumab with other therapies of known or potential efficacy in patients with metastatic TNBC enrolled in Part 1 of the BEGONIA study
- Here we present preliminary results from Arm 6 (durvalumab + trastuzumab deruxtecan)

Methods

- The first 6 patients treated with D+T-DXd were evaluated for dose-limiting toxicities (DLTs), with additional patients enrolled if D+T-DXd was tolerated.
- Tumors were assessed every 8 weeks for D+P or every 6 weeks for D+T-DXd per RECIST 1.1.
- HER2-low expression was determined by local testing and defined as immunohistochemistry (IHC) score 1+ or 2+ and in situ hybridization (ISH) negative or untested.
- PD-L1 expression was assessed retrospectively by IHC using an SP263-based assay.
- An exploratory analysis using an area-based scoring algorithm was employed. PD-L1 expression was defined as the proportion of the tumor area populated by tumor cells or immune cells with membranous PD-L1 staining.*
- A sample was considered positive if it demonstrated ≥5% PD-L1 expression.
- **Study arms were noncomparable due to differing eligibility criteria, treatment periods, and data maturity.**

* Optimal scoring algorithms and cutoffs for PD-L1 expression that are relevant to durvalumab treatment for metastatic TNBC have not yet been established.

ARM 1: Durvalumab + Paclitaxel

Arm 1: Patient Disposition and Characteristics (N=23)

- As of the data cutoff of September 2020, 23 patients received D+P with 7 still on treatment.
  - 2 patients discontinued D+P due to an AE.
  - 16 discontinued due to disease progression.
  - 2 of these patients discontinued for >1 reason.
- Median (range) follow-up time: 16.6 (8.5–19.8) months.

Characteristic	
Age, median (range), years	52 (30–63)
Race	
Asian	18 (78.3)
White	4 (17.4)
Other	1 (4.3)
No prior treatment	6 (26.1)
Prior treatments for early-stage disease	
Radiotherapy	15 (65.2)
Cytotoxic chemotherapy	17 (73.9)
Taxane	14 (60.9)
Anthracycline	15 (65.2)
Platinum compound	4 (17.4)
Hormonal therapy	1 (4.3)
Targeted therapy	1 (4.3)
Visceral metastases[a]	17 (73.9)
Lymph node metastases	16 (69.6)
PD-L1 expression ≥5%	
TIP ≥5% (positive)	7 (30.4)
TIP <5% (negative)	14 (60.9)
Missing	2 (8.7)

Data cutoff September 2020. n (%) unless otherwise stated.
[a]Visceral metastases is defined as liver/hepatic and/or respiratory metastases.
PD-L1, programmed death ligand-1.

Arm 1: Safety Summary (N=23)

- **Grade 3/4 AEs were mainly hematologic; the most frequent was decreased neutrophil count (n=4, 17.4%)**

	n (%)
Any AE	22 (95.7)
Common AEs (≥20% patients, any grade)	
Alopecia	14 (60.9)
Peripheral sensory neuropathy	13 (56.5)
Nausea	10 (43.5)
Rash	9 (39.1)
Fatigue, neutrophil count decreased	8 (34.8) each
Peripheral edema	7 (30.4)
Hypothyroidism, myalgia	6 (26.1) each
ALT increased, nail discoloration, pruritus	5 (21.7) each
Any Grade 3/4 AE	10 (43.5)
Any SAE	1 (4.3)
Any treatment-related AE	22 (95.7)
Any AESI for durvalumab	11 (47.8)
AE leading to death	0
AE leading to dose interruption	13 (56.5)
Any durvalumab dose delay	7 (30.4)

Arm 1: Safety Summary (N=23), cont'd

Grade 3/4 AEs

Preferred term	n (%)
Hematological	
Neutrophil count decreased	4 (17.4)
WBC count decreased	1 (4.3)
Febrile neutropenia	1 (4.3)
Neutropenia	1 (4.3)
Gastrointestinal	
Diarrhea	1 (4.3)
Stomatitis	1 (4.3)
Others	
Rash	1 (4.3)
ALT increased	1 (4.3)
AST increased	1 (4.3)
Neuropathy peripheral	1 (4.3)
Peripheral sensory neuropathy	1 (4.3)
Hypokalemia	1 (4.3)
Pneumonitis	1 (4.3)

Data cutoff September 2020.

Additional AE Details

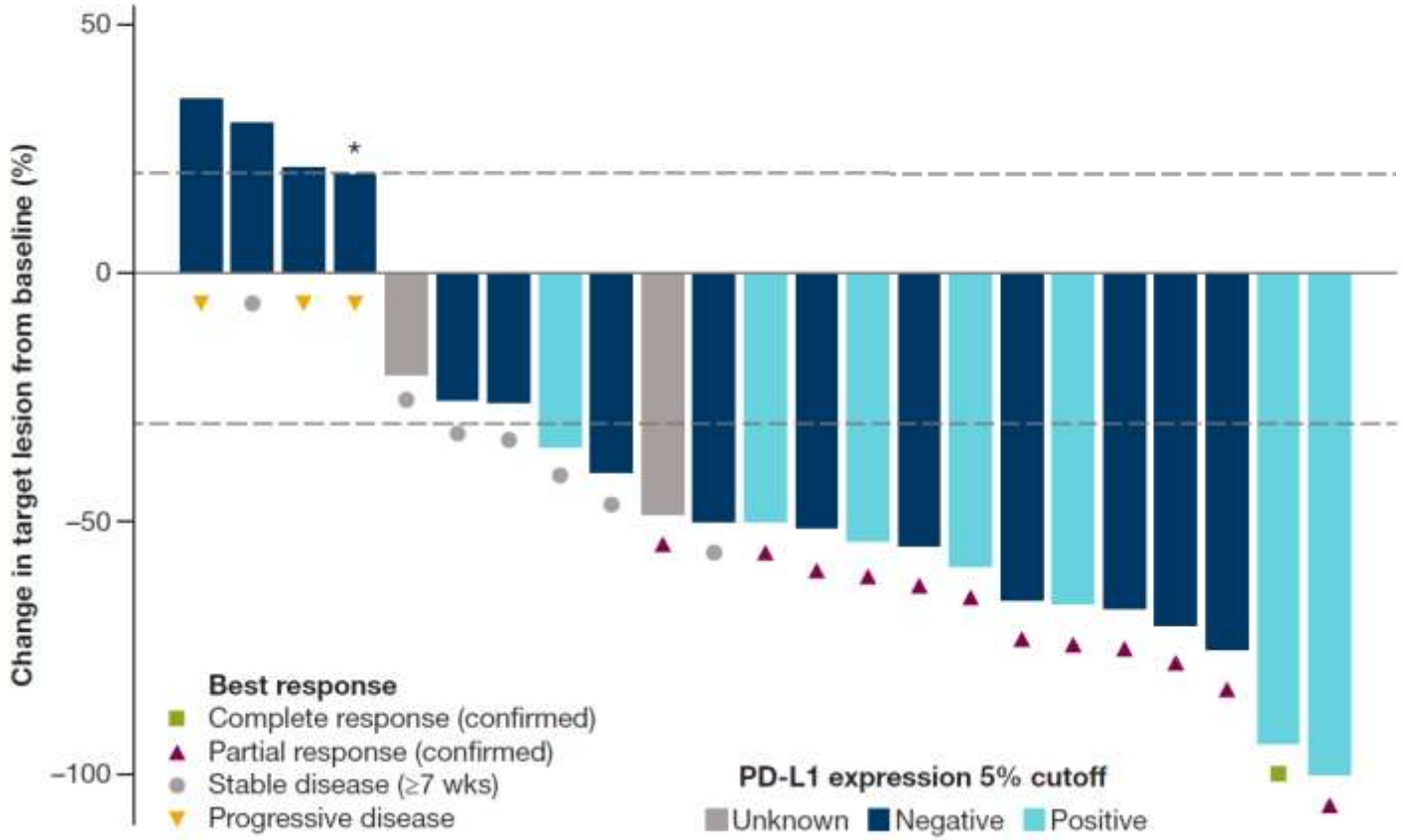
Any Grade 3/4 AE	10 (43.5)
Any SAE	1 (4.3)
Any treatment-related AE	22 (95.7)
Related to durvalumab only	11 (47.8)
Related to paclitaxel only	21 (91.3)
Any AESI for durvalumab	11 (47.8)
Rash	9 (39.1)
Hypothyroidism	6 (26.1)
Diarrhea	3 (13.0)
Hyperthyroidism	1 (4.3)
Pneumonitis	1 (4.3)
AE leading to death	0
AE leading to dose interruption	13 (56.5)
Any durvalumab dose delay	7 (30.4)

Data cutoff September 2020.

Arm 1: Best change from baseline of target tumor size

- In this small population, responses occurred for both PD-L1–positive (confirmed ORR 6/7 [85.7%]) and PD-L1–negative (confirmed ORR 6/14 [42.9%]) groups

Parameter	D+P
Response evaluable analysis set, N‡	23
Confirmed ORR,‡ n (%) 95% CI Complete response, n (%) Partial response, n (%)	13 (56.5) 34.5, 76.8 1 (4.3) 12 (52.2)
Unconfirmed ORR, n (%) 95% CI	16 (69.6) 47.1, 86.8
Stable disease, n (%)	7 (30.4)
Progressive disease, n (%)	3 (13.0)

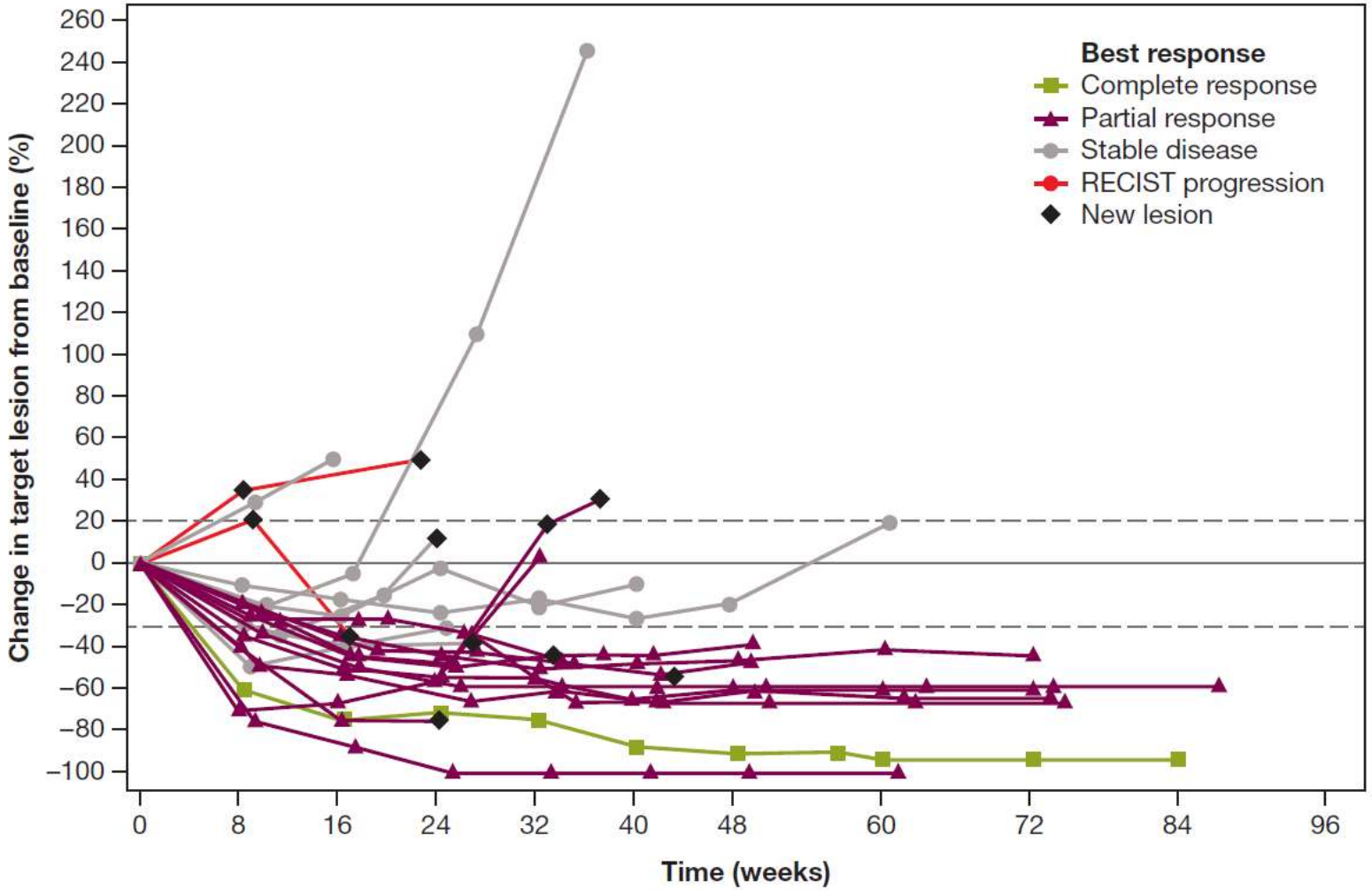


* If the best percentage change from baseline of target lesions cannot be calculated due to progression, withdrawal or death, the value is imputed at +20%

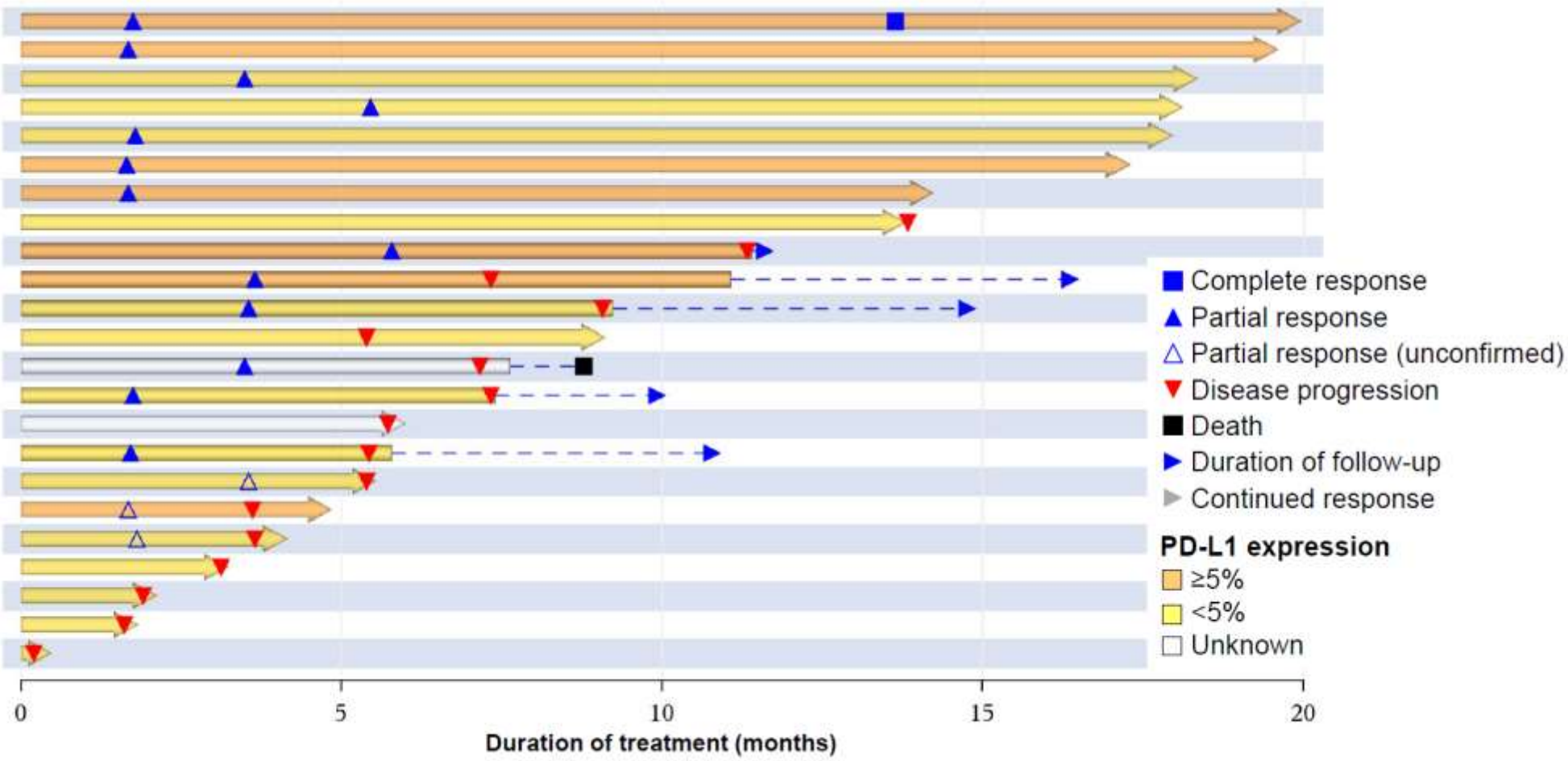
‡ Number of subjects that had the opportunity to complete at least two on-treatment disease assessments or have PD or death

Arm 1: Change from baseline in target tumor size over time

- A total of 7/13 (53.8%) patients remained in response at the time of data cutoff



Arm 1: Treatment Exposure & Duration of Response (N=23)

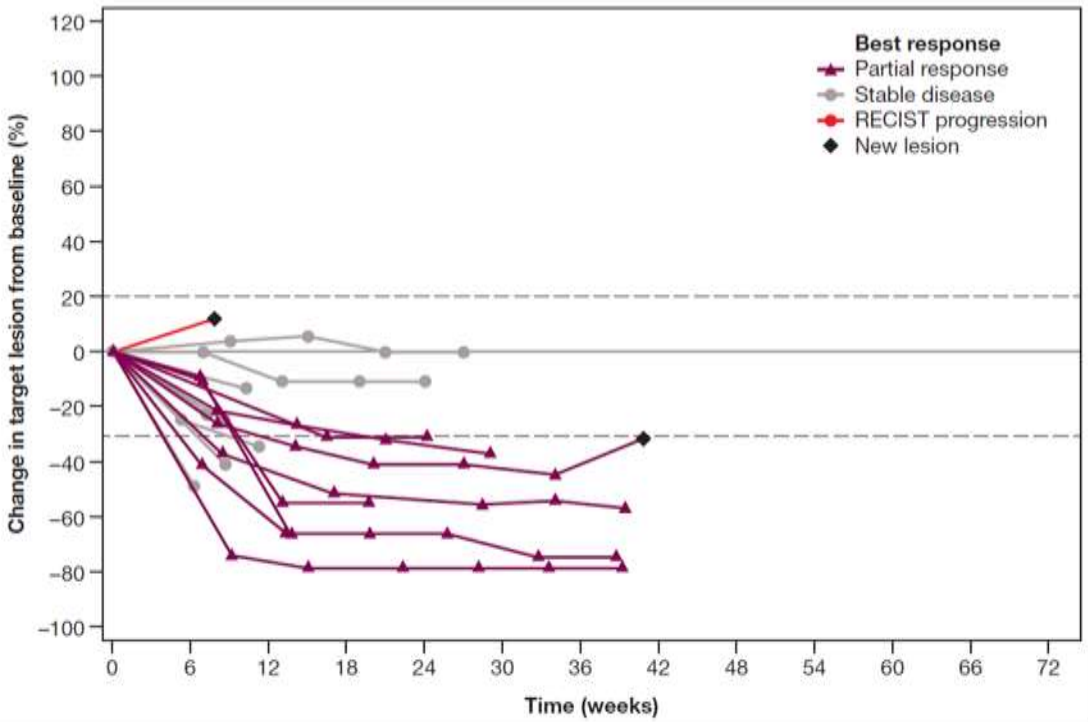


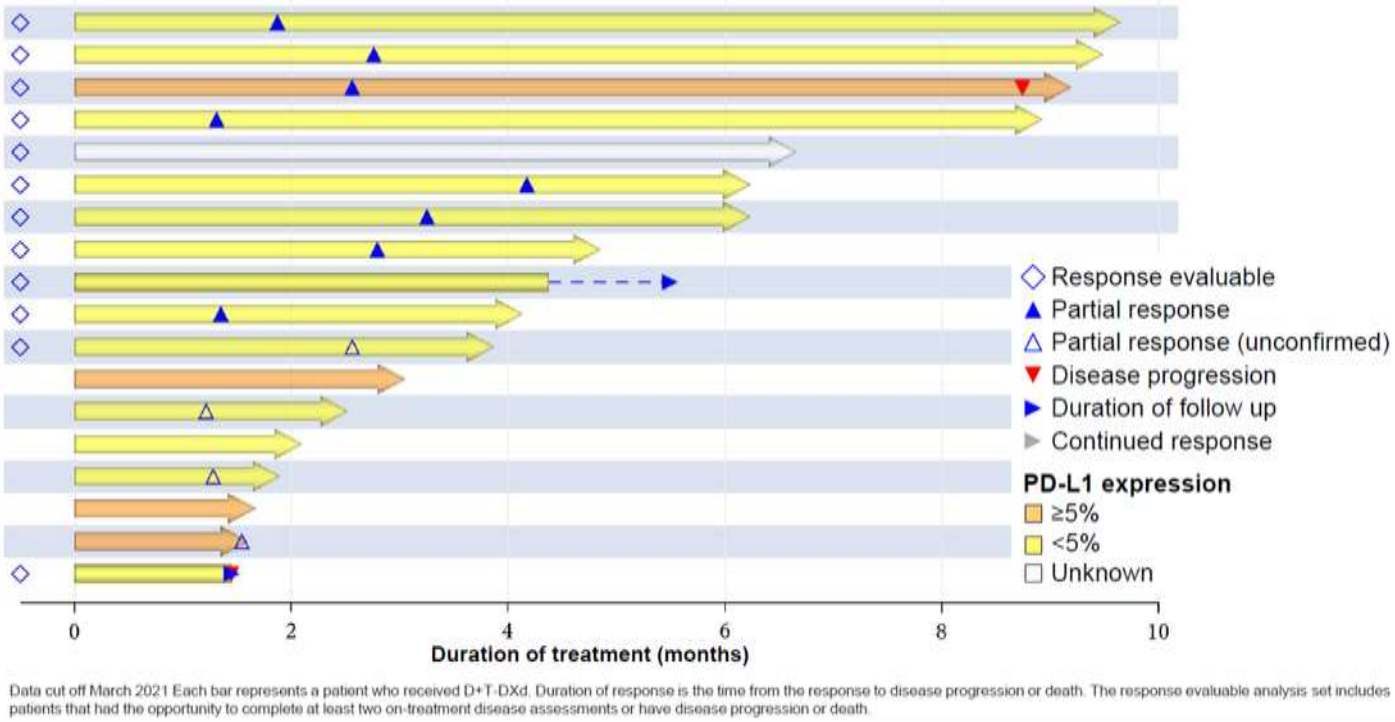
Data cutoff September 2020. Each bar represents a patient who received D+P. Duration of response is the time from the response to disease progression or death.

Arm 1 Conclusions: Durvalumab + Paclitaxel

- Acceptable safety/tolerability profile and demonstrates a response rate (confirmed ORR 56.5%) consistent with published data for 1L TNBC IO/taxane combination studies.
  - This was also consistent for patients with positive PD-L1 expression.
- Responses were observed regardless of PD-L1 expression (5% cutoff).
- Responses were durable with 53.8% of patients remaining in response for 12 months.

Arm 6: Change in target lesion & duration of treatment





Data cut off March 2021 Each bar represents a patient who received D+T-DXd. Duration of response is the time from the response to disease progression or death. The response evaluable analysis set includes patients that had the opportunity to complete at least two on-treatment disease assessments or have disease progression or death.

- **A total of 7/8 (87.5%) patients remained in response at the time of data cutoff**

Arm 6: Patient Disposition and Characteristics (N=21)

- As of the data cutoff of March 2021, 21 patients received D+T-DXd with 19 still on treatment.
- Median (range) follow-up time: 3.6 (0–9) months.

Characteristic	
Age, median (range), years	58 (35–81)
Race	
Asian	6 (28.6)
White	13 (61.9)
Black/African American	2 (9.5)
No prior treatment	4 (19.0)
Prior treatments for early-stage disease	
Radiotherapy	13 (61.9)
Cytotoxic chemotherapy	15 (71.4)
Taxane	11 (52.4)
Anthracycline	15 (71.4)
Platinum compound	7 (33.3)
Hormonal therapy	5 (23.8)
Visceral metastases[a]	17 (80.9)
Lymph node metastases	12 (57.1)
PD-L1 expression	
TIP ≥5% (positive)	6 (28.6)
TIP <5% (negative)	13 (61.9)
Missing	2 (9.5)
HER2 status per local testing	
IHC 2+/ISH–	6 (28.6)
IHC 1+/ISH–	2 (9.5)
IHC 1+/ISH untested	13 (61.9)

Data cutoff March 2021. n (%) unless otherwise stated.
[a]Visceral metastases is defined as liver/hepatic and/or respiratory metastases.

Arm 6: Safety Summary (N=21), cont'd

Grade 3/4 AEs

Preferred term	n (%)
Hematological	
Neutropenia	4 (19.0)
Anemia	3 (14.3)
Thrombocytopenia	2 (9.5)
Platelet count decreased	1 (4.8)
Hemolysis	1 (4.8)
Gastrointestinal	
Ascites	1 (4.8)
Diarrhea	1 (4.8)
Other	
Hypophosphatemia	2 (9.5)
Hyponatremia	2 (9.5)
CMV viremia	1 (4.8)
COVID-19	1 (4.8)
Decreased appetite	1 (4.8)
Fatigue	1 (4.8)
Lipase increased	1 (4.8)
Pneumonitis	1 (4.8)
Transaminases increased	1 (4.8)

Data cutoff March 2021.

Additional AE Details

Any Grade 3/4 AE	8 (38.1)
Any SAE	5 (23.8)
Any treatment-related AE	20 (95.2)
Related to durvalumab only	7 (33.3)
Related to T-DXd only	16 (76.2)
Related to both	13 (61.9)
Any AESI for durvalumab	11 (52.4)
Hypothyroidism	5 (23.8)
Diarrhea	4 (19.0)
Hyperthyroidism	3 (14.3)
Rash	3 (14.3)
Pneumonitis	2 (9.5)
Ulcerative Colitis	1 (4.8)
Thyroiditis	1 (4.8)
Urticaria	1 (4.8)
Any AESI for T-DXd	2 (9.5)
Pneumonitis	2 (9.5)
Troponin increased	1 (4.8)
AE leading to death	0
AE leading to dose interruption	7 (33.3)
Any durvalumab dose delay	9 (42.9)
Any T-DXd dose delay	9 (42.9)
T-DXd dose reduction	5 (23.8)

Data cutoff March 2021.

TRASTUZUMAB DERUXTECAN (T-DXD) IN PATIENTS WITH HER2+ METASTATIC BREAST CANCER WITH BRAIN METASTASES: A SUBGROUP ANALYSIS OF THE DESTINY-BREAST01 TRIAL

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On behalf of the investigators

Background

- Here we describe a subgroup analysis from the ongoing DESTINY- Breast01 study, analyzing the efficacy of T-DXd in patients with a history of brain metastases

Methods

- Patients with brain metastases who were treated, asymptomatic, and did not require therapy to control symptoms were eligible for enrollment
  - All treatment to control symptoms of brain metastases, including radiation, surgery, or other therapy (including steroids or anticonvulsants), had to be completed more than 60 days before randomization
- For patients with brain metastases at baseline, brain lesions were monitored by CT or MRI
  - A CT or MRI scan of the brain was required every 6 weeks in these patients
  - All measurements for brain lesions were retrospectively reported by the investigators
- The CNS subgroup included patients with a history of brain metastases who received T-DXd at the approved dose of 5.4 mg/kg every 3 weeks; CNS responses were analyzed among patients in the CNS subgroup who had brain lesions at baseline1

Baseline Characteristics & Clinical Activity Outcomes

Baseline Characteristics[9]

	CNS subgroup (n=24)	All patients (N=184)
Age, median (range), years	58.0 (33-85)	55.0 (28-96)
Female, %	100	100
Region, %		
Asia	37.5	34.2
Europe	37.5	37.0
North America	25.0	28.8
ECOG performance status, %		
0	62.5	55.4
1	37.5	44.0
2	0	0.5
HR status, %		
Positive	37.5	52.7
Negative	58.3	45.1
Unknown	4.2	2.2
HER2 expression, %[a]		
IHC 3+	79.2	83.7
IHC 2+; ISH+	20.8	15.2
IHC 1+; ISH+	0	1.1
Presence of visceral disease, %	100	91.8
Prior CNS treatment, %[b]		
Radiotherapy only	54.2	
Surgery only	4.2	
Radiotherapy + surgery	20.8	
None reported	20.8	

Clinical Activity Outcomes of T-DXd[1]

Intent-to-treat analysis	CNS subgroup (n=24)	All patients (N=184)
Confirmed ORR by ICR, n (%)	**14 (58.3)** (95% CI, 36.6-77.9)	**112 (60.9)** (95% CI, 53.4-68.0)
CR	1 (4.2)	11 (6.0)
PR	13 (54.2)	101 (54.9)
SD	8 (33.3)	67 (36.4)
PD	1 (4.2)	3 (1.6)
Not evaluable	1 (4.2)	2 (1.1)
Duration of response (CR or PR), median	16.9 months (95% CI, 5.7-16.9)	14.8 months (95% CI, 13.8-16.9)

- Efficacy of T-DXd in the CNS subgroup was comparable to that of the overall population
- In the overall population, 4 of 184 (2.2%) patients had CNS progression events
  - In the CNS subgroup, 2 of 24 (8.3%) patients had CNS progression events occur at 78 and 85 days
  - In the non-CNS subgroup, 2 of 160 (1.3%) patients without a history of CNS metastases had CNS progression events occur at 323 and 498 days

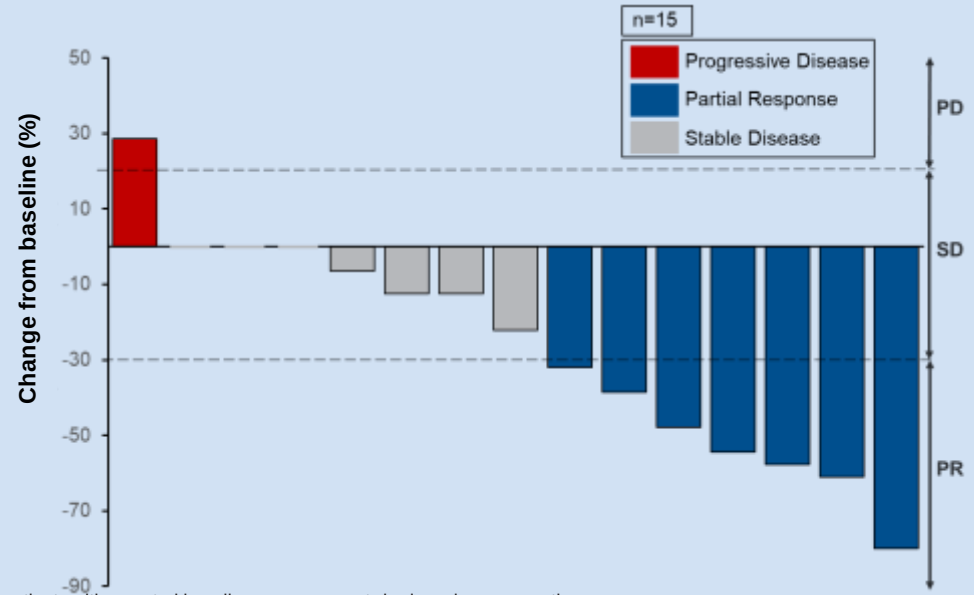
CNS, central nervous system; CR, complete response; ECOG, Eastern Cooperative Oncology Group; HR, hormone receptor; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease
Data cutoff: August 1, 2019.

1. Jerusalem G, et al. Presented at: European Society for Medical Oncology Breast Cancer 2020 Virtual Meeting. Abstract 138O.

CNS Response

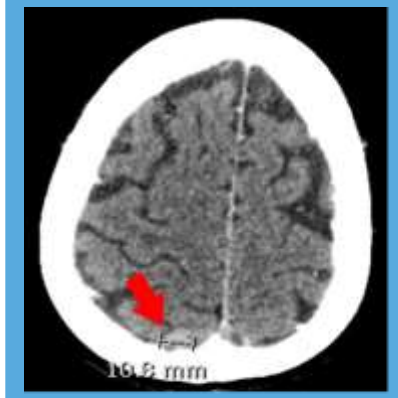
Best Response in Brain Lesions in Patients in the CNS Subgroup

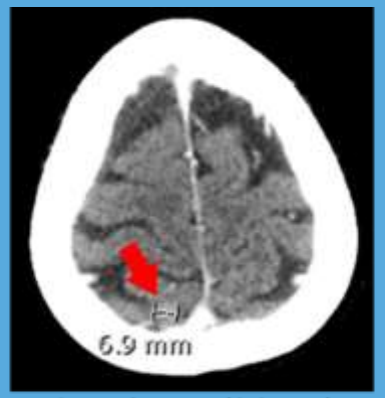
- Of 24 patients in the CNS subgroup, 17 had brain lesions at baseline; data were available to evaluate responses in the brain for 15 of these 17 patients
  - Of the 15 patients, 13 completed radiotherapy at least 60 days prior to randomization, which could have contributed to continued shrinkage in brain metastases during the study
- Per investigator assessment, 7of 17 patients (41.2%) had a reduction in brain lesion diameters consistent with a best response of PR in the brain



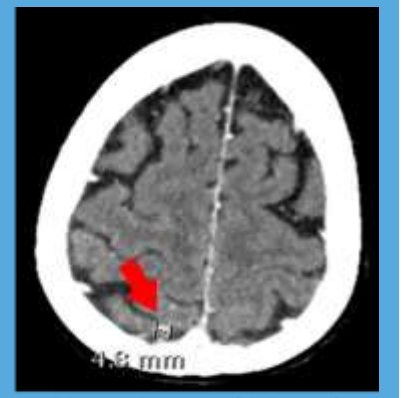
3 patients with reported baseline measurements had no change over time.
2 patients with brain metastases at baseline did not have sufficient data to evaluate response in the brain and are not shown.

Example Brain Scans


Baseline scan (10.6 mm)



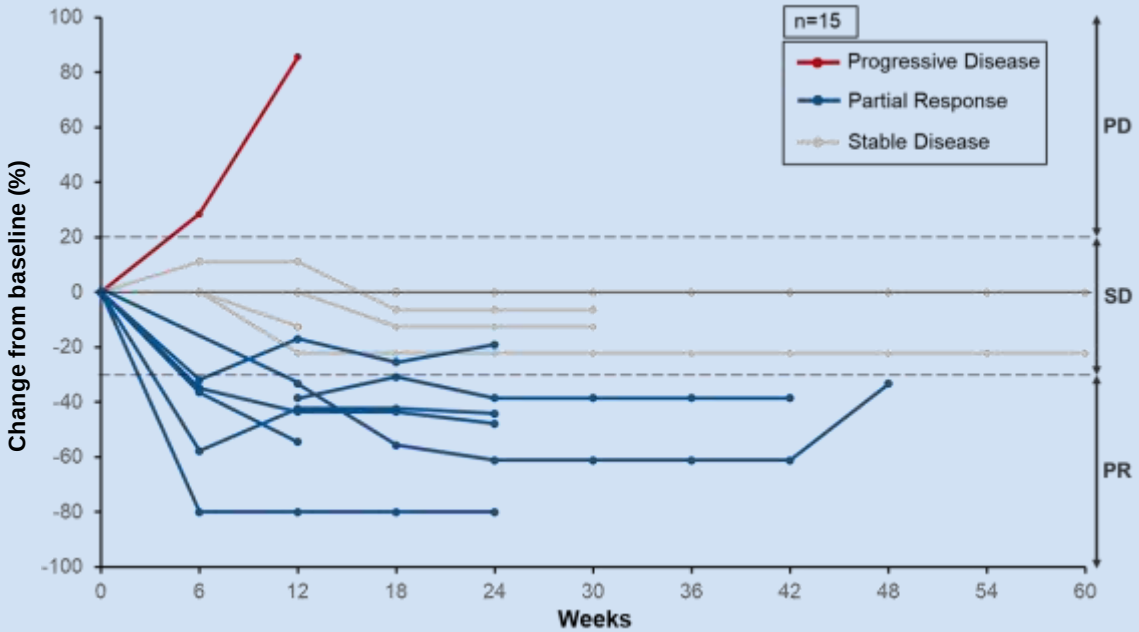
6-week scan (6.9 mm)
35% reduction


12-week scan (4.6 mm)
57% reduction

- Patient with HER2+ (IHC3+)/HR-negative mBC
- Prior brain lesion treatment included:
  - Whole-brain radiotherapy 5 years prior to enrollment
  - Stereotactic radiosurgery 3 years prior to enrollment
- This patient experienced tumor shrinkage consistent with a PR in the brain

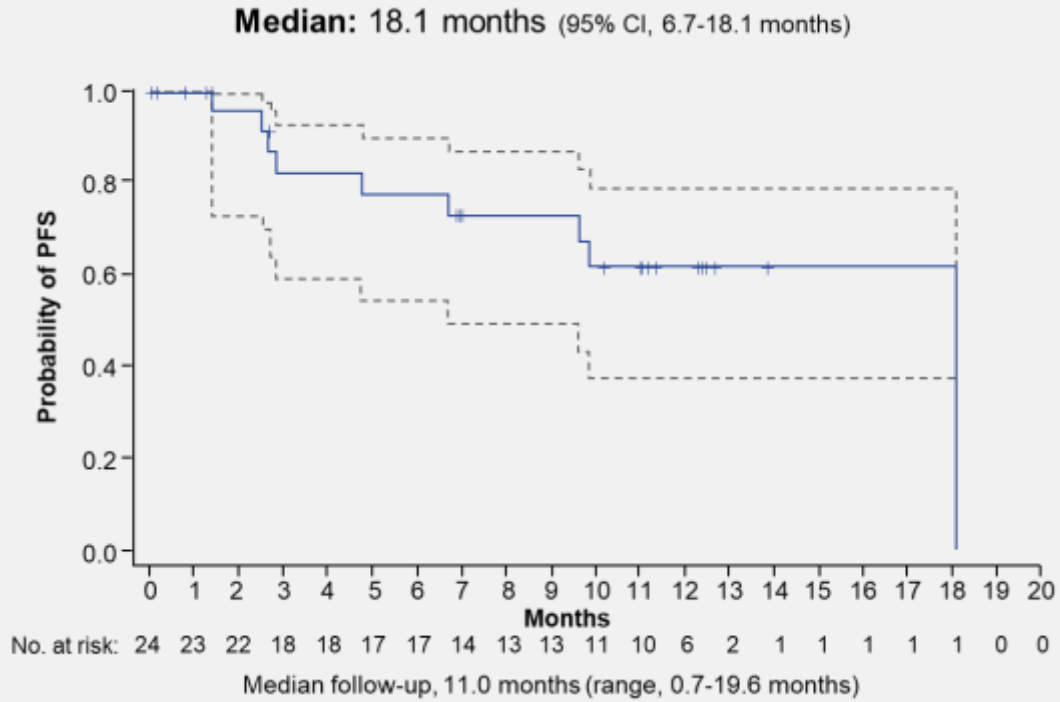
CNS Response

Brain Lesion Measurements Over Time in Patients in the CNS Subgroup



3 patients with reported baseline measurements had no change over time.
2 patients with brain metastases at baseline did not have sufficient data to evaluate response in the brain and are not shown.

Progression-Free Survival in the CNS Subgroup (n=24)



PFS, progression-free survival.
Data cutoff: August 1, 2019.

Conclusions

- T-DXd showed durable systemic disease control in patients with stable, treated brain metastases at baseline, with clinical outcomes similar to those of the overall population (as of the August 1, 2019, data cutoff)
- Of 17 patients with brain lesions at baseline, 41.2% (n=7) experienced tumor shrinkage consistent with a PR in the brain and 41.2% (n=7) were consistent with SD
- Interpretation of these results is limited by the small patient number and post hoc analysis of CNS response
- Ongoing trials will continue to assess the activity of T-DXd in patients with breast cancer and active brain metastases, for which treatment options remain limited
  - DESTINY-Breast07 (NCT04538742)
  - TUXEDO-1 (NCT04752059)
  - DESTINY-Breast12 (NCT04739761)
  - DEBBRAH (NCT04420598)

Trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2 (HER2)-expressing salivary duct carcinoma: Subgroup analysis of two phase 1 studies

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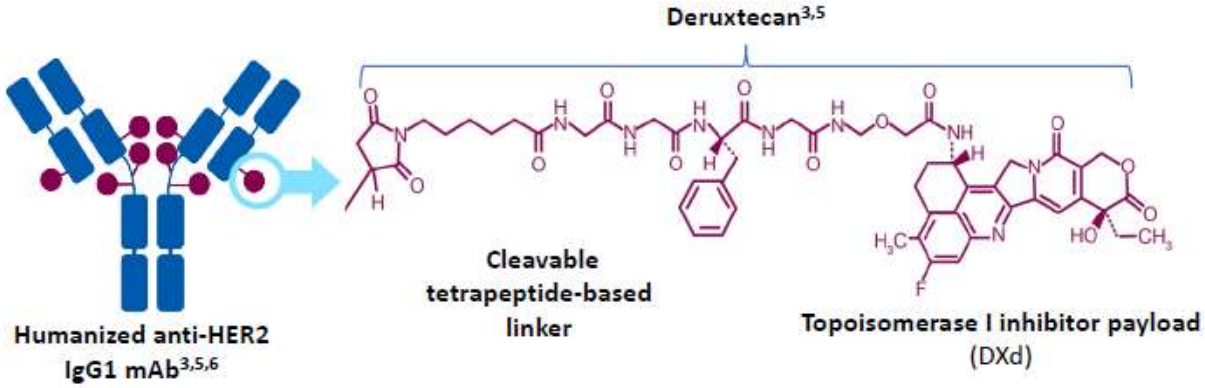
Background

- In salivary duct carcinoma (SDC), 16%–83% of patients are reported to show human epidermal growth factor receptor 2 (HER2) expression by immunohistochemistry (IHC) or HER2 amplification by in situ hybridization (ISH)/next-generation sequencing (NGS)[1]
- There are no established HER2-targeted therapies for SDC
- The National Comprehensive Cancer Network (NCCN) guidelines include HER2-targeted therapy (trastuzumab, ado-trastuzumab emtansine [T-DM1], or pertuzumab combined with trastuzumab) as a therapeutic option for the treatment of HER2-positive SDC[2]
- Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate composed of an anti-HER2 monoclonal antibody having the same amino acid sequence as trastuzumab, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor payload[3] (Figure 1)
- T-DXd was approved for treatment of patients with HER2-positive metastatic breast cancer in US, EU, UK and Japan. And it was also approved for treatment of patients with HER2-positive unresectable advanced or recurrent gastric cancer in US[4] and Japan
- Here we present the pooled analysis of HER2-expressing SDC who received T-DXd from 2 phase1 studies: DS8201-A-J101 (NCT02564900) and DS8201-A-A104 (NCT03383692)

Figure 1. Structure of trastuzumab deruxtecan



Methods

- DS8201-A-J101: first-in-human phase 1 study of T-DXd including patients with HER2-expressing SDC
  - –Dose-escalation phase: T-DXd 5.4 and 6.4 mg/kg (every 3 weeks) was recommended for the dose-expansion phase of the study[7]
  - –Dose-expansion phase: T-DXd demonstrated promising activity and an acceptable safety profile in a heterogeneous population, including in HER2-expressing or mutated solid tumors[8]
- DS8201-A-A104: a phase 1 crossover study evaluating the drug-drug interaction potential of T-DXd + ritonavir or T-DXd + itraconazole in patients with HER2-expressing advanced solid tumors[9]
  - –No clinically meaningful pharmacokinetic drug-drug interactions were observed with manageable safety profile
- 17 patients with SDC were pooled in this analysis: out of 289 and 40 patients (total 329) in DS8201-A-J101 and DS8201-A-A104, respectively
- HER2 expression was defined by IHC and/or amplification, by ISH or NGS via local testing at enrollment
  - –A retrospective IHC and ISH analysis of archived HER2 samples was conducted after enrollment by a central laboratory per the American Society of Clinical Oncology/College of American Pathologists guidelines for gastric cancer
- Patients received intravenous T-DXd every 3 weeks at 6.4 mg/kg and 5.4 mg/kg in DS8201-A-J101 (8 patients) and DS8201-A-A104 (9 patients), respectively
- Tumor response was evaluated by investigator per evaluation criteria In Solid Tumors (RECIST) version 1.1

Results

- Of the 17 patients with HER2-expressing SDC, 8 and 9 patients were enrolled from DS8201-A-J101 and DS8201-A-A104, respectively (Table 1)
- The cutoff date for the data analysis is 1 Aug 2019 for DS8201-A-J101 and 26 Sep 2018 for DS8201-A-A104
- At data cutoff, 41.2% of patients continued T-DXd treatment; the median duration of follow-up was 5.6 months (Table 2)

Results (cont'd)

Table 1. Demographics and baseline clinical characteristics

Characteristic	J101 (N=8)	A104 (N=9)	Pooled (N=17)
Age, years, median (range)	51.5 (44–69)	58.0 (34–71)	57.0 (34–71)
Sex, n (%)			
Male	6 (75.0)	9 (100.0)	15 (88.2)
Female	2 (25.0)	0 (0.0)	2 (11.8)
Race,[a] n (%)			
Asian	7 (87.5)	9 (100.0)	16 (94.1)
Other	1 (12.5)	0 (0.0)	1 (5.9)
ECOG performance status, n (%)			
0	6 (75.0)	4 (44.4)	10 (58.8)
1	2 (25.0)	5 (55.6)	7 (41.2)

[a]Other race was not provided.

Results (cont'd)

Daiichi-Sankyo

Table 1. Demographics and baseline clinical characteristics (cont'd)

Characteristic	J101 (N=8)	A104 (N=9)	Pooled (N=17)
HER2 expression (IHC),[a] n (%)			
0	0 (0.0)	0 (0.0)	0 (0.0)
1+	0 (0.0)	0 (0.0)	0 (0.0)
2+	0 (0.0)	1 (11.1)	1 (5.9)
3+	8 (100.0)	3 (33.3)	11 (64.7)
Nonevaluable	0 (0.0)	5 (55.6)	5 (29.4)
HER2 amplification (ISH),[b] n (%)			
Positive	6 (75.0)	0 (0.0)	6 (35.3)
Equivocal	0 (0.0)	0 (0.0)	0 (0.0)
Negative	1 (12.5)	1 (11.1)	2 (11.8)
Missing	1 (12.5)	0 (0.0)	1 (5.9)
Not examined	0 (0.0)	8 (88.9)	8 (47.1)

[a]HER2 status was assessed by a central laboratory according to the American Society of Clinical Oncology/College of American Pathologists guidelines for gastric cancer. [b]Positive, HER2/CEP17 ≥2.0 with any average HER2 copy number or HER2/CEP17 <2.0 with an average HER2 copy number ≥6.0; equivocal, HER2/CEP17 <2.0 with an average HER2 copy number ≥4.0 and <6.0; negative, HER2/CEP17 <2.0 with an average HER2 copy number <4.0.

Results (cont'd)

Daiichi-Sankyo

Table 1. Demographics and baseline clinical characteristics (cont'd)

Characteristic	J101 (N=8)	A104 (N=9)	Pooled (N=17)
Site of primary disease, n (%)			
Parotid gland	4 (50.0)	2 (22.2)	6 (35.3)
Submandibular gland	2 (25.0)	2 (22.2)	4 (23.5)
Glandula sublingualis	0 (0.0)	1 (11.1)	1 (5.9)
Unknown	2 (25.0)	4 (44.4)	6 (35.3)
Visceral disease at baseline, n (%)	7 (87.5)	8 (88.9)	15 (88.2)
Lines of prior systemic therapy,[a] median (range)	2.0 (0–6)	1.0 (1–5)	1.0 (0–6)
Prior cancer therapy, n (%)			
Platinum	1 (12.5)	2 (22.2)	3 (17.6)
Taxane	5 (62.5)	8 (88.9)	13 (76.5)
Trastuzumab	5 (62.5)	8 (88.9)	13 (76.5)
Trastuzumab emtansine	1 (12.5)	0 (0.0)	1 (5.9)

[a]All systemic therapy including adjuvant and locally advanced/metastatic disease.

Results (cont'd)

Table 2. Patient disposition

	J101 (N=8)	A104 (N=9)	Pooled (N=17)
Duration of follow-up, months, median (range)	13.0 (4.4–34.8)	2.8 (2.1–6.3)	5.6 (2.1–34.8)
Ongoing T-DXd, n (%)	1 (12.5)	6 (66.7)	7 (41.2)
Discontinued T-DXd, n (%)	7 (87.5)	3 (33.3)	10 (58.8)
Primary reason for discontinuation of T-DXd, n (%)			
AE	3 (37.5)	1 (11.1)	4 (23.5)
Progressive disease	3 (37.5)	2 (22.2)	5 (29.4)
Withdrawal of consent by patient	1 (12.5)	0 (0.0)	1 (5.9)

Efficacy Results

- The confirmed overall response rate in the pooled analysis was 47.1% (95% confidence interval [CI], 23.0–72.2) (Table 3)

- 15 patients had target lesions per RECIST version 1.1, of whom 93% (14/15) showed tumor shrinkage in 12 weeks post-baseline assessment (Figure 2) and one of case report was presented (Figure 3)

Efficacy Results (cont'd)

Table 3. Clinical activity outcomes

	J101 (N=8)	A104 (N=9)	Pooled (N=17)
Best overall response (confirmed), n (%)			
CR	0 (0.0)	0 (0.0)	0 (0.0)
PR	6 (75.0)	2 (22.2)	8 (47.1)
SD	2 (25.0)	7 (77.8)	9 (52.9)
PD	0 (0.0)	0 (0.0)	0 (0.0)
NE	0 (0.0)	0 (0.0)	0 (0.0)
Confirmed ORR, n (%) [95% CI][a]	6 (75.0) [34.9–96.8]	2 (22.2) [2.8–60.0]	8 (47.1) [23.0–72.2]

Efficacy Results (cont'd)

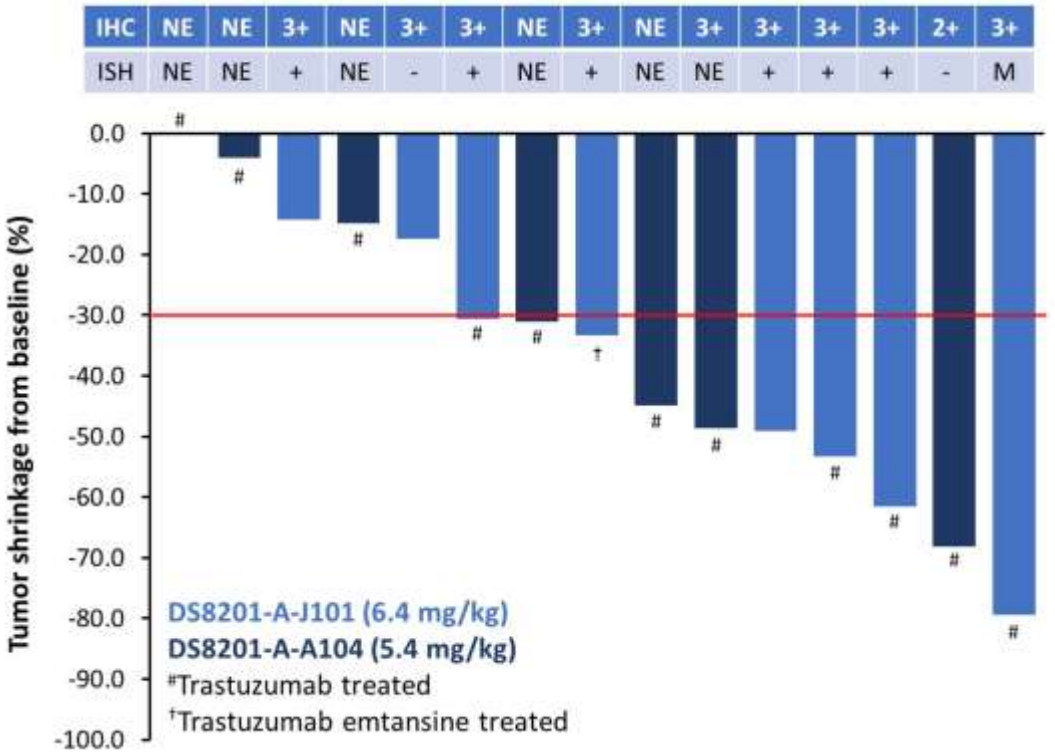
Table 3. Clinical activity outcomes (cont'd)

	J101 (N=8)	A104 (N=9)	Pooled (N=17)
DOR, months, median [95% CI][a]	12.9 [4.0–NE]	NE [NE–NE]	12.9 [4.0–NE]
Patients with events, n (%)	6 (75.0)	2 (22.2)	8 (47.1)
Patients censored, n (%)	2 (33.3)	2 (100.0)	4 (50.0)
Ongoing without events	1 (16.7)	2 (100.0)	3 (37.5)
Other	1 (16.7)	0 (0.0)	1 (12.5)
PFS, months, median [95% CI][a]	20.5 [5.6–NE]	NE [2.1–NE]	14.1 [5.6–NE]
Patients with events, n (%)	4 (50.0)	2 (22.2)	6 (35.3)
Patients censored, n (%)	4 (50.0)	7 (77.8)	11 (64.7)

[a]Using the Brookmeyer-Crowley method.

Efficacy Results (cont'd)

Figure 2. Best percentage change in tumor size



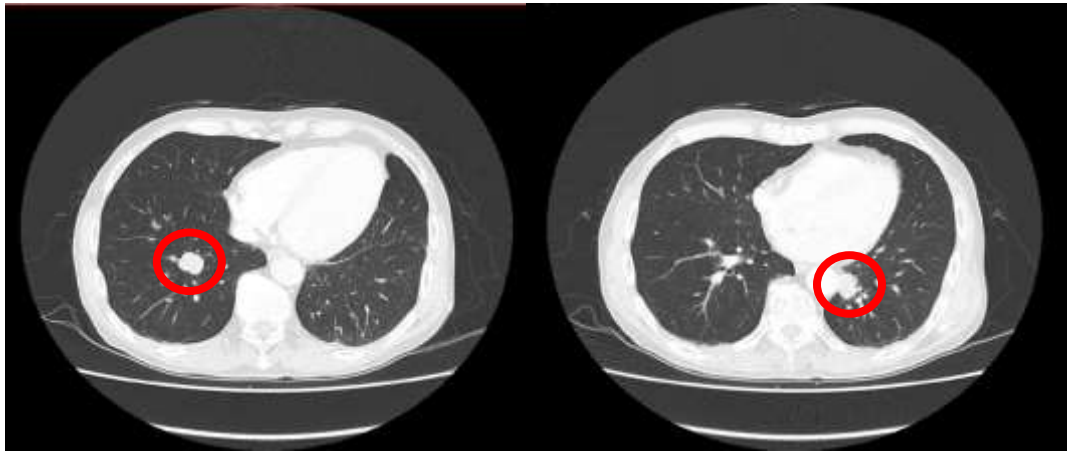
HER2 expression shown is based on central laboratory assessment. HER2 expression status at enrollment was determined via local assessment. The red line denotes a 30% reduction in tumor size.

Efficacy Results (cont'd)

Figure 3. Case report: 69% (Lung left) or 67% (Lung right) regression of a metastatic lung lesion

- 65-year-old man with IHC 2+/ISH negative (central assessment) for HER2 metastatic sublingual gland
- 1 prior line of treatment, including bicalutamide and leuprorelin

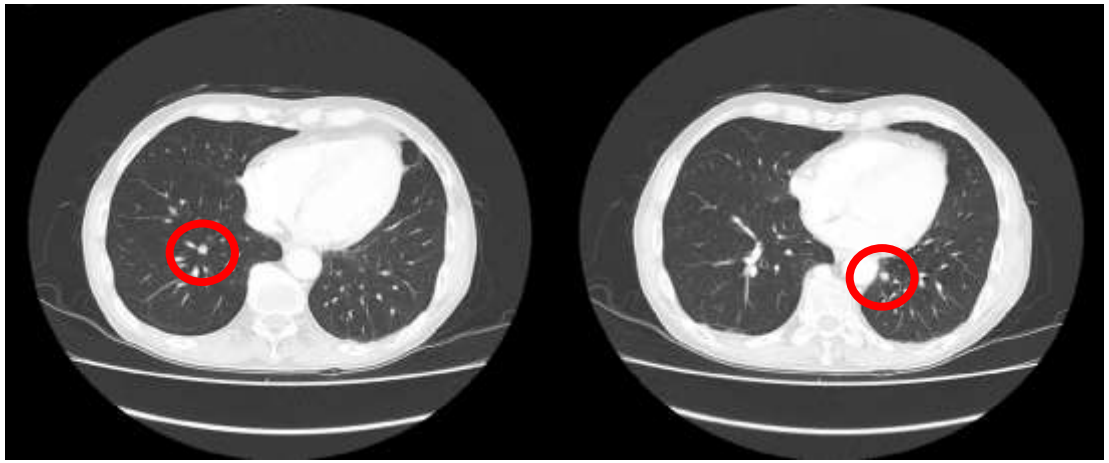
Baseline scan



Lung right lesion was 21 mm

Lung left lesion was 26 mm

6-week scan



Lung right lesion (7 mm) reduced by 67% from baseline

Lung left lesion (8 mm) reduced by 69% from baseline

Safety Results

- Treatment-emergent adverse events (TEAEs) occurred in all 17 patients; 23.5% of patients discontinued treatment and 17.6% and 41.2% of patients experienced dose reduction and dose interruption, respectively, due to TEAEs (Table 4)
- The most common grade ≥3 TEAEs (64.7%) were decreased neutrophil count (47.1%) and decreased white blood cell count (35.3%) (Table 5)
- Three patients (17.6%) had adjudicated drug-related interstitial lung disease but no related death

Safety Results (cont'd)

Table 4. Safety summary

n (%)	Pooled (5.4 or 6.4 mg/kg) (N=17)
All TEAEs	17 (100)
Drug related	17 (100)
TEAE grade ≥3	11 (64.7)
Drug related	9 (52.9)
Serious TEAEs	3 (17.6)
Drug related	1 (5.9)
TEAE associated with discontinuation	4 (23.5)
Drug related	3 (17.6)
TEAE associated with dose reduction	3 (17.6)
Drug related	2 (11.8)
TEAE associated with dose interruption	7 (41.2)
Drug related	7 (41.2)

Safety Results (cont'd)

Table 5. Common TEAEs (≥20%) and adjudicated drug-related ILD

TEAEs (≥20%)	Pooled (5.4 or 6.4 mg/kg) (N=17)	
n (%)	All Grades	Grade ≥3
Any TEAE	17 (100)	11 (64.7)
Decreased appetite	15 (88.2)	1 (5.9)
Nausea	15 (88.2)	0 (0.0)
Neutrophil count decreased[a]	13 (76.5)	8 (47.1)
White blood count decreased[a]	10 (58.8)	6 (35.3)
Aspartate aminotransferase increased	9 (52.9)	2 (11.8)
Alanine aminotransferase increased	8 (47.1)	2 (11.8)
Platelet count decreased[a]	8 (47.1)	2 (11.8)
Constipation	8 (47.1)	0 (0.0)

[a]Grouped preferred terms are neutrophil count decreased (neutropenia, neutrophil count decreased), white blood cell count decreased (leukopenia, white blood cell count decreased), platelet count decreased (platelet count decreased, thrombocytopenia).

Safety Results (cont'd)

Table 5. Common TEAEs (≥20%) and adjudicated drug-related ILD (cont'd)

TEAEs (≥20%)	Pooled (5.4 or 6.4 mg/kg) (N=17)	
n (%)	All Grades	Grade ≥3
Any TEAE	17 (100)	11 (64.7)
Malaise	6 (35.3)	0 (0.0)
Alopecia	6 (35.3)	0 (0.0)
Anemia[a]	5 (29.4)	2 (11.8)
Cough	5 (29.4)	0 (0.0)
Diarrhea	5 (29.4)	0 (0.0)
Fatigue[a]	5 (29.4)	0 (0.0)
Vomiting	4 (23.5)	0 (0.0)
Stomatitis[a]	4 (23.5)	0 (0.0)
Adjudicated drug-related ILD	3 (17.6)	1 (5.9)

[a]Grouped preferred terms are fatigue (asthenia, fatigue), anemia (hemoglobin decreased, red blood cell count decreased, anemia, hematocrit decreased), stomatitis (aphthous ulcer, mouth ulceration, oral mucosa erosion, oral musosal blistering, stomatitis).

Conclusions

- T-DXd 5.4 and 6.4 mg/kg showed promising antitumor activity in HER2-expressing SDC with durable responses
  - Confirmed objective response rate: 47.1%
  - Median duration of response: 12.9 months
  - Median progression-free survival: 14.1 months
- The safety profile was generally consistent with previous results of studies with other solid tumors and no new safety signals were reported
- Interpretation of these results is limited by the short follow-up in DS8201-A-A104 and the small patient number
- Our results support further investigation of T-DXd in HER2-expressing SDC

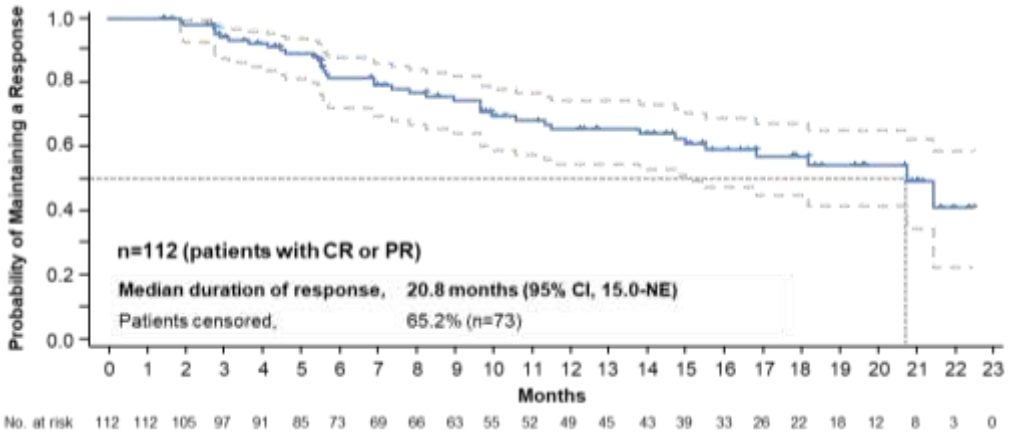
Background

- T-DXd has been approved for use in patients with HER2-positive metastatic breast cancer that has progressed on ≥2 prior anti-HER2 therapies (US, EU, UK) or after chemotherapy (Japan) and in patients with HER2-positive metastatic gastric cancer who have received a prior trastuzumab-based regimen (US) or progressed after chemotherapy (Japan)

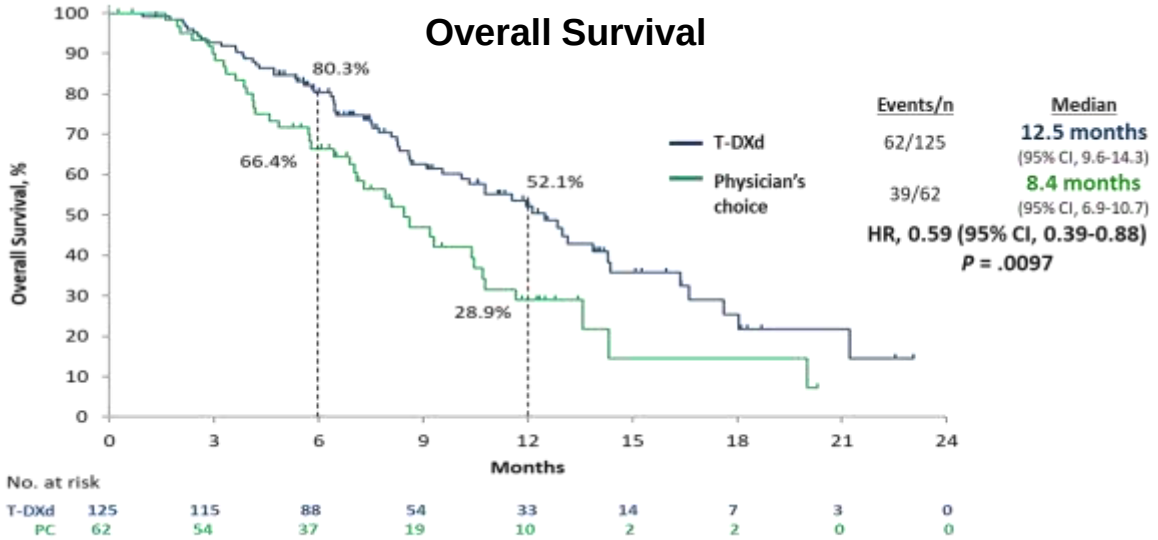
DESTINY-Breast01: June 2020 Data Cutoff[1]	T-DXd 5.4 mg/kg (N=184)
Objective response rate, n (%)	113 (**61.4**)

DESTINY-Gastric01: November 2019 Data Cutoff[2]	T-DXd 6.4 mg/kg (N=119)	Physician's choice (N=56)
Objective response rate, n (%)	61 (**51.3**)	8 (14.3)

Duration of Response



Overall Survival

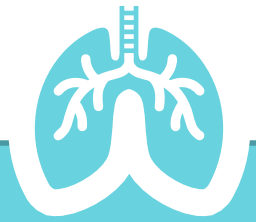


- Interstitial lung disease (ILD) is an important identified risk for patients treated with T-DXd[3-8]
- Here we further characterize ILD and assess potential associated factors in a pooled analysis of 8 single arm phase 1 and 2 T-DXd monotherapy studies, including the first-in-human study

1. Modi S, et al. SABCS 2020 [abstract PD3-06]; 2. Shitara K, et al. *N Engl J Med*. 2020;382;2419-2430; 3. Doi T, et al. *Lancet*. 2017;18(11):1512-22; 4. Shitara K, et al. *Lancet*. 2019;20(6):827-36; 5. Tamura K, et al. *Lancet*. 2019;20(6):816-26; 6. Modi S, et al. *J Clin Oncol*. 2020;38(17):1887-96; 7. Tsurutani J, et al. *Cancer Discov*. 2020;10(5):688-701; 8. Modi S, et al. *N Engl J Med*. 2020;382(7):610-21.

Methods

Data as of 08 June 2020 were pooled from 879 patients who received ≥1 dose of T-DXd monotherapy at 5.4, 6.4, 7.4, or 8.0 mg/kg across 8 phase 1 or 2 studies representing all available single-arm monotherapy studies in the T-DXd developmental program.



An independent adjudication committee retrospectively reviewed all potential ILD cases using imaging and clinical data (from baseline through the time of the potential ILD case) to assess whether the reported event was a case of ILD and, if such, if it was related to the study drug; **events adjudicated as study drug related are reported**. In addition, ILD cases with a fatal outcome were assessed to determine if the cause of death was due to ILD

A multivariate stepwise Cox regression model was used to explore the association between baseline factors and the time to occurrence of the outcome with stepwise variable selection entry criterion of $P<.05$ and remain criterion of $P<.10$. This analysis is exploratory and hypothesis generating in nature.

Baseline characteristics and T-DXd treatment

Patients were heavily pretreated with advanced disease

	N=879
Age, median (range), years	58.0 (23-96)
≥ 65 years, n (%)	271 (30.8)
Female, n (%)	674 (76.7)
Japanese, n (%)	364 (41.4)
ECOG PS, n (%)	
0	476 (54.2)
1 / 2	401 (45.6) / 2 (0.2)
Tumor type, n (%)[a]	
Breast cancer	510 (58.0)
Gastric cancer	78 (8.9)
Lung cancer	148 (16.8)
Colorectal cancer	107 (12.2)
Other	34 (3.9)
Lung comorbidities, n (%)[b]	101 (11.5)

	N=879
No. of prior regimens, median (range)	5.0 (1-27)
T-DXd dose, n (%)	
5.4 mg/kg	315 (35.8)
6.4 mg/kg	537 (61.1)
> 6.4 mg/kg	27 (3.1)
Duration of treatment, median (range), mo	6.90 (0.7-50.1)
0 to 6 mo, n (%)	407 (46.3)
> 6 to 12 mo, n (%)	223 (25.4)
> 12 to 24 mo, n (%)	192 (21.8)
> 24 mo, n (%)	57 (6.5)
No. of treatment cycles, median (range)	9.0 (1-67)

ECOG PS, Eastern Cooperative Oncology Group performance status. [a] Tumor type was missing for 2 patients. [b] Includes asthma, COPD, prior interstitial lung disease/pneumonitis, pulmonary fibrosis, pulmonary emphysema, pleural effusion, and radiation pneumonitis.

Investigator-assessed ILD onset date vs adjudication committee

	Adjudicated drug-related ILD events (n=148)
Concordant, n (%)	**72 (48.6%)**
Discordant, n (%)	
Earlier than the adjudication committee	**5 (3.4%)**
Median difference (range), days	**7.0 (1-44)**
Later than the adjudication committee	**71 (48.0%)**
Median difference (range), days	**49.0 (1-288)**

Scans occurred every 6 weeks (42 days).

The adjudication committee frequently identified ILD onset earlier than investigators

Summary of steroid use

Systemic steroid use by grade of adjudicated drug-related ILD

	Grade 2-4	Events leading to Grade 5
No. of events	80	21
Events treated with systemic steroids, n (%)	48 (60.0)	16 (76.1)

Defined as any systemic steroids initiated within 90 days of the adjudicated ILD onset date.
Steroids were recommended for grade ≥2 ILD.

- Median time from adjudicated ILD onset date (any grade) to start of systemic steroid treatment was long, 21.0 days (range, 1-87 days)
- 141 of 148 (95%) adjudicated ILD events occurred prior to 15 December 2019 when updated toxicity management guidelines were implemented in clinical trials
  - Updated guidelines included information on optimal steroid dosing and duration

Assessment of factors potentially associated with ILD

A stepwise multivariate Cox regression model evaluated the association of potential factors with the time to occurrence of any-grade ILD, and the following 6 were identified as factors of interest:

- Patients treated in Japan vs non-Japan
- Dose of ≥ 7.4 mg/kg vs 5.4 mg/kg
- Baseline SpO2 < 95% vs ≥ 95%
- Moderate/severe renal impairment at baseline vs no impairment
- Presence of lung comorbidities (yes vs no; asthma, chronic obstructive pulmonary disease, prior ILD/pneumonitis, pulmonary fibrosis, pulmonary emphysema, or radiation pneumonitis)
- Time since initial diagnosis of ≥ 3.9 years vs <3.9 years

Notably, when accounting for other factors, lung cancer or lung metastases/ lymphangitic carcinomatosis at baseline and prior chest/lung radiotherapy were not associated with ILD in this analysis

Given the limitations of the present analysis (extensive prior treatment, differences in treatment durations, and heterogeneity of the patient population), the identified factors of interest remain to be confirmed and will be further evaluated with future data in a larger, more homogenous patient population

Factors included in the model were: age group, sex, tumor type, ECOG Performance Status, lung cancer or lung metastases/lymphangitic carcinomatosis at baseline, prior chest/lung radiotherapy, lung comorbidities, baseline renal function, number of prior regimens category, baseline white blood cell count ($x10^9$/L), baseline albumin (g/L), time since initial disease diagnosis (year) category, time since the end date of last anticancer therapy to first infusion of T-DXd (months) category, dose (mg/kg) category and baseline SpO2 (%) category.

Conclusions

- **T-DXd had shown significant antitumor activity in HER2-positive metastatic breast[1] and gastric cancer,[2] as well as other tumor types[3]**
- **The majority of independently adjudicated ILD cases (78%) were low grade**
- **ILD risk may decrease after ≈12 months of treatment; longer follow-up is needed to confirm the observed trend**
- **Optimal steroid management was not observed, with delay in detection of ILD and underdosing of steroids; new toxicity guidelines have now been implemented and education provided**
  - After implementation of these guidelines, data suggest a lower rate of high-grade ILD events
- **Potential clinical factors of interest associated with ILD may include low oxygen saturation, lung comorbidities, and renal insufficiency**
  - Identification of specific risk factors requires confirmation in larger trials
- **This pooled analysis further supports the benefit/risk profile of T-DXd in advanced cancer**
  - Phase 3 randomized controlled trials across multiple tumor types are ongoing

1. Modi S, et al. SABCS 2020 [abstract PD3-06]; 2. Shitara K, et al. *N Engl J Med*. 2020;382;2419-2430; Tsurutani J, et al. *Cancer Discov*. 2020;10(5):688-701.

Patient Disposition

Treatment status, n (%)	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
Ongoing study treatment	15 (30)	13 (26)	10 (13)
Discontinued from study treatment	35 (70)	37 (74)	70 (88)
Progression[a]	26 (52)	27 (54)	42 (53)
Adverse events	6 (12)	4 (8)	16 (20)
Death	1 (2)	2 (4)	4 (5)
Follow-up, median (range), mo	9.2 (4.3-25.9)	6.6 (3.1-24.0)	13.9 (7.3-22.0)
Exposure, median (range), mo	4.1 (0.7-24.1)	3.5 (0.7-23.4)	3.3 (0.7-17.1)

[a] Includes progressive disease per Response Evaluation Criteria in Solid Tumors v1.1 and clinical progression.

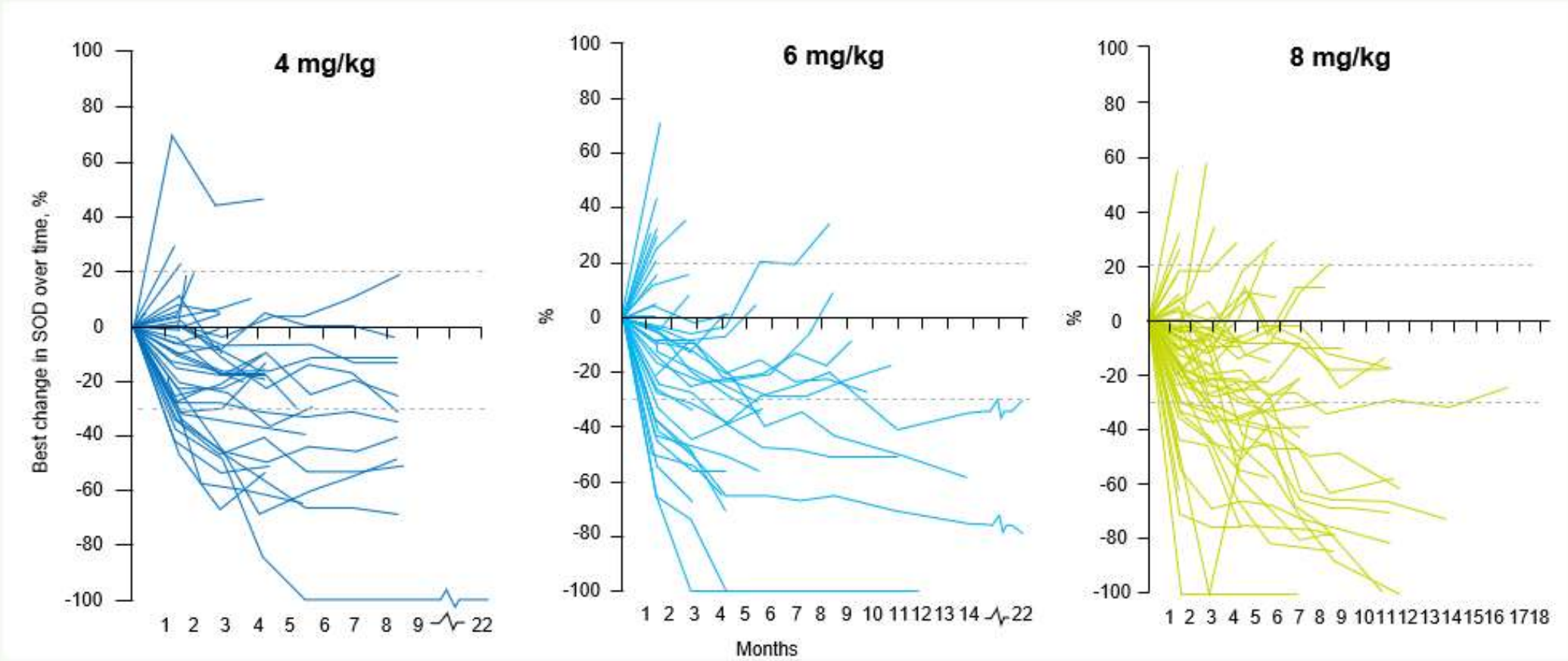
Due to later time of enrollment, follow-up was shorter for patients treated with the 4- and 6-mg/kg doses than the 8-mg/kg dose

Patient Demographics and Baseline Characteristics

Characteristic	Dato-DXd dose		
	4 mg/kg (n=50)	6 mg/kg (n=50)	8 mg/kg (n=80)
Age, ≥ 65 years, %	36	40	46
Weight, median (range), kg	72 (38-156)	66 (39-104)	70 (38-115)
Sex, male, %	54	56	51
Country, %			
United States	58	76	79
Japan	42	24	21
Histology, %			
Nonsquamous	82	90	88
Squamous	18	10	13
≥3 Prior lines of therapy, %	58	62	65
Previous systemic treatment, %			
Immunotherapy	86	74	88
Platinum-based chemotherapy	94	96	98
Tyrosine kinase inhibitor	20	18	18
***EGFR* mutations, %**	16	16	20

Baseline characteristics were generally balanced across dosing cohorts

Efficacy: Change in Sum of Diameters for Target Lesions (BICR) Over Time



BICR, blinded independent central review; SOD, sum of diameters.

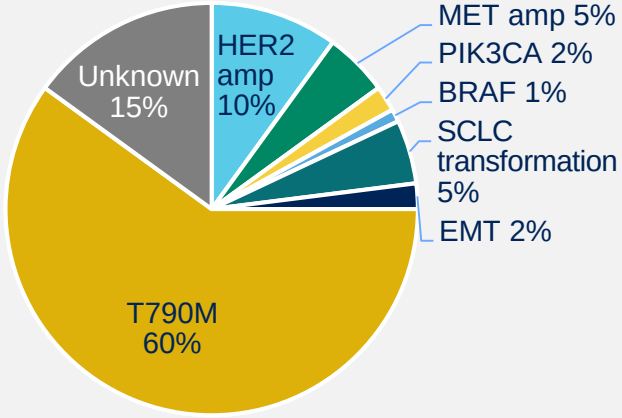
Most responses were durable over time

Broad Range of Resistance Mechanisms in *EGFR*m NSCLC Following the Failure of EGFR Tyrosine Kinase Inhibitor (TKI) Therapy

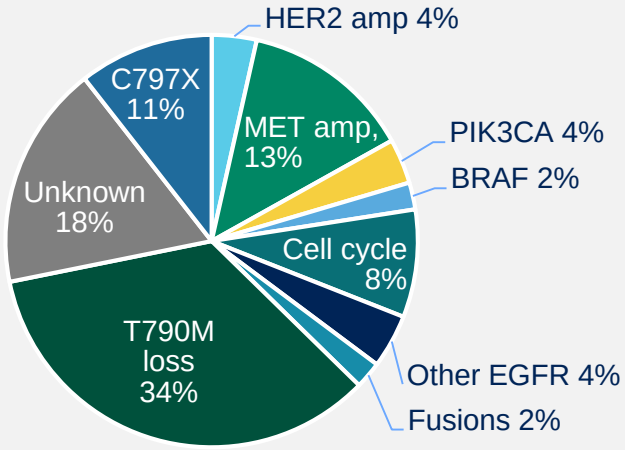
- Efficacy of EGFR TKI in *EGFR*m NSCLC has been established; however, the development of various resistance mechanisms commonly leads to disease progression[1-2]
- Platinum-based chemotherapy following EGFR TKI failure has limited efficacy (ORR, 25%–44%; PFS, 2.7–6.4 months)[3]
- Salvage therapies after EGFR TKI and platinum-based chemotherapy have not been effective (PFS, 2.8–3.2 months)[4]

Wide variety of genomic alterations associated with EGFR TKI resistance[1,2]

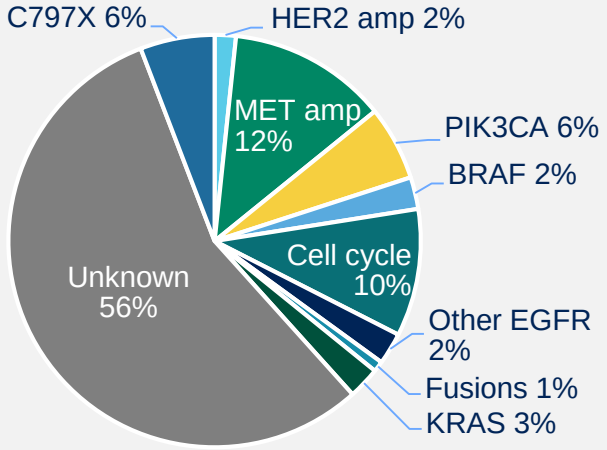
First-line erlotinib, gefitinib, afatinib



Second-line osimertinib



First-line osimertinib



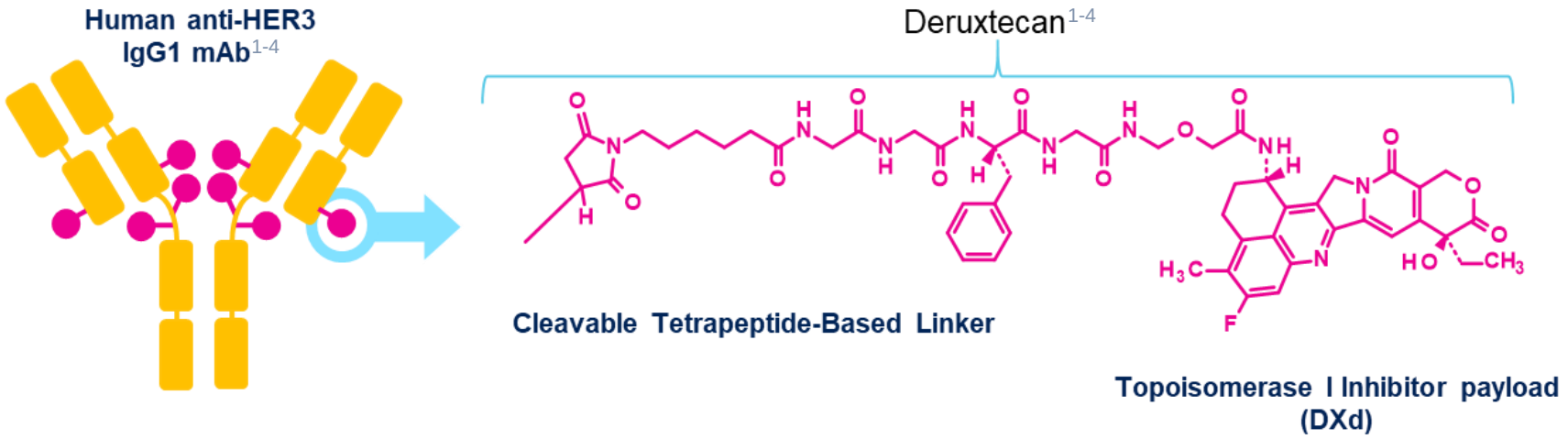
1. Engelman JA, et al. *Science*. 2007;316:1039-1043. 2. Schoenfeld AJ, Yu HA. *J Thorac Oncol*. 2020;15:18-21. 3. Han B, et al. *Onco Targets Ther*. 2018;11:2121-9. 4. Yang CJ, et al. *BMC Pharmacol Toxicol* 2017;18(1).

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

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

HER3 is expressed in 83% of NSCLC tumors[7,a]

HER3 alterations are not known to be a mechanism of resistance to EGFR TKI in *EGFR*m NSCLC



[a] HER3 overexpression is associated with metastatic progression and decreased relapse-free survival in patients with NSCLC.

1. Hashimoto Y, et al. *Clin Cancer Res.* 2019;25:7151-7161. 2. Nakada T, et al. *Chem Pharm Bull (Tokyo).* 2019;67(3):173-185. 3. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. 4. Koganemaru S, et al. *Mol Cancer Ther.* 2019;18:2043-2050. 5. Haratani K, et al. *J Clin Invest.* 2020;130(1):374-388. 6. Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046. 7. Scharpenseel H et al, *Sci Rep* 2019;9(1):7406.

HER3-DXd Antitumor Activity by History of CNS Metastases

In Patients Previously Treated with an EGFR TKI and Platinum-based Chemotherapy

Outcomes (BICR per RECIST 1.1) Median Follow Up: 9.6 (range, 5.2-19.9) mo[a]	History of Brain Metastases HER3-DXd 5.6 mg/kg (N=52)[a] Yes (N=25)	 No (N=27)
Confirmed ORR, % (95% CI)	32 (15-54)	41 (22-61)
Best overall response, n (%)		
CR	1 (4)	0
PR	7 (28)	11 (41)
SD, Non-CR/Non-PD	12 (48)	7 (26)
PD	4 (16)	4 (15)
Not evaluable	1 (4)	5 (19)
PFS, median (95% CI), mo	8.2 (4.0-NE)	8.3 (3.0-NE)

The response rate and PFS were similar in patients with and without prior brain metastases

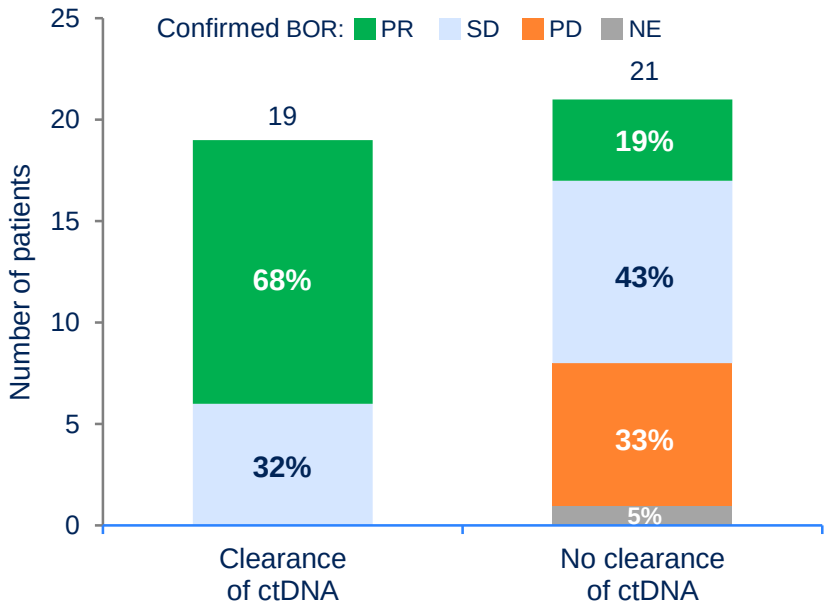
BICR, blinded independent central review; CR, complete response; NE, not evaluable; ORR, objective response rate; OSI, osimertinib; PBC, platinum-based chemotherapy; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.
Data cutoff: September 24, 2020.

[a] For patients treated with the recommended dose for expansion of HER3-DXd who had prior treatment with any EGFR TKI and platinum-based chemotherapy.

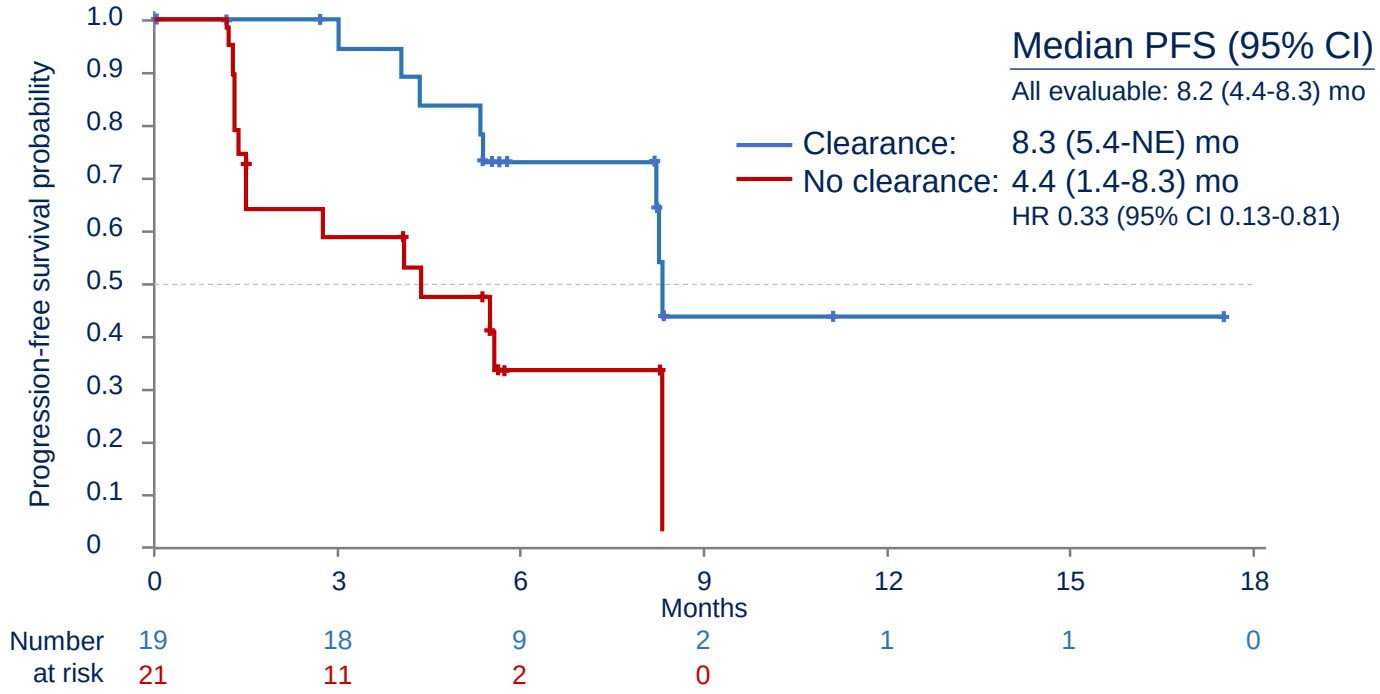
Early Clearance of *EGFR* Ex19del or L858R Mutations in ctDNA is Associated With Favorable BOR and PFS

Early clearance of ctDNA was defined as non-detectable plasma of either *EGFR* Ex19del or *EGFR* L858R at Week 3 or 6, where either mutation was detectable at baseline (evaluable in 40/57 patients[a])

Confirmed ORR higher with early clearance of ctDNA



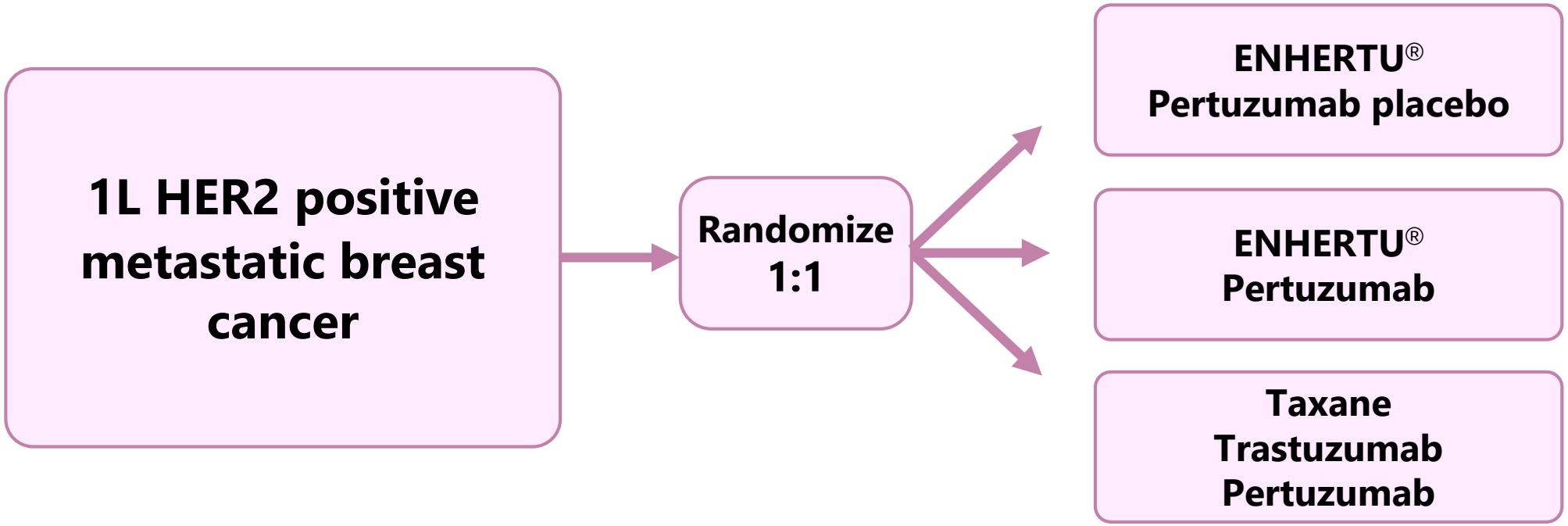
PFS prolonged in patients with early clearance of ctDNA



BOR, best overall response; PR, partial response; NE, not evaluable; PD, progressive disease; SD stable disease.
[a] Serial ctDNA samples were collected from 45 patients, but 5 did not have evaluable ctDNA data for either Weeks 3 or 6.

ENHERTU®: DESTINY-Breast09 Study

ENHERTU® with or without pertuzumab compared to taxane+ trastuzumab+pertuzumab in 1L HER2+ metastatic breast cancer



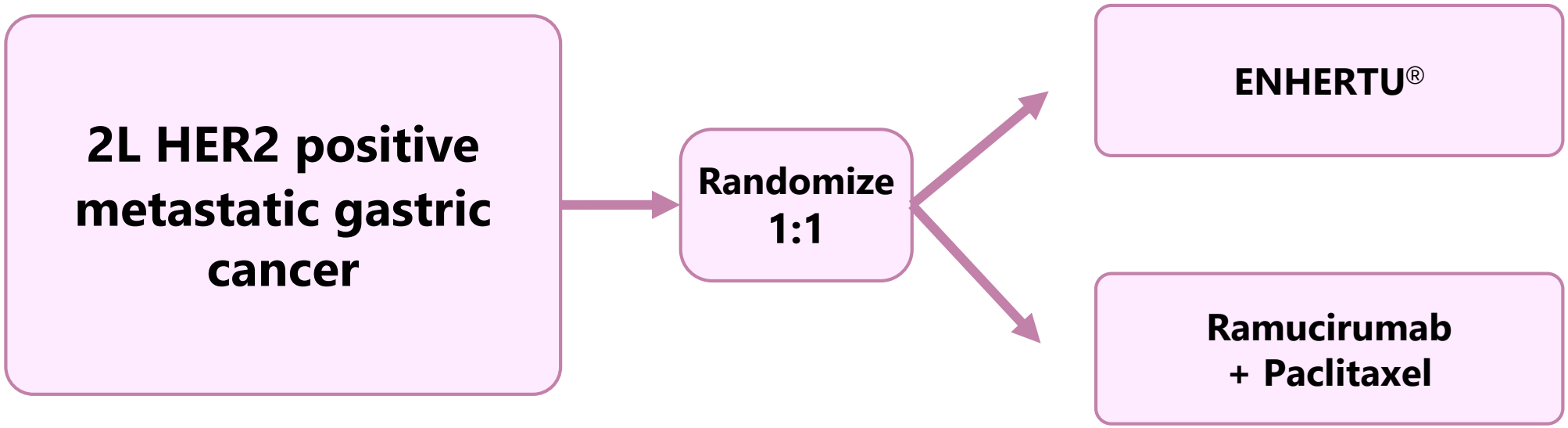
Endpoints: PFS as well as other endpoints

Study started: Jun 2021

ClinicalTrials.gov Identifier: NCT04784715

ENHERTU®: DESTINY-Gastric04 Study

ENHERTU® vs ramucirumab+paclitaxel in 2L HER2+ metastatic gastric cancer



Endpoints: OS as well as other endpoints

Study start: FY2021 1H planned

ClinicalTrials.gov Identifier: NCT04704934

HER3-DXd: Significance and Future Direction

EGFRm NSCLC

Post-TKI Post-PBC

Clear medical need in a difficult to treat patient population

- Salvage therapy is minimally effective, and offers short durations of efficacy (PFS, 2.8–3.2 months)
- HER3-DXd offers clinically meaningful, durable efficacy in a heavily pretreated population (ORR, 39%; median PFS, 8.2 months)
- Efficacy shown across multiple EGFR TKI resistance mechanisms and a broad range of baseline membrane HER3 expression

Post-TKI Pre-PBC

Potential to displace platinum-based chemotherapy

- Pt-based chemotherapy (PBC) is often used following EGFR TKI failure
- High activity observed in post-TKI/post-PBC and preliminary evidence suggests promising efficacy in chemotherapy-naïve patients

Other Indications

Transform treatment across HER3 expressing tumors

- NSCLC: Ongoing Ph1 study in EGFRwt
- CRC: Ongoing Ph2 study in 3L+
- BC: Ongoing Ph1/2 study in 2L+; collaborations ongoing with GRCC, SCRI, SOLTI
- Ongoing assessment of multiple additional HER3 expressing malignancies

BC: breast cancer, CRC: colorectal cancer, GRCC: Gustave Rossy Cancer Center. NSCLC: non-small cell lung cancer, PBC: platinum based chemotherapy, SCRI: Sarah Cannon Research Institute, SOLTI: Spanish Breast Cancer Research Group, TKI: tyrosine kinase inhibitor

本資料に関するお問い合わせ先

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