DESTINY-PanTumor02

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: biomarker and subgroup analyses from the cervical, endometrial, and ovarian cancer cohorts of the DESTINY-PanTumor02 study

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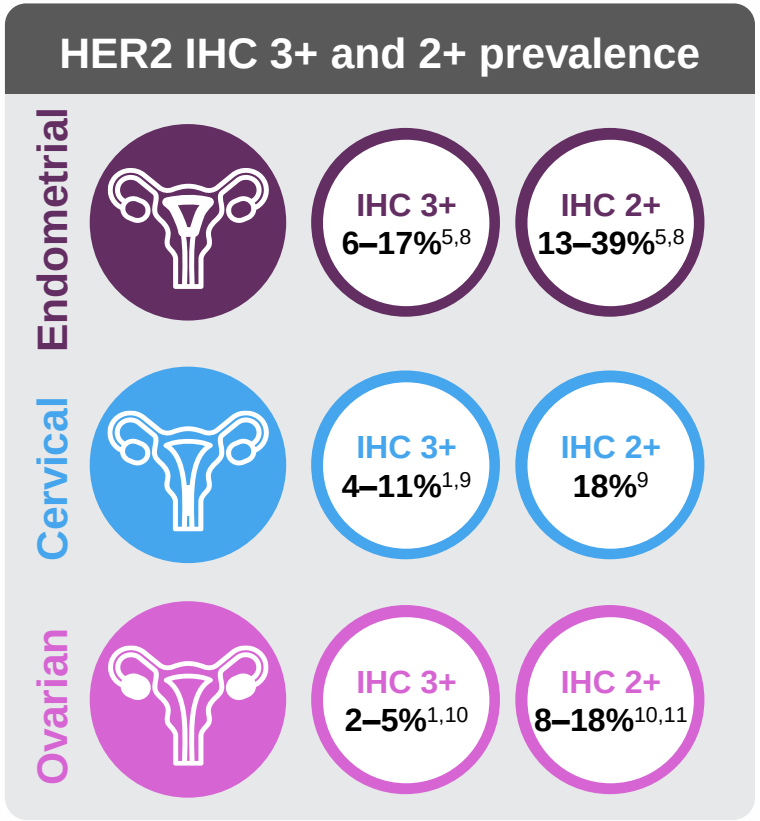
Declaration of interests
Vicky Makker

- Institutional grants or contracts from AstraZeneca, Bristol Myers Squibb, Clasi, Cullinan Oncology, DualityBio, Eisai, Faeth Therapeutics, Karyopharm Therapeutics, Merck, Takeda, and Zymeworks
- Personal meeting/travel support from Eisai and Merck
- Consultant relations with Clovis Oncology, Cullinan Oncology, DualityBio, Eisai, Faeth Therapeutics, GlaxoSmithKline, Immunocore, iTeos Therapeutics, Karyopharm Therapeutics, Lilly, Merck, Mereo BioPharma, MorphoSys, MSD, Novartis, Regeneron, Sutro Biopharma, and Zymeworks

Unmet need in HER2-expressing tumors

- **HER2 expression is seen in a wide range of solid tumors, including gynecological tumors**, and is associated with a biologically aggressive phenotype[1–5]
- In DESTINY-PanTumor02, **T-DXd demonstrated clinically meaningful response rates, progression-free survival, and overall survival** in HER2-expressing tumors, with particular benefit in gynecological tumors[6]
  - **Antitumor activity was observed with T-DXd** in heavily pre-treated patients with **endometrial, cervical, and ovarian tumors across HER2 IHC expression levels, and in ISH+ or plasma *ERBB2*-amplified subgroups**[7]
- Today's presentation reports further subgroup and biomarker analyses from the DESTINY-PanTumor02 **endometrial, cervical, and ovarian cancer cohorts**



ERBB2, erb-b2 receptor tyrosine kinase 2; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; T-DXd, trastuzumab deruxtecan

1. Yan M, et al. *Cancer Metastasis Rev*. 2015;34:157–164; 2. Li Z, et al. *EBioMedicine*. 2020;62:103074; 3. Uzunparmak B, et al. *Ann Oncol*. 2023;34:1035–1046; 4. Xing F, et al. *Mol Cancer*. 2023;22:6; 5. Halle MK, et al. *Br J Cancer*. 2018;118:378–387; 6. Meric-Bernstam F, et al. *J Clin Oncol*. 2024;42:47–58; 7. Lee J-Y, et al. Oral presentation at IGCS 2023 (Abstract 1550); 8. Vermij L, et al. *Cancers*. 2021;13:44; 9. Shi J, et al. *J Pathol Clin Res*. 2021;7:86–95; 10. Tuefferd M, et al. *PLoS One*. 2007;2:e1138.doi:10.1371/journal.pone.0001138; 11. Ersoy E, et al. *Int J Gynecol Pathol*. 2022;41:313–319

DESTINY-PanTumor02: T-DXd for HER2-expressing solid tumors

A Phase 2, open-label, multicenter study (NCT04482309)

Key eligibility criteria

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)*
  - Cervical cohort was expanded to include five IHC 1+ patients†
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd 5.4 mg/kg Q3W

n≈40 per cohort‡

Primary endpoint

- Confirmed ORR (investigator)

Secondary endpoints

- DOR, DCR, PFS, OS
- Safety

Exploratory analyses

- Subgroup analyses by HER2 status§
- Subgroup analyses by biomarkers§

Primary analysis DCO

- June 8, 2023

- Endometrial
- Cervical
- Ovarian
- Bladder
- Other tumors¶
- Biliary tract
- Pancreatic

*Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer scoring[1]); patients were eligible for either test. All patients were centrally tested; †if ≥3 objective responses were observed in the first 15 patients in any of the tumor-specific cohorts (with IHC 3+ or 2+ confirmed by central testing), confirmed on repeat scan 4 weeks or later after first response documented, subsequent patients with IHC 1+ were also eligible for recruitment, up to a maximum of 10 patients with IHC 1+ per cohort; ‡planned recruitment; cohorts with no objective responses in the first 15 patients were to be closed; §subgroup analyses were based on central HER2 testing ¶patients with tumors that express HER2 (IHC 3+ or 2+), excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. 2L, second line; ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; DCO, data cutoff; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PS, performance status; Q3W, every 3 weeks; T-DXd, trastuzumab deruxtecan; WHO, World Health Organization.

1. Hofmann M, et al. *Histopathology*. 2008;52:797–805

Patient disposition

	Endometrial cancer	Cervical cancer	Ovarian cancer
Patients assigned to treatment, n	41	40	40
Patients treated, n	40	40	40
Patients with T-DXd treatment ongoing at data cutoff,* n (%)	10 (25.0)	7 (17.5)	5 (12.5)
Patients who discontinued treatment at data cutoff,* n (%)	30 (75.0)	33 (82.5)	35 (87.5)
Objective disease progression	16 (40.0)	23 (57.5)	28 (70.0)
Adverse event	3 (7.5)	4 (10.0)	3 (7.5)
Patient decision	3 (7.5)	2 (5.0)	1 (2.5)
Investigator decision	0	1 (2.5)	1 (2.5)
Patient lost to follow up	1 (2.5)	0	0
Subjective disease progression	3 (7.5)	1 (2.5)	2 (5.0)
Other†	4 (10.0)	2 (5.0)	0
Median treatment cycles received,‡ (range)	13.0 (1–43)	8.5 (1–39)	7.5 (1–39)
Median follow up, months (range)	19.94 (0.8–31.1)	12.60 (0.9–31.0)	13.13 (0.7–30.6)

*Data cutoff was June 8, 2023; †in case of death whilst on treatment, investigators did not specifically record a reason for discontinuation of T-DXd; ‡a treatment cycle was 21 days
T-DXd, trastuzumab deruxtecan

Demographics and baseline characteristics (1/2)

Characteristic			Endometrial cancer (n=40)	Cervical cancer (n=40)	Ovarian cancer (n=40)
Age, median (range), years			67.0 (37–79)	48.5 (28–78)	56.0 (34–72)
Race, n (%)	White		23 (57.5)	29 (72.5)	22 (55.0)
	Asian		10 (25.0)	7 (17.5)	17 (42.5)
	Black / African American		4 (10.0)	0	1 (2.5)
	Other / not reported		3 (7.5)	4 (10.0)	0
ECOG PS*, n (%)	0		23 (57.5)	22 (55.0)	26 (65.0)
	1		17 (42.5)	18 (45.0)	13 (32.5)
Prior regimens†	Median (range)		2 (0–7)	2 (1–6)	3 (1–12)
	n (%)	≤1	9 (22.5)	6 (15.0)	8 (20.0)
		≥2	31 (77.5)	34 (85.0)	32 (80.0)
HER2 status by central testing‡, (%)		IHC 3+	13 (32.5)	8 (20.0)	11 (27.5)
		IHC 2+	17 (42.5)	20 (50.0)	19 (47.5)
Prior anti-HER2 therapy, n (%)			9 (22.5)	1 (2.5)	2 (5.0)
Prior TOP1 inhibitor therapy, n (%)			0	8 (20.0)	11 (27.5)

*One patient with ovarian cancer had an ECOG PS of 2; †one patient with endometrial cancer had received no prior regimens; ‡in the endometrial, cervical, and ovarian cancer cohorts, nine, twelve, and ten patients were IHC 1+/0 by central testing, respectively; one patient in the endometrial cancer cohort was IHC unknown by central testing
ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; PS, performance status; TOP1, topoisomerase I

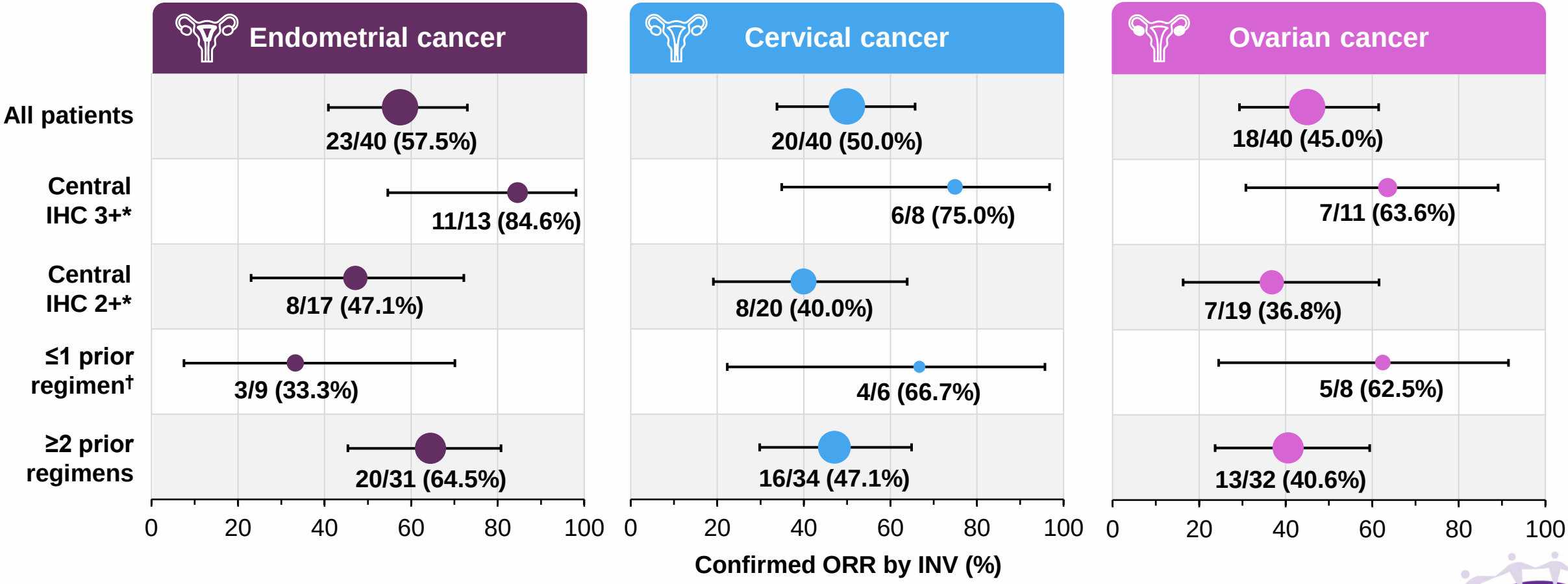
Demographics and baseline characteristics (2/2)

Characteristic			Endometrial cancer (n=40)
Biomarker prevalence, n (%)	PD-L1 IC*	≥1%	19 (47.5)
		<1%	17 (42.5)
	MMR genes in ctDNA	Mutation detected	3 (7.5)
		Mutation not detected	37 (92.5)
			Cervical cancer (n=40)
Biomarker prevalence, n (%)	PD-L1 IC*	≥1%	23 (57.5)
		<1%	10 (25.0)
			Ovarian cancer (n=40)
Biomarker prevalence, n (%)	*BRCA1/2*† in ctDNA	Mutation detected	7 (17.5)
		Mutation not detected	31 (77.5)
	HRR†‡ genes in ctDNA	Mutation detected	8 (20.0)
		Mutation not detected	30 (75.0)
	CA 125§	≤ULN	11 (27.5)
		>ULN	27 (67.5)

*Data not available for four patients with endometrial cancer and seven patients with cervical cancer owing to insufficient or no tumor tissue available, or technical problems; †ctDNA analysis was not possible for two patients with ovarian cancer; one patient with ovarian cancer was a low shedder (considered low shedder if no tumoral mutations detected, or very low-frequency mutations detected, or only variants of uncertain significance detected), and one patient with ovarian cancer was not profiled owing to consent withdrawal; ‡HRR gene list includes *BRCA1* and *BRCA2* genes; §CA 125 result was not available for two patients with ovarian cancer

BRCA1/2, *BRCA1* or *BRCA2* gene; CA, cancer antigen; ctDNA, circulating tumor DNA; HRR, homologous recombinant repair gene; IC, immune cells; MMR, mismatch repair; PD-L1, programmed cell death ligand 1; ULN, upper limit of normal

ORR in all patients, and by central IHC status and number of prior regimens



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Error bars represent 95% confidence intervals

*In patients with IHC 1+/0/unknown by central testing, responses were observed in 4/10 patients with endometrial cancer, 6/12 patients with cervical cancer, and 4/10 patients with ovarian cancer; †one patient with endometrial cancer was reported to have received no prior regimens

IHC, immunohistochemistry; INV, investigator; ORR, objective response rate

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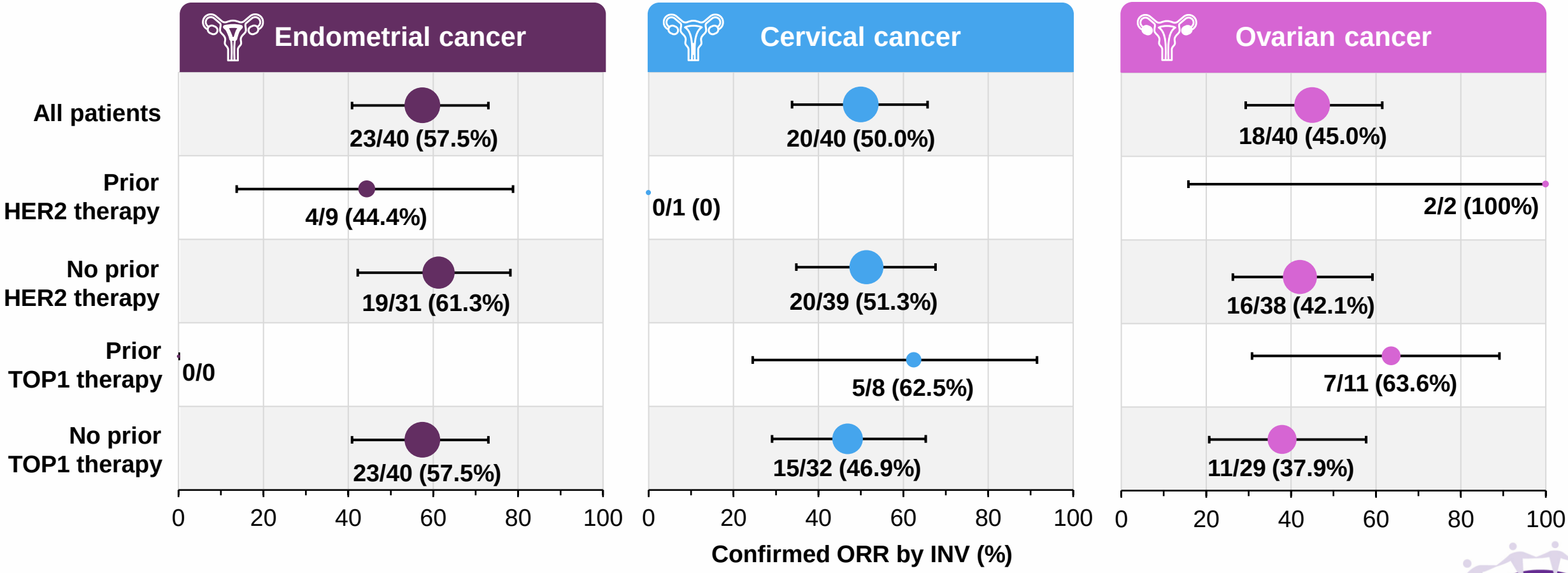
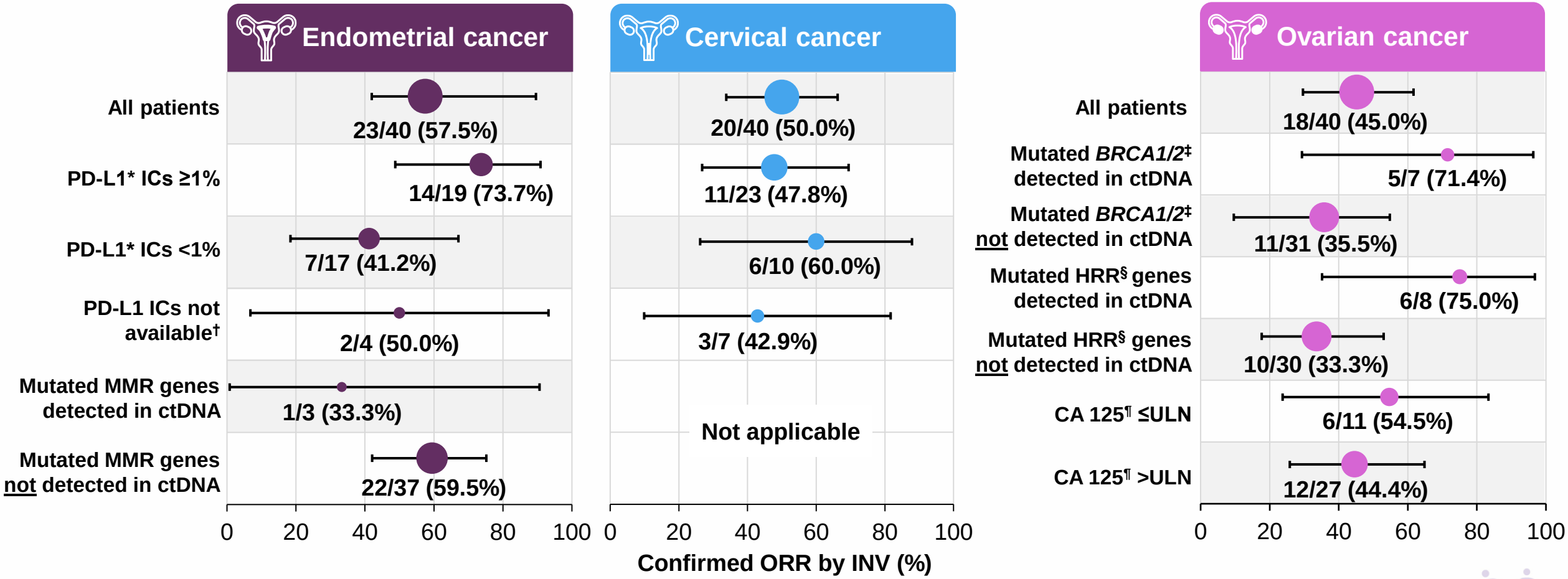
ORR by prior HER2 and TOP1 inhibitor therapy



Error bars represent 95% confidence intervals; confidence intervals not included for 0%
HER2, human epidermal growth factor receptor 2; INV, investigator; ORR, objective response rate; TOP1, topoisomerase I

ORR by biomarker status



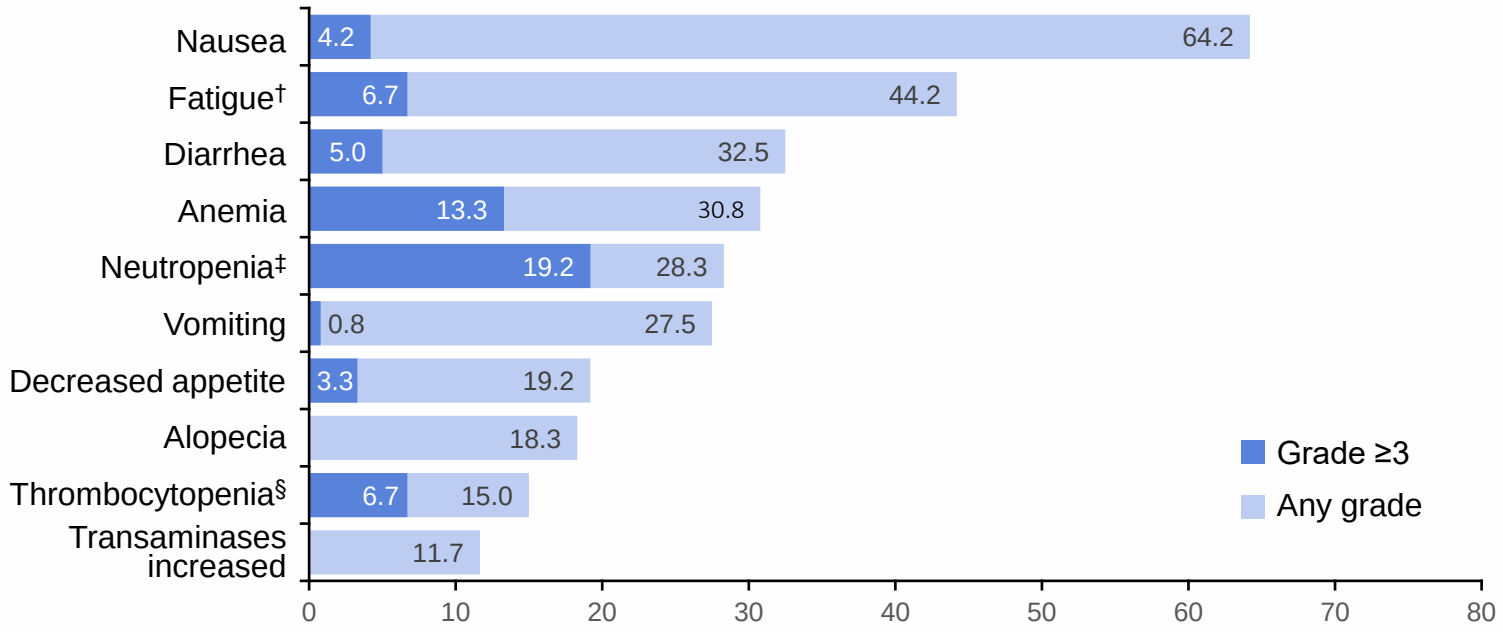
Error bars represent 95% confidence intervals. *Evaluated using the VENTANA PD-L1 (SP263) assay; †data not available owing to insufficient or no tumor tissue available, or technical problems; ‡ctDNA analysis was not possible in two patients with ovarian cancer; one patient was a low shedder (considered low shedder if no tumoral mutations detected, or very low-frequency mutations detected, or only variants of uncertain significance detected), and one patient was not profiled owing to consent withdrawal; §HRR gene list includes BRCA1 and BRCA2 genes; ¶CA 125 result not available for two patients with ovarian cancer

BRCA1/2, *BRCA1* or *BRCA2* gene; CA, cancer antigen; ctDNA, circulating tumor DNA; HRR, homologous recombinant repair gene; IC, immune cell; INV, investigator; MMR, mismatch repair; ORR, objective response rate; PD-L1, programmed cell death ligand 1; ULN, upper limit of normal

Safety summary: gynecological cohorts

n (%)	Gynecological cohorts N=120
Any drug-related TEAEs	106 (88.3)
Drug-related TEAEs Grade ≥3	54 (45.0)
Serious drug-related TEAEs	18 (15.0)
Drug-related TEAEs associated with dose discontinuations	7 (5.8)
Drug-related TEAEs associated with dose interruptions	24 (20.0)
Drug-related TEAEs associated with dose reductions	35 (29.2)
Drug-related TEAEs associated with deaths	2 (1.7)*

Most common drug-related TEAEs (>10%) in gynecological cohorts



ILD/pneumonitis adjudicated as T-DXd related¶, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Gynecological cohorts N=120	4 (3.3)	8 (6.7)	0	0	1 (0.8)	13 (10.8)

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Analyses were performed in patients who received ≥1 dose of T-DXd (N=120); median total treatment duration was 9.0, 6.0, and 5.9 months in the endometrial, cervical, and ovarian cohorts, respectively
*Included pneumonia (n=1) and organizing pneumonia (n=1); †category includes the preferred terms fatigue, asthenia, and malaise; ‡category includes the preferred terms neutrophil count decreased and neutropenia; §category includes the preferred terms platelet count decreased and thrombocytopenia; ¶all ILD/pneumonitis cases were reviewed by an Adjudication Committee
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event

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Conclusions

- **T-DXd demonstrated clinically meaningful ORRs in heavily pre-treated patients with HER2-expressing endometrial, cervical, and ovarian tumors in DESTINY-PanTumor02; responses were observed in patients across:**
  - IHC 3+ and IHC 2+ expression, with the greatest response seen in those with IHC 3+ tumors by central testing (ORR 84.6% for endometrial, 75.0% for cervical, and 63.6% for ovarian tumors)
  - Numbers of prior treatment regimens, and with or without use of prior HER2 (endometrial and ovarian) or TOP1 inhibitor (cervical and ovarian) therapy
  - Biomarker status, including in the presence or absence of biomarkers relevant to the individual cancer cohorts
- **The safety findings were consistent with the established profile for T-DXd**
  - The three most commonly reported drug-related TEAEs were nausea, fatigue,* and diarrhea
  - ILD/pneumonitis remains an important identified risk; proactive monitoring, early detection, and active management are critical in preventing high-grade ILD/pneumonitis

These data suggest T-DXd is a potential treatment for patients with these gynecological HER2-expressing tumors who have disease progression, including those with varied prior treatment regimens and with and without disease-relevant biomarkers

*Category includes the preferred terms fatigue, asthenia, and malaise
HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ILD, interstitial lung disease; ORR, objective response rate; T-DXd, trastuzumab deruxtecan; TEAE, treatment-emergent adverse event; TOP1, topoisomerase I

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