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2020年9月24日

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1 U3-1402 Ph1 NSCLC

2 DS-8201 DESTINY-Gastric01
HER2低発現コホート

3 Q&A

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Efficacy and Safety of Patritumab Deruxtecan (U3-1402), a Novel HER3 Directed Antibody Drug Conjugate, in Patients With EGFR-Mutated NSCLC

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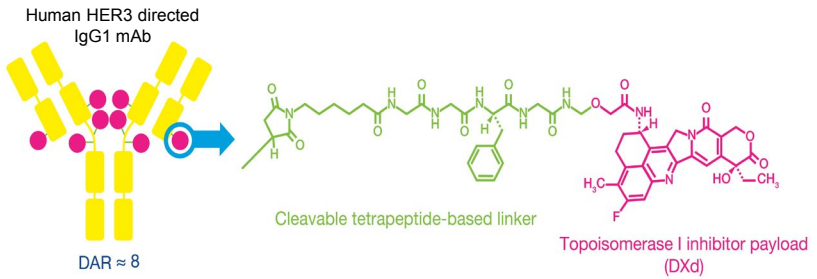
This study is sponsored by Daiichi Sankyo, Inc.
Presentation LBA62.

Phase 1 Study of Patritumab Deruxtecan (U3-1402), a HER3 Directed Antibody Drug Conjugate, in EGFR-mutated NSCLC

HER3 is expressed in most lung cancers, (~80% of *EGFR*-mutated NSCLC), overexpression is associated with worsened clinical outcomes[1]

Patritumab Deruxtecan (U3-1402)

A novel HER3 directed antibody drug conjugate composed of the monoclonal antibody patritumab, a tetrapeptide-based linker, and a topoisomerase I inhibitor payload



Dose Escalation[a]

*Metastatic/unresectable **EGFR-mutated NSCLC** either after progression on osimertinib or T790M-negative after progression on erlotinib, gefitinib, or afatinib*

Patritumab deruxtecan 5.6 mg/kg Q3W
n = 12

Dose Expansion Cohort 1[b]

Metastatic/unresectable ***EGFR*-mutated NSCLC** and treatment with ≥ 1 EGFR TKI and ≥ 1 prior platinum-based chemotherapy regimen

Patritumab deruxtecan 5.6 mg/kg Q3W
n = 45

Primary Objective: Antitumor activity of patritumab deruxtecan

Secondary Objectives: Safety and tolerability of patritumab deruxtecan

- Stable brain metastases were allowed
- Pretreatment tumor tissue (after progression on TKIs) required for retrospective analysis of HER3 expression
- As of 4/30/20, 57 patients from dose escalation and dose expansion had been treated with 5.6 mg/kg patritumab deruxtecan
- 56 patients were evaluable for response (1 patient did not have any evaluable post-baseline tumor assessments)
- 6 patients had only 1 tumor evaluation

A phase 1 study of patritumab deruxtecan in NSCLC (NCT03260491). Safety and activity in patients with *EGFR*-mutated NSCLC treated with 5.6 mg/kg patritumab deruxtecan. Data cutoff April 30, 2020.

1. Tan CS, et al. *Mol Cancer*. 2018;17(1):29.

[a]Patients in dose escalation had NSCLC (adenocarcinoma) and received 3.2 mg/kg-6.4 mg/kg of patritumab deruxtecan, which was guided by mCRM following EWOC principle.

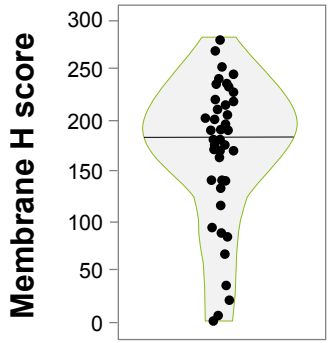
[b]Patients in dose expansion were enrolled into 3 cohorts; **data for patients with NSCLC (adenocarcinoma) enrolled in Cohort 1 are included in this analysis**. Patients with squamous or nonsquamous NSCLC without *EGFR* activating mutations will enroll into Cohort 2. Patients with *EGFR*-mutated NSCLC adenocarcinoma (including any histology other than combined cell and non-small cell) will be randomized 1:1 to receive 5.6 mg/kg or aRDE (Cohort 3a) or an up-titration of patritumab deruxtecan (Cohort 3b).

Characteristics, Disposition, and Exposure in Patients Treated With 5.6 mg/kg Patritumab Deruxtecan

- Median follow-up was 5 months (range, 0-15 months)
- Median treatment duration was 3.5 months (range, 1-14 months)

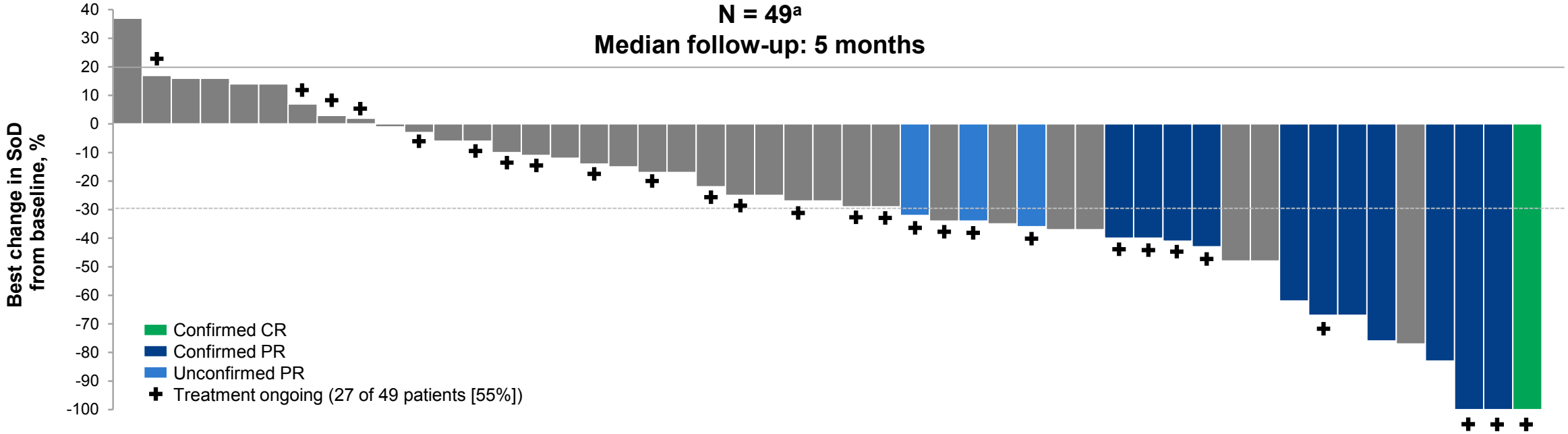
Baseline Demographics and Disease Characteristics	N = 57
Median age (range), years	65 (40-80)
Female, n (%)	36 (63)
Race, n (%)	
Asian	27 (47)
White	25 (44)
African American	2 (4)
Other	3 (5)
ECOG PS, n (%)	
0	23 (40)
1	34 (60)
Median number of therapies for advanced/metastatic disease (range)	4 (1-9)
Prior therapy, n (%)	
EGFR TKI	57 (100)
Osimertinib	49 (86)
Other EGFR targeted therapy	3 (5)
Platinum-based chemotherapy	51 (90)
Anti-PD-1/PD-L1	23 (40)
History of CNS metastases	27 (47)

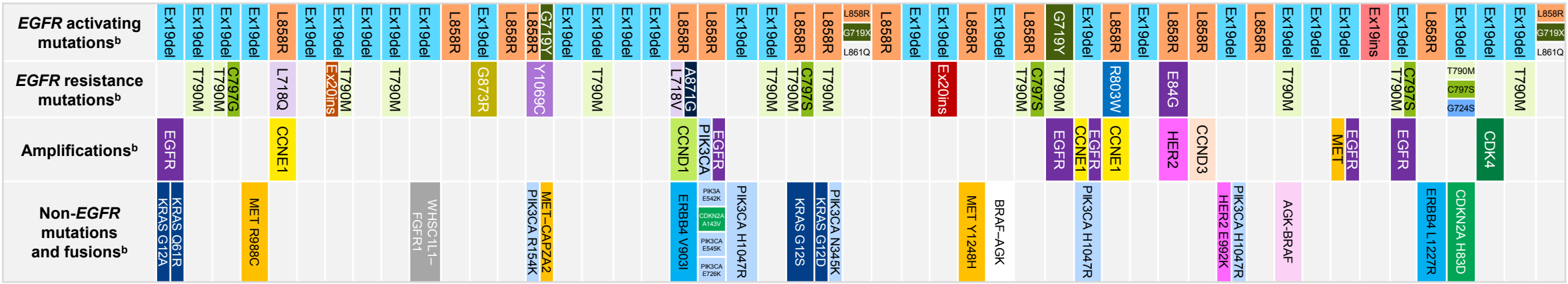
Disposition	N = 57
Ongoing on study treatment	28 (49)
Discontinued study	29 (51)
Progressive disease	13 (23)
Clinical progression	5 (9)
Adverse event	5 (9)
Consent withdrawal	3 (5)
Investigator decision	1 (2)
Death	2 (3)
HER3 expression	
Evaluable patients, n	43
Median membrane H score (range)	180 (2-280)



A phase 1 study of patritumab deruxtecan in NSCLC (NCT03260491). Safety and activity in patients with *EGFR*-mutated NSCLC treated with 5.6 mg/kg patritumab deruxtecan. Data cutoff April 30, 2020.

Patritumab Deruxtecan 5.6 mg/kg Demonstrated Antitumor Activity In EGFR-mutated NSCLC With Diverse TKI Resistance Mechanisms





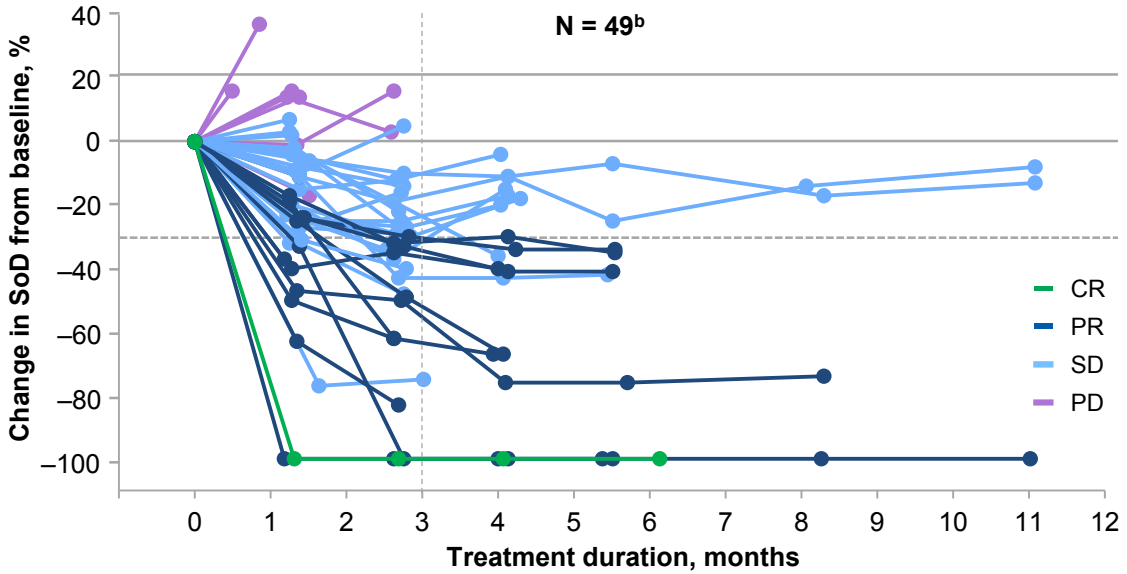
A phase 1 study of patritumab deruxtecan in NSCLC (NCT03260491). Safety and activity in patients with *EGFR*-mutated NSCLC treated with 5.6 mg/kg patritumab deruxtecan. Data cutoff April 30, 2020.

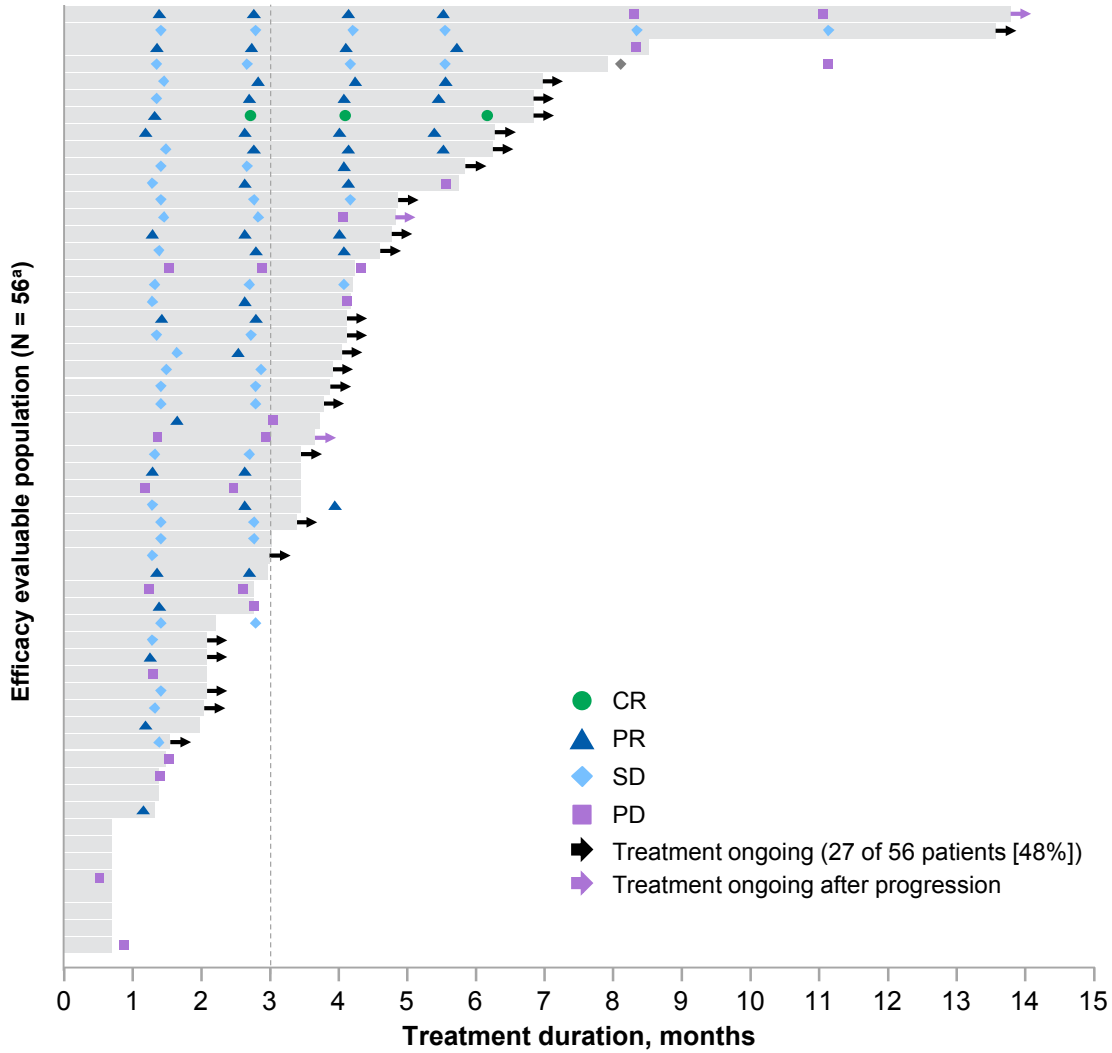
[a]This analysis does not include 7 patients without post-baseline tumor assessments by the data cutoff date.

[b]Performed centrally using Oncomine™ Comprehensive Assay v3 from pretreatment tumor tissue. Results from local testing are included for patients where tissue was unavailable for central analysis. Additional mutations detected from cfDNA in blood collected prior to treatment with U3-1402 using GuardantOMNI™ assay are included. For cfDNA analysis, a minor allelic frequency of 1% was used as a threshold for detection of mutations. The copy number data from cfDNA are not shown.

Antitumor Response Occurs Within 3 Months in Patients Treated With 5.6 mg/kg Patritumab Deruxtecan

Activity according to BICR evaluation (efficacy-evaluable population) N = 56[a]	
Confirmed BOR, n/N (%)	
CR	1/56 (2%)
PR	13/56 (23%)
SD	25/56 (45%)
PD	9/56 (16%)
NE	8/56 (14%)
Confirmed ORR, % (n/N; 95% CI)	25% (14/56; 14.4-38.4)
DCR, % (n/N; 95% CI)	70% (39/56; 55.9-81.2)
Median TTR, months (range)	2.0 (1.2-2.8)
Median DoR, months (range)	6.9 (3.0-7.0)





A phase 1 study of patritumab deruxtecan in NSCLC (NCT03260491). Safety and activity in patients with *EGFR*-mutated NSCLC treated with 5.6 mg/kg patritumab deruxtecan. Data cutoff April 30, 2020.

[a]Of 56 patients, 22 (39%) had best percentage decrease in sum of tumor diameters ≥ 30%. [b]This analysis does not include 7 patients without post-baseline tumor assessments by the data cutoff date.

Safety Summary of Patients Treated With 5.6 mg/kg Patritumab Deruxtecan

- Patritumab deruxtecan continued to demonstrate a manageable safety profile
  - The most common grade ≥3 TEAEs were thrombocytopenia (16 patients [28%]) and neutropenia (11 patients [19%])
  - TEAEs associated with discontinuation (9%) included fatigue (n = 2), decreased apetite (n = 1), ILD (n = 1), pneumonitis (n = 1), and URTI (n = 1)
    - There were no discontinuations due to thrombocytopenia or neutropenia
  - Three (5.3%) ILD events were adjudicated by an independent central review committee as being related to treatment
  - There were no treatment-related TEAEs associated with death

TEAEs (regardless of causality), n (%)	N = 57
TEAEs	57 (100)
Grade ≥3	38 (67)
Associated with discontinuation	5 (9)
Associated with dose reduction	10 (18)
Associated with dose interruption	17 (30)
Associated with death	3 (5)
Treatment-emergent SAEs	21 (37)
Grade ≥3	18 (32)
Treatment related	11 (19)

TEAEs in ≥20% of patients, n (%)	N = 57	
	All grades	Grade ≥3
Fatigue	33 (58)	5 (9)
Nausea	31 (54)	2 (4)
Thrombocytopenia[a]	30 (53)	16 (28)
Decreased appetite	20 (35)	1 (2)
Neutropenia[b]	19 (33)	11 (19)
Vomiting	17 (30)	1 (2)
Alopecia	17 (30)	NA
Anemia[c]	15 (26)	5 (9)
Constipation	14 (25)	0

A phase 1 study of patritumab deruxtecan in NSCLC (NCT03260491). Safety and activity in patients with *EGFR*-mutated NSCLC treated with 5.6 mg/kg patritumab deruxtecan. Data cutoff April 30, 2020.

[a]Thrombocytopenia includes decreased platelet count and thrombocytopenia. [b]Neutropenia includes decreased neutrophil count and neutropenia. [c]Anemia includes decreased hemoglobin, decreased red blood cell count, anemia, and decreased hematocrit.

Phase 1 Study of Patritumab Deruxtecan (U3-1402) in *EGFR*-mutated NSCLC: Conclusions

- Patritumab deruxtecan, a HER3 directed ADC, continued to demonstrate a **manageable safety profile** and **clinically meaningful antitumor activity at 5.6 mg/kg** (the recommended dose for expansion)
- Early antitumor activity was observed in this heavily pretreated patient population, with a median follow-up time of 5 months
  - 28 patients are ongoing treatment
  - 3 PRs are not yet confirmed
  - 6 patients had only 1 tumor evaluation
- Activity was observed in patients without and with **diverse mechanisms of TKI resistance**, including *EGFR* C797S mutation, *MET* amplification, *HER2* mutation, *BRAF* fusion, and *PIK3CA* mutation
- These data support further clinical investigation of this HER3 directed ADC in a patient population with no available targeted therapy treatments
  - A **phase 2 study** of single-agent patritumab deruxtecan in patients after failure of EGFR TKIs and platinum-based chemotherapy therapy is planned

A phase 1 study of patritumab deruxtecan in NSCLC (NCT03260491). Safety and activity in patients with *EGFR*-mutated NSCLC treated with 5.6 mg/kg patritumab deruxtecan. Data cutoff April 30, 2020.

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Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-low, advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: results of the exploratory cohorts in the phase 2, multicenter, open-label DESTINY-Gastric01 study

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On behalf of the DESTINY-Gastric01 investigators

DESTINY-Gastric01

An open-label, multicenter, randomized, phase 2 study

T-DXd is an antibody-drug conjugate consisting of an anti-HER2 antibody, cleavable tetrapeptide-based linker, and topoisomerase I inhibitor payload

In the DESTINY-Gastric01 (NCT03329690) primary cohort[1] of 187 patients with HER2-positive gastric or GEJ cancer previously treated with trastuzumab, T-DXd 6.4 mg/kg compared with standard chemotherapy demonstrated:

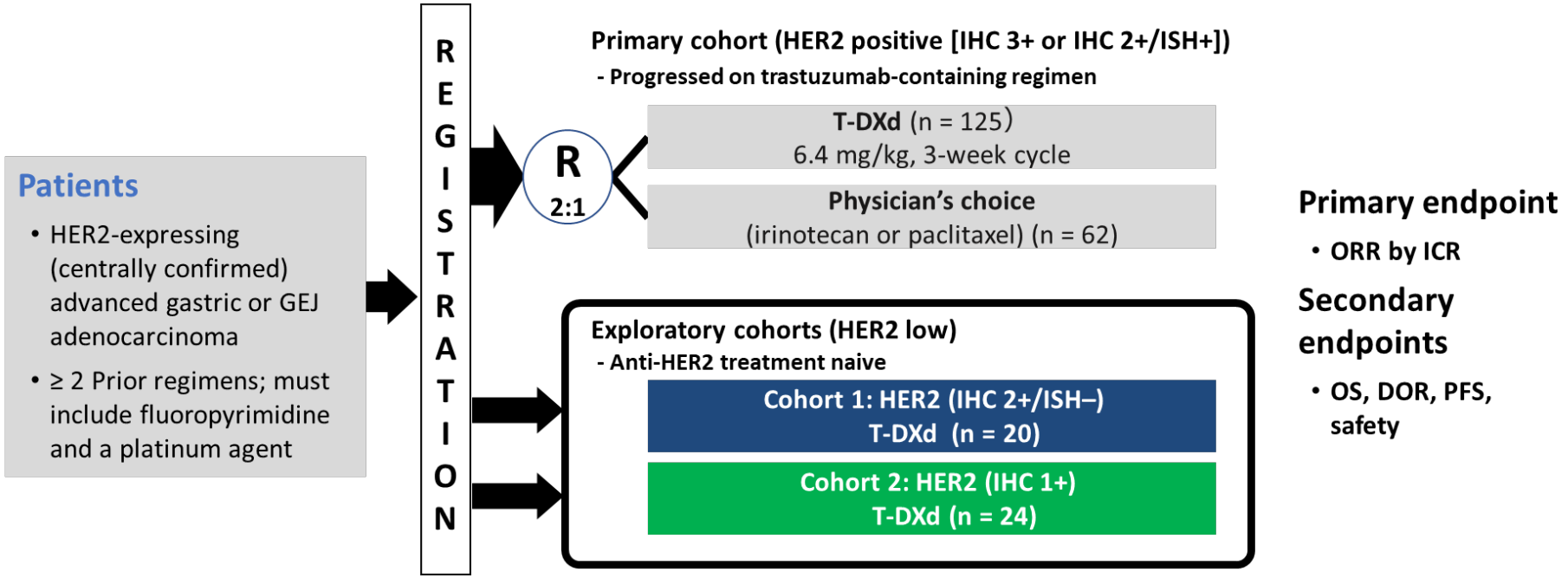
- A significantly higher ORR (51.3% vs 14.3%) and greater confirmed ORR (42.9% vs 12.5%)
- Longer OS (median, 12.5 vs 8.4 months)
- Improved mPFS (5.6 vs 3.5 months)

Here, we present results for the exploratory cohorts of DESTINY-Gastric01

1. Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.

DESTINY-Gastric01

An open-label, multicenter, randomized, phase 2 study



- All patients received T-DXd 6.4 mg/kg q3w
  - Cohort 1 IHC 2+/ISH− (n = 20); cohort 2 IHC 1+ (n = 24)
- Patients had not previously received anti-HER2 treatment
- Median of 2 prior lines of therapy for advanced/metastatic disease
  - 18% had irinotecan, 84% had ramucirumab, 32% had anti–PD-1/PD-L1
- At data cutoff (8 November 2019), no patients in cohort 1 and 2 in cohort 2 (8.3%) remained on treatment

Primary Endpoint: ORR

DESTINY-Gastric Exploratory Cohort

	Primary Cohort[1]		Exploratory Cohorts	
	T-DXd (n = 119)	**PC Overall (n = 56)**	**Cohort 1 IHC 2+/ISH− (n = 19)**	**Cohort 2 IHC 1+ (n = 21)**
ORR by ICR (CR + PR)	**51.3% (n = 61)** **95% CI, 41.9-60.5; *P* < .0001[a]**	**14.3% (n = 8)** **95% CI, 6.4-26.2**	**36.8% (n = 7)** **95% CI, 16.3%-61.6%**	**19.0% (n = 4)** **95% CI, 5.4%-41.9%**
Confirmed ORR by ICR (CR + PR)	**42.9% (n = 51)** **95% CI, 33.8-52.3**	**12.5% (n = 7)** 95% CI, 5.2-24.1	**26.3% (n = 5)** **95% CI, 9.1%-51.2%**	**9.5% (n = 2)** **95% CI, 1.2%-30.4%**
CR	8.4% (n = 10)	0	0	0
PR	34.5% (n = 41)	12.5% (n = 7)	26.3% (n = 5)	9.5% (n = 2)
SD	42.9% (n = 51)	50.0% (n = 28)	63.2% (n = 12)	61.9% (n = 13)
PD	11.8% (n = 14)	30.4% (n = 17)	10.5% (n = 2)	28.6% (n = 6)
NE	2.5% (n = 3)	7.1% (n = 4)	0	0
Confirmed DCR (CR + PR + SD)	85.7% (n = 102) 95% CI, 78.1-91.5	62.5% (n = 35) 95% CI, 48.5-75.1	89.5% (n = 17) 95% CI, 66.9%-98.7%	71.4% (n = 15) 95% CI, 47.8%-88.7%
Median confirmed DOR	11.3 months 95% CI, 5.6 months-NE	3.9 months 95% CI, 3.0-4.9 months	7.6 months 95% CI, 4.1 months-NE	12.5 months 95% CI, NE-NE

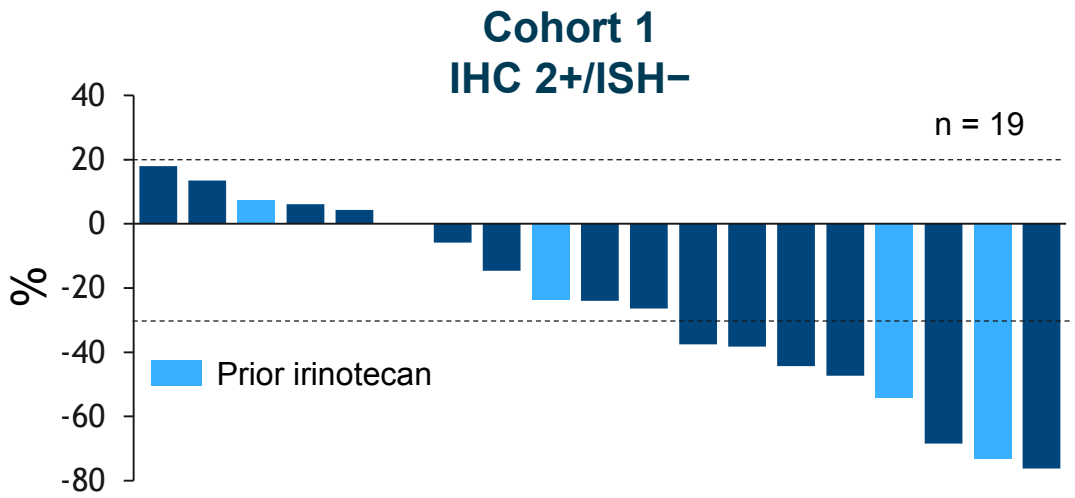
Includes data for the response-evaluable set: all randomized (for primary cohort) patients who received ≥ 1 dose of study drug and had measurable tumors based on independent central review at baseline.

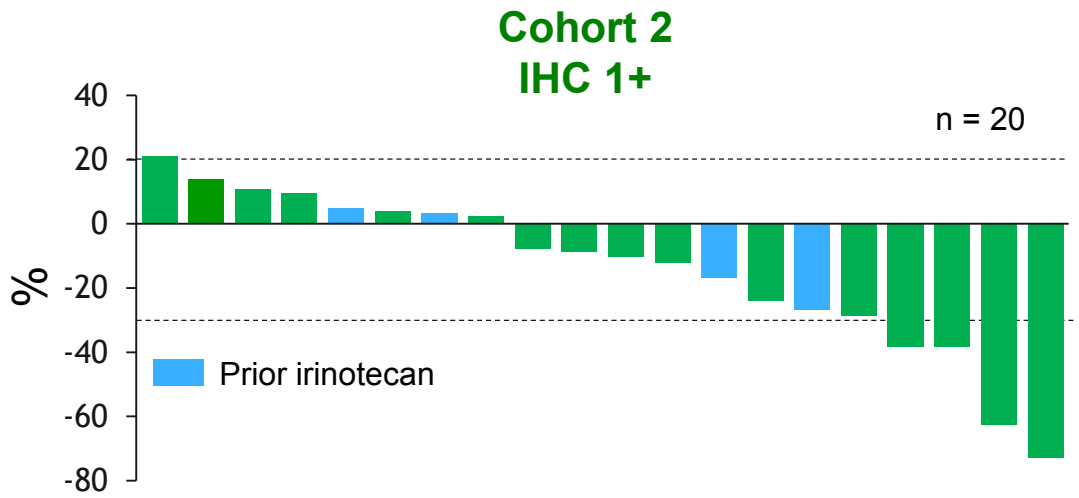
[a]Comparison between T-DXd and PC overall using Cochran-Mantel-Haenszel test stratified by region.

1. Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.

Best Percentage Change From Baseline in Tumor Size

DESTINY-Gastric Exploratory Cohort



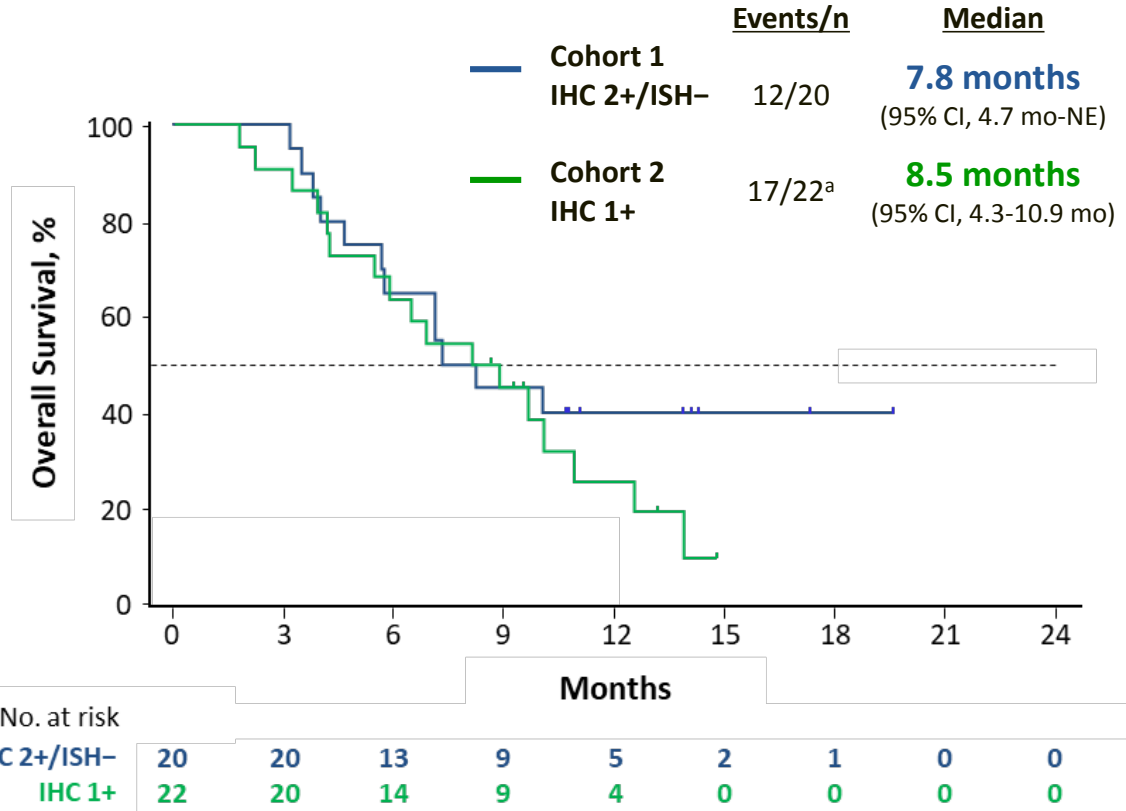


The line at 20% indicates progressive disease; line at −30% indicates partial response. Includes patients in both cohorts who had both baseline and postbaseline target lesion assessments by independent central review. One patient in each cohort was excluded due to no baseline measurable disease by ICR. Three additional patients in the IHC 1+ cohort were excluded due to no postbaseline assessment (n = 1) or a missing HER2 status by central laboratory (n = 2).

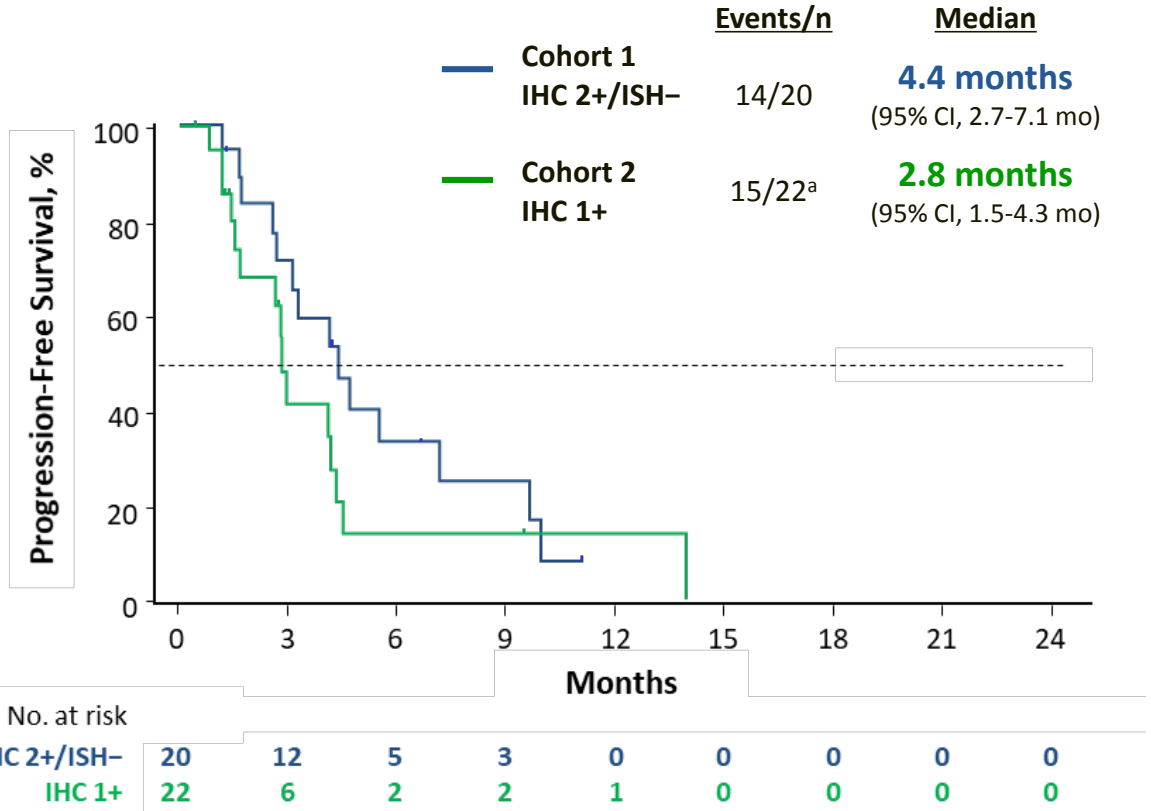
Overall and Progression-Free Survival

DESTINY-Gastric Exploratory Cohort

Overall Survival



Progression-Free Survival



[a] Two patients were excluded from analysis due to a missing HER2 status by central laboratory.

Safety Summary

DESTINY-Gastric Exploratory Cohort

Adverse Events (≥ 20% in either cohort)	Cohort 1 IHC 2+/ISH− (n = 20)		Cohort 2 IHC 1+ (n = 24)	
Preferred Term, n (%)	**Any Grade**	**Grade ≥ 3**	**Any Grade**	**Grade ≥ 3**
Decreased appetite	65	20	75	21
Nausea	55	5	79	4
Anemia	50	30	42	29
Neutrophil count decrease	45	25	50	29
Diarrhea	30	0	33	4
Constipation	25	0	21	0
Fatigue	25	10	25	8
Malaise	20	0	38	0
White-cell count decrease	20	0	33	13
Vomiting	20	0	29	0
Weight decrease	20	0	29	8
Peripheral edema	20	0	4	0
Dysgeusia	20	0	4	0
Pyrexia	15	0	25	0
Platelet count decrease	15	0	29	13
Hypoalbuminemia	10	0	21	8

All hematologic terms are grouped terms. Febrile neutropenia occurred in 1 patient (cohort 1, grade 3).

TEAEs Associated With:	Cohort 1 IHC 2+/ISH− (n = 20)	Cohort 2 IHC 1+ (n = 24)
Drug discontinuation, %	10	4
Dose reduction, %	30	33
Dose interruption, %	40	42

- There were no drug-related deaths in either cohort
- Median treatment duration was 4.2 months (range, 1.3-10.5 months) in cohort 1 and 2.8 months (range, 0.7-14.9 months) in cohort 2
- One patient in each cohort had T-DXd–related ILD/pneumonitis (cohort 1, grade 1; cohort 2, grade 2) as determined by an independent adjudication committee
  - Time to onset was 248 days in cohort 1 and 171 days in cohort 2
  - At data cutoff, the case in cohort 2 was resolving and the case in cohort 1 had not resolved

Conclusions
DESTINY-Gastric Exploratory Cohort

- T-DXd demonstrated antitumor activity in patients with HER2-low gastric or GEJ adenocarcinoma
  - Cohort 1 (IHC 2+/ISH−): confirmed ORR, 26.3%; median OS, 7.8 months; median PFS, 4.4 months
  - Cohort 2 (IHC 1+): confirmed ORR, 9.5%; median OS, 8.5 months; median PFS, 2.8 months
- The safety profile of T-DXd was generally manageable and consistent with that in previous studies[1-4] and with the DESTINY-Gastric01 primary cohort[5]
  - The most common AEs were gastrointestinal or hematologic in nature
  - Signs and symptoms of ILD, a known risk with T-DXd, were actively monitored and managed with dose modification or discontinuation, corticosteroids, and supportive care in accordance with the study protocol
    - One case was reported in cohort 1 (grade 1) and 1 case in cohort 2 (grade 2)
- These findings provide preliminary evidence that T-DXd has clinical activity in patients with previously treated, HER2-low (IHC 2+/ISH−, IHC 1+) gastric or GEJ adenocarcinoma

1. Shitara K, et al. *Lancet Oncol.* 2019;20:827-836. 2. Modi S, et al. *N Engl J Med.* 2020;382:610-621. 3. Modi S, et al. *J Clin Oncol.* 2020;38:1887-1896. 4. Tsurutani J, et al. *Cancer Discov*. 2020;10:688-701.
5. Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.

DXd-ADC パイプライン

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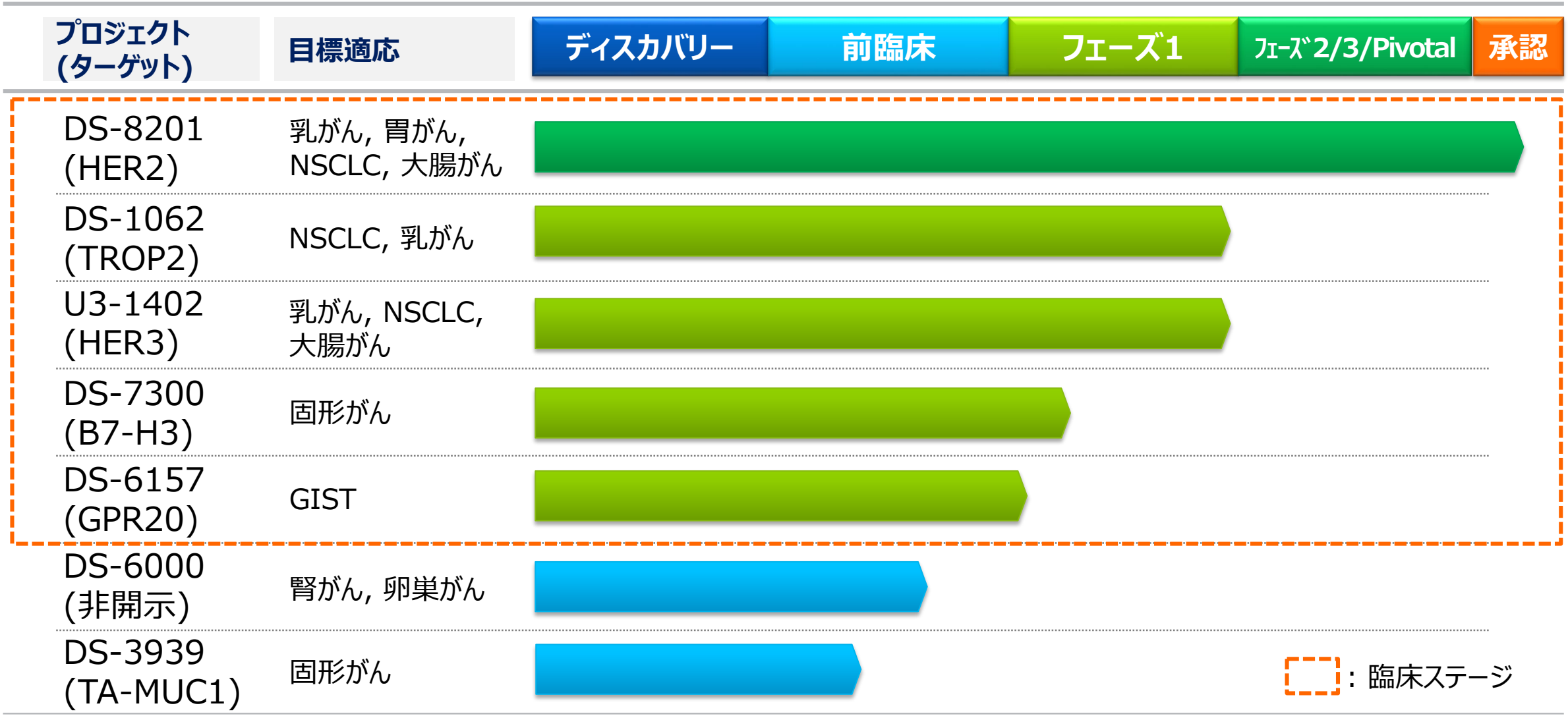
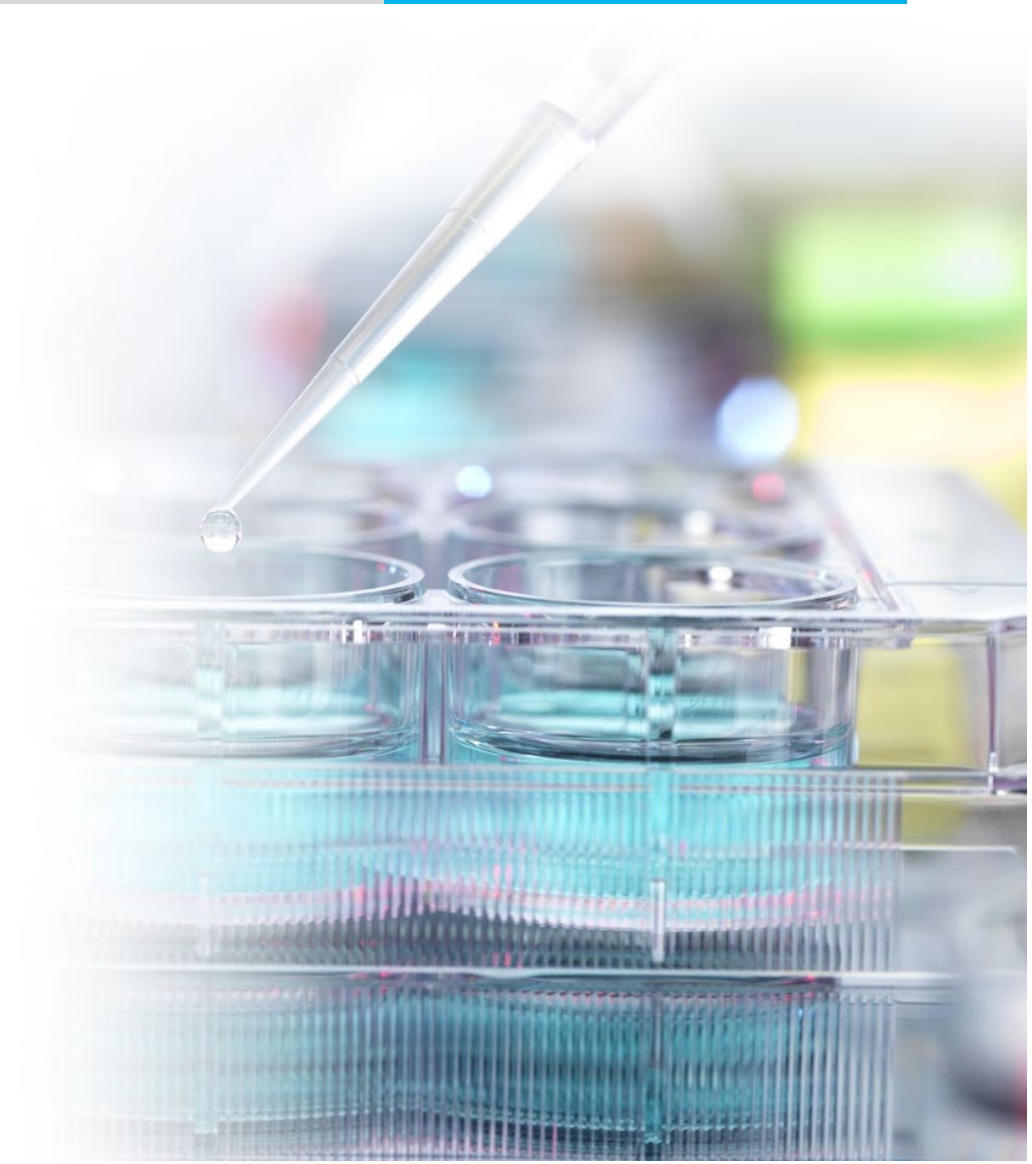


Q&A



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