Trastuzumab deruxtecan in patients with HER2-low recurrent/metastatic salivary gland carcinoma: Results from the phase II MYTHOS trial

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Key Takeaway Points

- Trastuzumab deruxtecan (T-DXd) demonstrated antitumor activity in HER2-low* recurrent/metastatic (R/M) salivary gland carcinoma (SGC), although the prespecified Simon two-stage efficacy criterion was not met.
- In the descriptive FAS analysis, ORR was 38.9% and DCR was 94.4% by independent central review (ICR).
- Responses were observed in salivary duct carcinoma (SDC) but not in the small non-SDC subgroup**.
- ILD/pneumonitis remained an important risk requiring careful monitoring.

*HER2-low was defined as IHC 2+/ISH– or IHC 1+.
**Non-SDC subgroup, n = 6.

Background

- Salivary gland carcinoma (SGC) is rare and heterogeneous, with limited treatment options.[1-4]
- HER2 overexpression is observed in certain subtypes, most frequently in salivary duct carcinoma (SDC).[2,5,6]
- Trastuzumab deruxtecan (T-DXd) has demonstrated efficacy in HER2-overexpressing malignancies,[7-9] and HER2-low breast cancer.[10]
- T-DXd showed a confirmed ORR of 68.4% by ICR in HER2-overexpressing SGC in MYTHOS Cohort 1.[11]
- However, its activity in HER2-low SGC remains largely unexplored.[6,12]

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MYTHOS Study Design

Study Design: Open-label, multicenter, investigator-initiated phase II study in patients with R/M SGC

Treatment: T-DXd 5.4 mg/kg Q3W

HER2 status (Central assessment of archival or biopsy samples*)

*HER2 assay
VENTANA ultraView PATHWAY HER2 (4B5)
PATHVISION® HER-2 DNA Probe Kit
ASCO/CAP 2018 breast cancer criteria

REGISTRATION

Cohort 1: HER2-overexpressing SGC (IHC 3+ or IHC 2+/ISH+)
N = 19
Previously reported confirmed ORR by ICR: 68.4%[1]

1. Kinoshita et al. Presented at ESMO Congress 2024 (Abstract 849O).

Current analysis

Cohort 2: HER2-low SGC (IHC 2+/ISH– or IHC 1+)
Primary efficacy decision set: first 33 patients
FAS: N = 36

Primary endpoint:
- Confirmed ORR by ICR

Secondary endpoints:
- PFS, OS, ORR by investigator, DCR, safety, etc.

Abbreviations: FAS, full analysis set; ICR, independent central review; ORR, objective response rate

Statistical considerations for Cohort 2:
- Simon's two-stage minimax design for the first 33 patients in Cohort 2
- Threshold/expected ORR: 25%/50%; 83% power; two-sided α = 0.05
- Efficacy criterion: ≥14 confirmed objective responses among the first 33 patients

Patient Characteristics (FAS)

Patient enrollment: January 2022 to April 2024
Data cutoff: April 30, 2025

Characteristics	All patients, N = 36
Age, years, median (range)	62.4 (28–80)
Sex, n (%)	
Male	33 (91.7)
Female	3 (8.3)
HER2 status, n (%)	
IHC 2+ and ISH–	17 (47.2)
IHC 1+	19 (52.8)
Histology, n (%)	
SDC	30 (83.3)
Non-SDC*	6 (16.7)
Disease status, n (%)	
Local recurrence	19 (52.8)
Metastasis	33 (91.7)

Characteristics	All patients, N = 36
Prior therapies, n (%)	
Surgery	29 (80.6)
Radiotherapy	21 (58.3)
Systemic therapy	26 (72.2)
No. of regimens	
0	10 (27.8)
1	11 (30.6)
2	9 (25.0)
≥3	6 (16.7)

*Non-SDC histologies included adenocarcinoma NOS (n = 1), adenoid cystic carcinoma (n = 1), mucoepidermoid carcinoma (n = 1), myoepithelial carcinoma (n = 1), and salivary gland carcinoma NOS (n = 2).

Abbreviations: FAS, full analysis set; SDC, salivary duct carcinoma

- Patients who were enrolled and received at least one dose of the investigational drug, excluding those with major protocol deviations, GCP violations, or post-enrollment ineligibility were defined as FAS.
- After enrollment of the first 33 patients in Cohort 2, which constituted the prespecified primary efficacy decision set for the Simon two-stage minimax design, three additional patients who had already provided informed consent were enrolled (Total No. of FAS = 36).

ORR Assessed by ICR in the First 33 Patients: Simon's Two-Stage Design

Response assessment	N = 33* n (%)
Best Overall Response	
Confirmed CR	1 (3.0)
Confirmed PR	11 (33.3)
SD	19 (57.6)
PD	1 (3.0)
NE	1 (3.0)
ORR	
CR + PR	12 (36.4)

The prespecified Simon's two-stage criterion was not met in the first 33 patients: 12 responses were observed versus the required threshold of ≥14 responses.

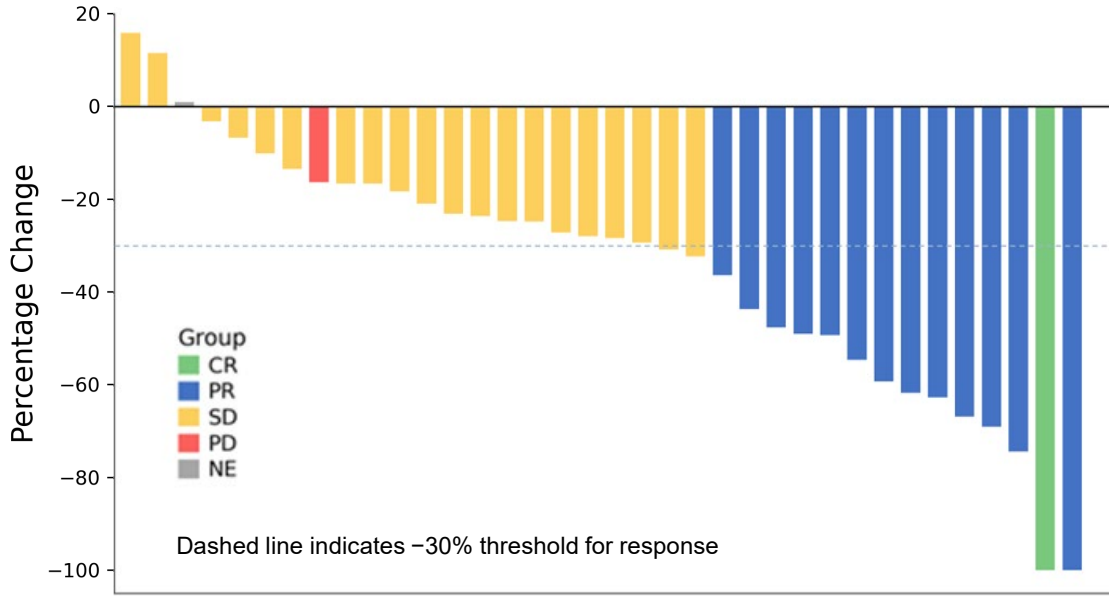
*The first 33 patients were selected by date of registration.

Abbreviations: ICR, independent central review; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate (CR + PR)

ORR Assessed by ICR (FAS)

Response assessment	All patients, N = 36
Best Overall Response, n (%)	
Confirmed CR	1 (2.8)
Confirmed PR	13 (36.1)
SD	20 (55.6)
PD	1 (2.8)
NE	1 (2.8)
ORR, % (95% CI)	38.9 (23.1–56.5)
DCR, % (95% CI)	94.4 (81.3–99.3)

The best percent change from baseline (N = 36)

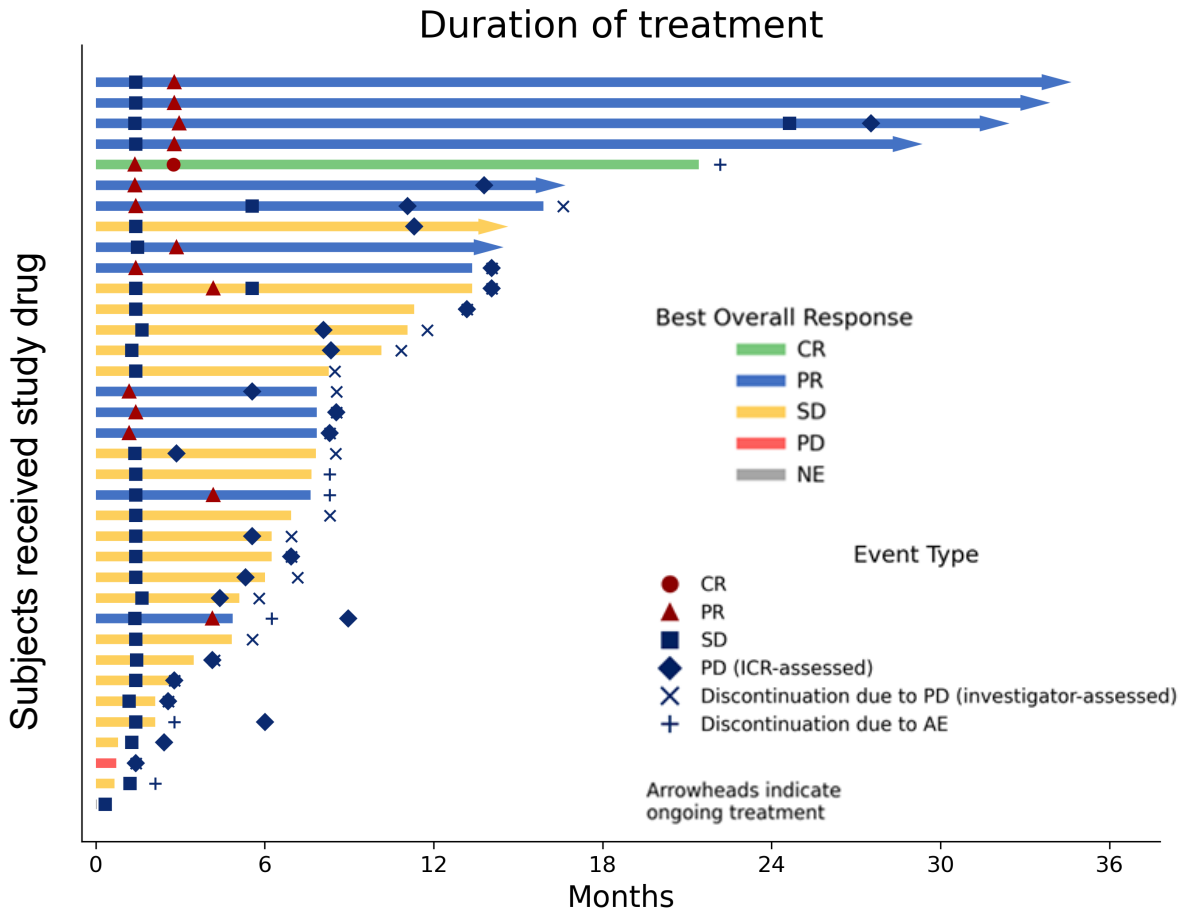


In the descriptive FAS analysis, ORR was 38.9% and DCR was 94.4% by ICR

Abbreviations: FAS, full analysis set; ICR, independent central review; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; ORR, objective response rate (CR + PR); DCR, disease control rate (CR + PR + SD); CI, confidence interval.

- Patients who were enrolled and received at least one dose of the investigational drug, excluding those with major protocol deviations, GCP violations, or post-enrollment ineligibility were defined as FAS (N = 36).

Duration of treatment and response by ICR (FAS)



Median duration of treatment (DOT)* (n = 36): 8.5 months (range, 0.7–35.2)

Median duration of response (DOR)** (n = 14): 12.5 months (95% CI, 4.9–NE)

Abbreviations: ICR, independent central review; FAS, full analysis set; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; AE, adverse event; DOT, duration of treatment; DOR, duration of response; CI, confidence interval; NE, not estimable.

Durable responses were observed in a subset of patients

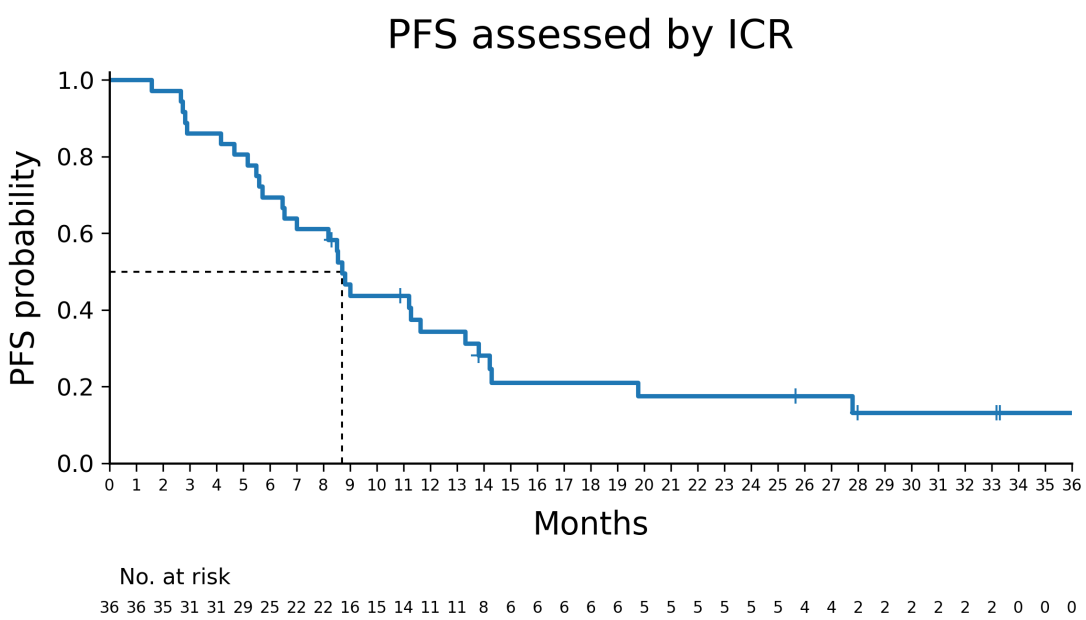
- Patients who were enrolled and received at least one dose of the investigational drug, excluding those with major protocol deviations, GCP violations, or post-enrollment ineligibility were defined as FAS (N = 36).

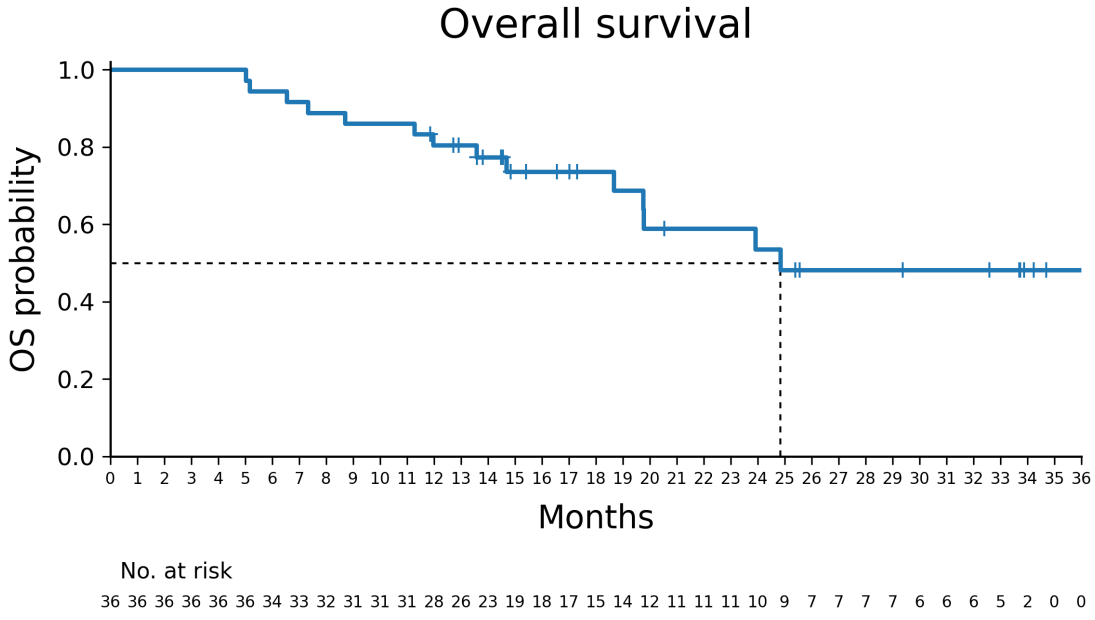
*DOT was measured from the initiation of the treatment until its discontinuation.

**DOR was measured from the time of initial response (PR/CR) to the first occurrence of PD, clinical progression or death, whichever occurred first and assessed by ICR.

PFS by ICR and OS (FAS)

Tick marks indicate censored observations





Median PFS 8.7 months (95% CI, 6.5–13.3)

Median follow-up for PFS: 28.0 months (95% CI, 13.8–NE)

Median OS 24.8 months (95% CI, 18.7–NE)

Median follow-up for OS: 25.4 months (95% CI, 15.4–32.6)

Median PFS and OS were 8.7 and 24.8 months, respectively

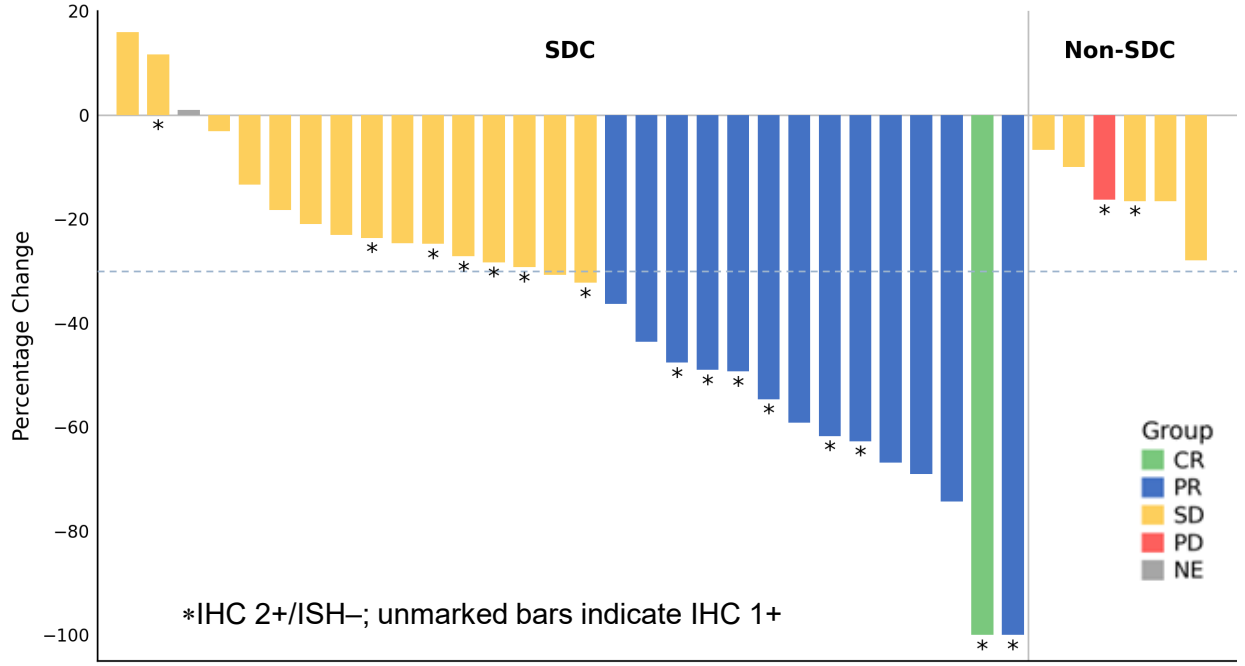
- Patients who were enrolled and received at least one dose of the investigational drug, excluding those with major protocol deviations, GCP violations, or post-enrollment ineligibility were defined as FAS (N = 36).
- Median follow-up time was estimated using the reverse Kaplan–Meier method.

Abbreviations: PFS, progression-free survival; OS, overall survival; FAS, full analysis set; ICR, independent central review; CI, confidence interval.

Tumor Response by Subgroup (FAS)

Subgroup	All patients, N = 36			
	Subtotal (n)	CR or PR (n)	ORR (%)	(95% CI)
HER2 Status				
IHC 2+ and ISH–	17	8	47.1	(23.0–72.2)
IHC 1+	19	6	31.6	(12.6–56.6)
Histological Type				
SDC	**30**	**14**	**46.7**	**(28.3–65.7)**
Non-SDC	6	0	0.0	(0.0–45.9)
Prior Treatment				
Presence of Chemotherapy	26	10	38.5	(20.2–59.4)
Absence of Chemotherapy	10	4	40.0	(12.2–73.8)

The best percent change from baseline (N = 36)



Responses were observed in SDC but not in non-SDC

- Prespecified subgroup analysis; interpretation is limited by the small non-SDC subgroup (n = 6).
- Patients who were enrolled and received at least one dose of the investigational drug, excluding those with major protocol deviations, GCP violations, or post-enrollment ineligibility were defined as FAS (N = 36).

Abbreviations: FAS, full analysis set; SDC, salivary duct carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; AE, adverse event; NE, not evaluable; CI, confidence interval.

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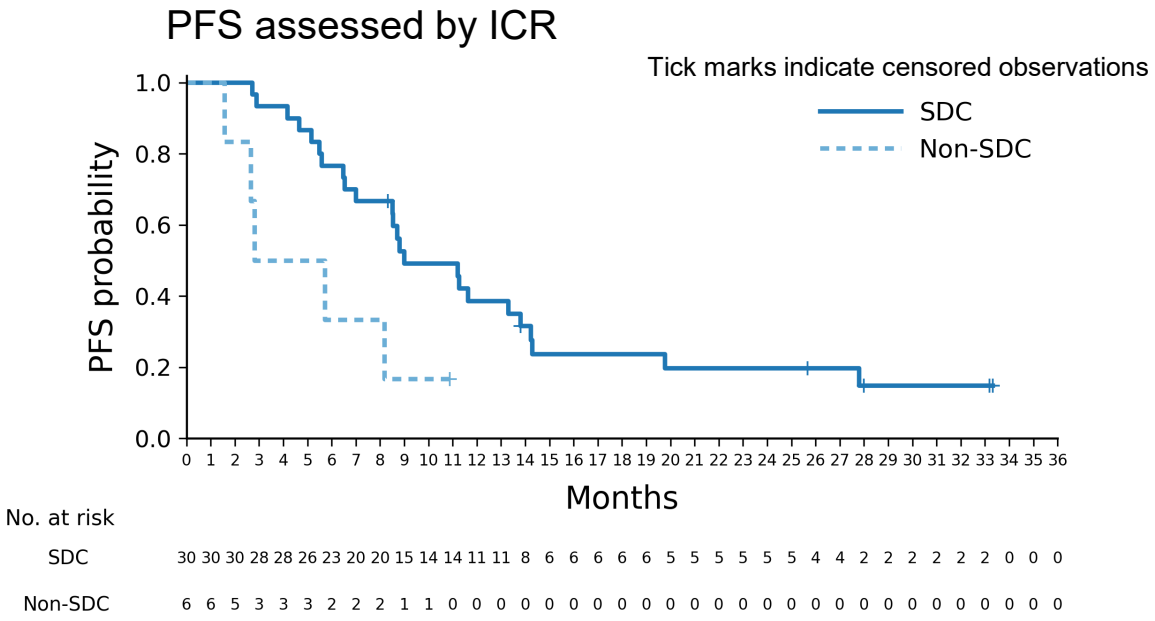
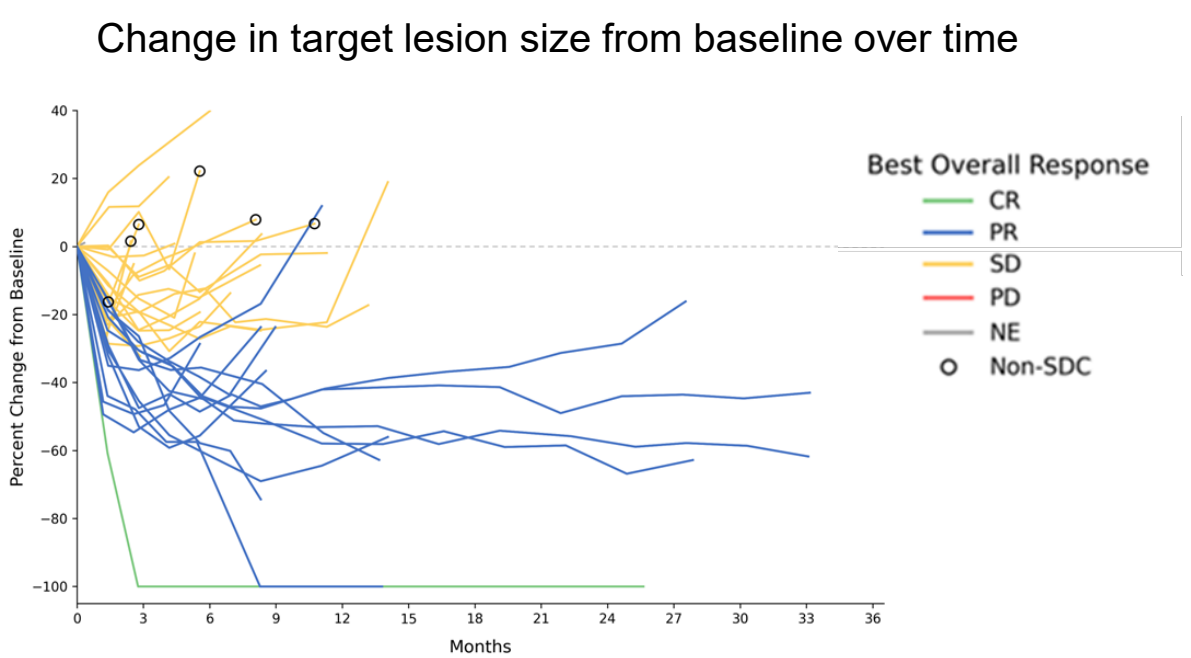
PFS and Tumor Change Over Time by Histology (ICR) (FAS)





Median PFS

SDC (n = 30)	**9.0 months** (95% CI, 7.0–13.8)
Non-SDC (n = 6)	4.3 months (95% CI, 1.6–NE)

Nominal log-rank P = 0.017

In an exploratory analysis, PFS was longer in SDC than in non-SDC

- Exploratory analysis; interpretation is limited by the small non-SDC subgroup (n = 6).
- Patients who were enrolled and received at least one dose of the investigational drug, excluding those with major protocol deviations, GCP violations, or post-enrollment ineligibility were defined as FAS (N = 36).

Abbreviations: PFS, progression-free survival; ICR, independent central review; FAS, full analysis set; SDC, salivary duct carcinoma; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not estimable for CI or not evaluable for response; CI, confidence interval.

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Overall Safety Summary

	All patients (N = 36), n (%)
Treatment-emergent adverse events (TEAEs)	**36 (100%)**
TEAEs with CTCAE Grade ≥3	**20 (55.6%)**
Serious TEAEs	8 (22.2%)
TEAEs leading to death	1 (2.8%)
ILD/pneumonitis*	**1 (2.8%)**
TEAEs leading to dose reduction	13 (36.1%)
TEAEs leading to dose delay	21 (58.3%)
TEAEs leading to T-DXd discontinuation	7 (19.4%)
ILD/pneumonitis*	**6 (16.7%)**
Weight decreased	1 (2.8%)
Drug-related TEAEs	**35 (97.2%)**
Drug-related TEAEs with CTCAE Grade ≥3	17 (47.2%)
Drug-related serious TEAEs	5 (13.9%)
Drug-related TEAEs leading to death	1 (2.8%)
Drug-related TEAEs leading to dose reduction	13 (36.1%)
Drug-related TEAEs leading to dose delay	18 (50.0%)
Drug-related TEAEs leading to T-DXd discontinuation	7 (19.4%)

Median duration of T-DXd treatment: 8.5 months (range, 0.7–35.2)

- **Grade ≥3 TEAEs occurred in 55.6% of patients**
- **ILD/pneumonitis led to T-DXd discontinuation in 16.7%**

*ILD/pneumonitis was assessed by investigators.

Abbreviations: TEAEs, treatment-emergent adverse events; T-DXd, trastuzumab deruxtecan; ILD, interstitial lung disease.

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Common TEAEs and Adverse Events of Special Interest

	All patients (N = 36)				
	Any grade	Grade 1–2	Grade 3	Grade 4	Grade 5
TEAEs: any grade ≥ 30% or grade ≥ 3 in >5%, excluding events of special interest, n (%)					
Nausea	25 (69.4%)	25 (69.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Neutrophil count decreased	22 (61.1%)	9 (25.0%)	11 (30.6%)	2 (5.6%)	0 (0.0%)
White blood cell count decreased	21 (58.3%)	17 (47.2%)	4 (11.1%)	0 (0.0%)	0 (0.0%)
Aspartate aminotransferase increased	18 (50.0%)	18 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Decreased appetite	17 (47.2%)	13 (36.1%)	4 (11.1%)	0 (0.0%)	0 (0.0%)
Constipation	17 (47.2%)	17 (47.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Anaemia	16 (44.4%)	13 (36.1%)	3 (8.3%)	0 (0.0%)	0 (0.0%)
Lymphocyte count decreased	14 (38.9%)	7 (19.4%)	6 (16.7%)	1 (2.8%)	0 (0.0%)
Weight decreased	12 (33.3%)	11 (30.6%)	1 (2.8%)	0 (0.0%)	0 (0.0%)
Alanine aminotransferase increased	11 (30.6%)	11 (30.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Platelet count decreased	11 (30.6%)	11 (30.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Pyrexia	11 (30.6%)	11 (30.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
TEAEs of special interest, n (%)					
ILD/pneumonitis*	**9 (25.0%)**	**7 (19.4%)**	**1 (2.8%)**	**0 (0.0%)**	**1 (2.8%)**
Decreased left ventricular ejection fraction	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

*ILD/pneumonitis was assessed by investigators.

Abbreviations: TEAE, treatment-emergent adverse event; ILD, interstitial lung disease

Conclusions

- Although the prespecified Simon two-stage efficacy criterion was not met, T-DXd demonstrated clinically meaningful antitumor activity in patients with HER2-low R/M SGC, particularly in those with SDC.
- In the descriptive FAS analysis, ORR was 38.9% and DCR was 94.4% by ICR.
- Responses were observed in SDC but not in the small non-SDC subgroup.
- ILD/pneumonitis, including one grade 5 event, requires careful monitoring and prompt management.

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