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Datopotamab deruxtecan (Dato-DXd) in patients with Ovarian or Endometrial Cancer: Results from the Phase 2 TROPION-PanTumor03 Study

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Declaration of Interests

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Ana Oaknin

- **Consulting or Advisory Role** at Agenus, Amgen, AstraZeneca, Clovis Oncology, Roche, Corcept Therapeutics, Deciphera, Eisai, EMD Serono, F. Hoffmann-La Roche, Genmab, GSK, Immunogen, ITeos Therapeutics, Medison, Merck Sharp & Dohme, Mersana, Novocure, PharmaMar, prIME Oncology, Shattuck Labs, Sutro Biopharma, Tesaro.

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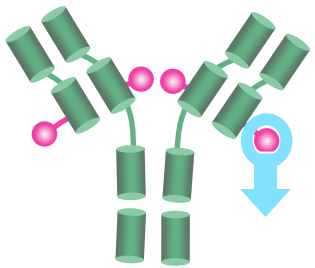
Background

- TROP2 is a transmembrane protein that is highly expressed in a majority of ovarian and endometrial cancers[1]
- Dato-DXd is a TROP2-directed ADC that delivers a potent Topo-I inhibitor payload into tumour cells,[2] and has several unique properties:*
  - Optimised drug to antibody ratio ≈ 4†
  - Plasma-stable, tumour-selective cleavable linker-payload
  - High potency of payload with short systemic half-life†
  - Bystander antitumour effect
- Dato-DXd has demonstrated clinically relevant efficacy and manageable safety in Phase 3 trials in patients with pretreated non-squamous NSCLC and HR+/HER2– breast cancer[3,4]

Dato-DXd: Humanised anti-TROP2 IgG1 monoclonal antibody[5]



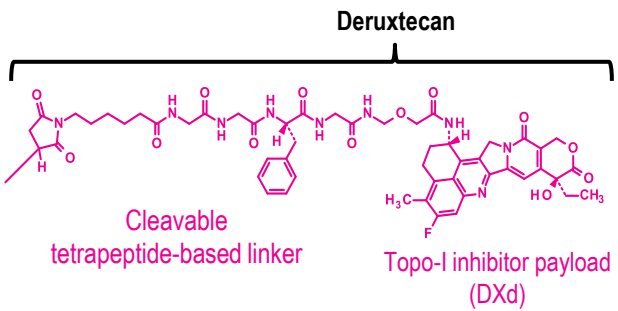


Image is for illustrative purposes only; actual drug positions may vary.

*The clinical relevance of these features is under investigation. †Based on animal data.
ADC, antibody-drug conjugate; Dato-DXd, datopotamab deruxtecan; HR+, hormone receptor positive; HER2–, human epidermal growth factor receptor 2 negative; IgG, immunoglobulin G; NSCLC, non-small cell lung cancer; TROP2, trophoblast cell-surface antigen 2; Topo-I, topoisomerase-I.

1. Shvartsure A, et al. Genes Cancer 2015;6:84–105; 2. Okajima D, et al. Mol Cancer Ther 2021;20:2329–40; 3. Ahn M-J, et al. Ann Oncol 2023;34:S1665–66; 4. Bardia A, et al. Ann Oncol 2023;34(suppl_2):S1264–5; 5. Dent R, et al. Future Oncol 2024;19:2349–59.

TROPION-PanTumor03: Study Design

A Phase 2, open-label, global study (NCT05489211) evaluating Dato-DXd as monotherapy and in combination with various anticancer agents across several tumour types

- Here, we present results of Dato-DXd monotherapy in the ovarian and endometrial cancer cohorts

Ovarian cancer (TROP2 expression unselected)

- High-grade serous or endometrioid ovarian, fallopian tube, or primary peritoneal carcinoma
- ECOG PS 0 or 1
- Progressed on ≥1 line of platinum chemotherapy but no more than 2 lines of therapy for advanced or metastatic disease; platinum-sensitive and resistant disease allowed*

Endometrial cancer (TROP2 expression unselected)

- Advanced/metastatic endometrial carcinoma
- All histologies (except sarcoma)
- ECOG PS 0 or 1
- Progressed on ≥1 line of platinum chemotherapy but no more than 2 lines of therapy for advanced or metastatic disease

N=35

N=40

Dato-DXd† 6 mg/kg IV Q3W

Endpoints

Primary

- ORR by investigator per RECIST v1.1
- Safety & tolerability

Secondary

- PFS, DoR, DCR by investigator
- PK and immunogenicity

Exploratory

- OS
- Biomarker analyses

*Platinum-sensitive is defined as relapse/progression ≥6 months after completion of platinum-based chemotherapy; platinum-resistant is defined as progression <6 months of platinum-based therapy, including primary-refractory patients who progressed on or within 3 months of platinum-based chemotherapy (modified definition implemented by IMG); †Patients continued to receive treatment until they met one of the discontinuation criteria, including disease progression, unacceptable toxicity, withdrawal of consent, or study termination. Per protocol, a daily oral care protocol for stomatitis prophylaxis was provided to all patients prior to initiation of Dato-DXd; the use of a steroid-containing mouthwash was highly recommended.

DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IMG, International Medical Graduates; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; Q3W, every 3 weeks; RECIST v1.1, Response evaluable criteria in solid tumours version 1.1.

Baseline Characteristics and Demographics

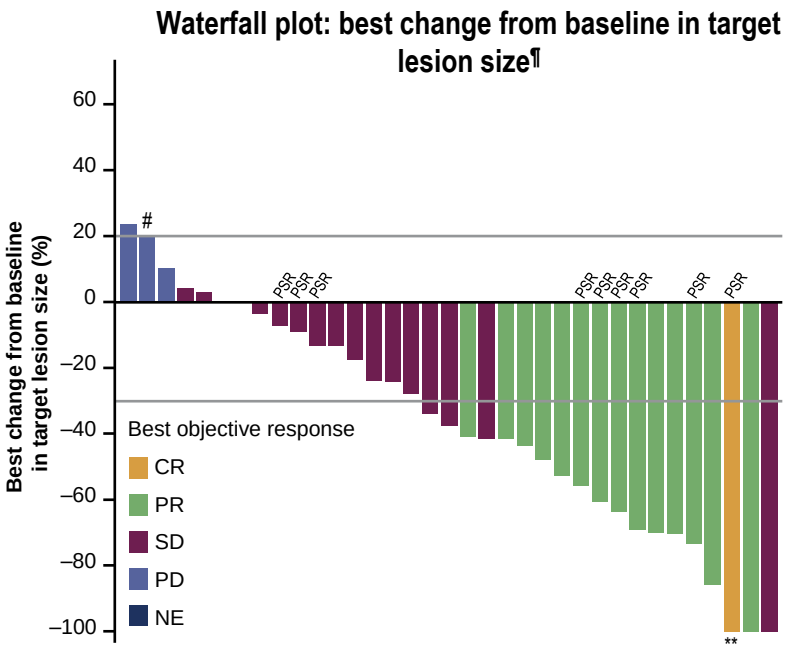
Characteristic		Ovarian (N=35)	Endometrial (N=40)
Age	Median (range), years	61.0 (35–80)	66.5 (48–78)
Race, n (%)	Asian	8 (22.9)	16 (40.0)
	White	23 (65.7)	18 (45.0)
	Other or not reported	4 (11.4)*	6 (15.0)†
ECOG PS, n (%)	0	21 (60.0)	25 (62.5)
	1	14 (40.0)	15 (37.5)
Major histology types, n (%)	High-grade endometrioid	0 (0.0)	11 (27.5)
	High-grade serous	27 (77.1)	10 (25.0)
	Low-grade endometrioid	0 (0.0)	7 (17.5)
	Clear cell	6 (17.1)	3 (7.5)
	Other‡	2 (5.7)	9 (22.5)
Previous lines of therapy, n (%)§	1	11 (31.4)	29 (72.5)
	≥2	24 (68.6)	11 (27.5)
Prior therapy, n (%)‖	Platinum therapy	35 (100)	40 (100)
	Bevacizumab/Lenvatinib	25 (71.4)	8 (20.0)
	PARP inhibitors	18 (51.4)	1 (2.5)
	Immunotherapy	2 (5.7)	9 (22.5)
	Hormone therapy	0 (0.0)	5 (12.5)
Platinum-sensitivity	Platinum-resistant¶	26 (74.3)	–
	Platinum-sensitive	9 (25.7)	–

*Including other (n=1), missing (n=1) and not reported (n=2); †Including American Indian or Alaska Native (n=1), Black or African American (n=1), not reported (n=3) and missing (n=1); ‡Including carcinosarcoma; §A patient who has received multiple lines of therapy is counted under the higher line of therapy only. No more than 2 previous lines of systemic therapy in the advanced or metastatic setting were allowed, neoadjuvant/adjuvant was counted as a line of therapy in the ovarian cohort; ‖A patient can be counted in multiple rows since more than one therapy can be taken. Within each row, a patient is counted only once; ¶Includes patients with platinum-refractory disease, defined as progression within 3 months of platinum therapy. PARP, Poly-ADP ribose polymerase.

Efficacy in Ovarian Cancer

- As of June 14, 2024, median duration of follow-up* was 14.5 months (range 10.4–15.4) in the ovarian cohort

	Ovarian		
	Total (N=35)	Platinum-sensitive (n=9)	Platinum-resistant (n=26)
Confirmed ORR, % (95% CI)	42.9 (26.3–60.6)	66.7 (29.9–92.5)	34.6 (17.2–55.7)
Best overall response, n (%)			
CR	1 (2.9)	1 (11.1)	0 (0.0)
PR	14 (40.0)	5 (55.6)	9 (34.6)
SD†	17 (48.6)	3 (33.3)	14 (53.8)
PD‡	3 (8.6)	0 (0.0)	3 (11.5)
NE§	0 (0.0)	0 (0.0)	0 (0.0)
Median time to response, months (range)	1.4 (1.2–8.2)	–	–
Median DoR, months (95% CI)	5.7 (2.9–NC)	8.5 (2.7–NC)	5.6 (2.9–NC)
DCR at 12 weeks,‖ % (80% CI)	85.7 (75.1–92.9)	100 (77.4–100.0)	80.8 (67.2–90.3)
Median PFS, months (95% CI)	5.6 (4.1–7.0)	–	–



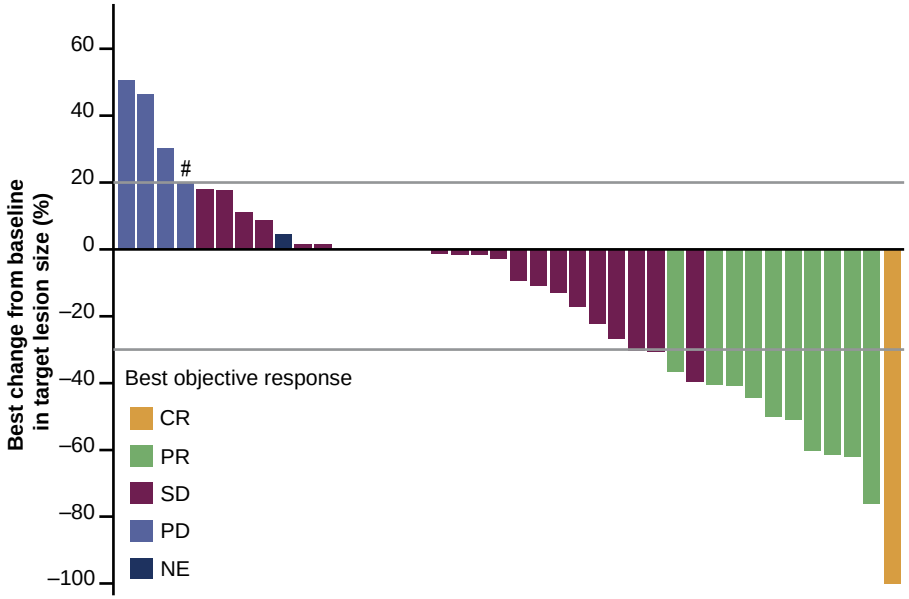
*Duration of follow-up calculated as the median time from randomisation to the date of censoring, in censored patients only; †Unconfirmed CR/PR, or SD ≥35 days; ‡RECIST progression or death ≤13 weeks; §SD <35 days, no valid baseline assessment or evaluable follow-up assessment; ‖Defined as the percentage of patients who achieved CR, PR or SD; ¶Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. Lines at -30% and 20% indicate thresholds for PR and PD, respectively. If best percentage change cannot be calculated due to missing data, +20% will be imputed as the best percentage change in the following situations (otherwise left as missing): patient has no post-baseline assessment, has died, has new lesions or progression of lesions, or has withdrawn due to PD and has no evaluable target lesion data. Patients with imputed values marked with #; **Patient had PR at the first visit (with a change from baseline in the target lesion of 100%) and PD at the subsequent two visits and was therefore an unconfirmed PR and classified as SD. CI, confidence interval; CR, complete response; NC, not calculable; NE, not evaluable; PD, progressive disease; PR, partial response; PSR, platinum-sensitive relapsed; SD, stable disease.

Efficacy in Endometrial Cancer

- As of June 14, 2024, median duration of follow-up* was 13.6 months (range 2.1–19.6) in the endometrial cohort

	Endometrial (N=40)
Confirmed ORR, % (95% CI)	27.5 (14.6–43.9)
Best overall response, n (%)	
CR	1 (2.5)
PR	10 (25.0)
SD†	23 (57.5)
PD‡	5 (12.5)
NE§	1 (2.5)
Median time to response, months (range)	2.8 (1.4–4.2)
Median DoR, months (95% CI)	16.4 (7.1–NC)
DCR at 12 weeks,‖ % (80% CI)	57.5 (46.1–68.3)
Median PFS, months (95% CI)	6.3 (2.8–NC)

Waterfall plot: best change from baseline in target lesion size¶



*Duration of follow-up calculated as the median time from randomisation to the date of censoring, in censored patients only; †Unconfirmed CR/PR, or SD ≥35 days; ‡RECIST progression or death ≤13 weeks; §SD <35 days, no valid baseline assessment or evaluable follow-up assessment; ‖Defined as the percentage of patients who achieved CR, PR or SD; ¶Best change in target lesion size is the maximum reduction from baseline or the minimum increase from baseline in the absence of a reduction. Lines at -30% and 20% indicate thresholds for PR and PD, respectively. If best percentage change cannot be calculated due to missing data, +20% will be imputed as the best percentage change in the following situations (otherwise left as missing): patient has no post-baseline assessment, has died, has new lesions or progression of lesions, or has withdrawn due to PD and has no evaluable target lesion data. Patients with imputed values marked with #.

Exposure and Safety

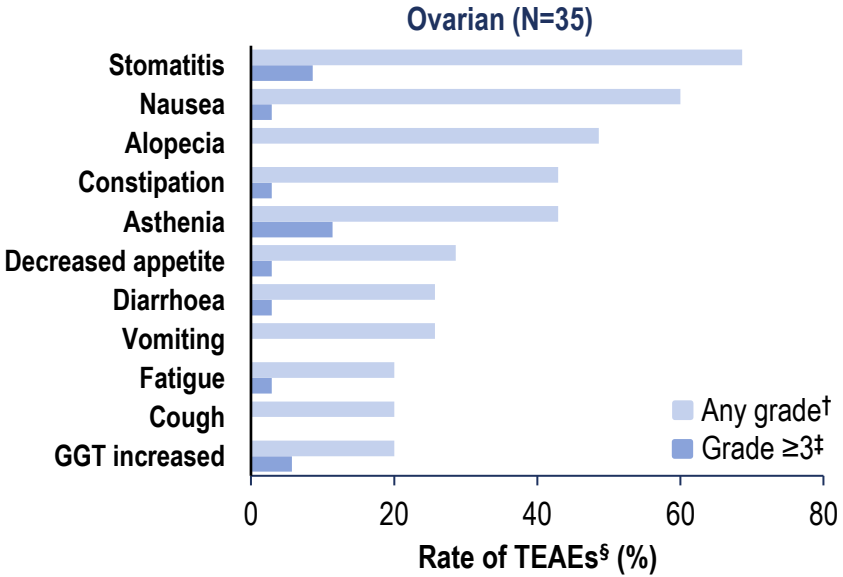
- The median treatment duration* for Dato-DXd was 5.6 months (range 1.4–14.8) in the ovarian cohort and 5.2 months (range 0.7–19.3) in the endometrial cohort

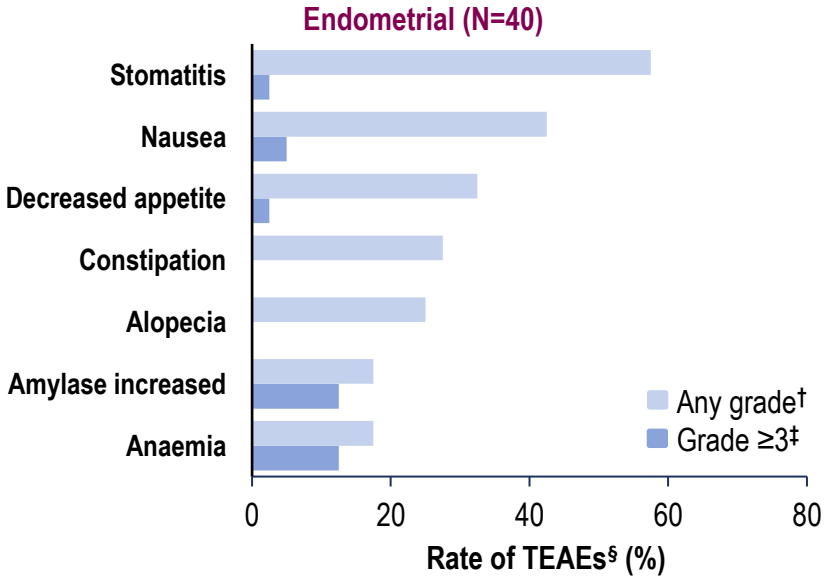
TEAEs, n (%)†	Ovarian (N=35)	Endometrial (N=40)
All grade	35 (100.0)	39 (97.5)
Grade ≥3‡	19 (54.3)	23 (57.5)
Serious	10 (28.6)	11 (27.5)
Leading to		
Dose reduction§	13 (37.1)	10 (25.0)
Dose interruption‖	16 (45.7)	14 (35.0)
Discontinuation¶	2 (5.7)	3 (7.5)
Death	0 (0)	0 (0)

*Actual treatment duration, defined as the total treatment duration (period from the first dose data of study drug to earliest of date of study discontinuation, date of death, data cutoff) minus the total duration of interruptions;
†Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories;
‡According to Common Terminology Criteria for Adverse Events (CTCAE) v5.0; §The most common reason for dose reduction in both cohorts was stomatitis (ovarian cohort: n=4; endometrial cohort: n=7); ‖The most common reasons for dose interruptions were punctate keratitis (n=2), vision blurred (n=2), and stomatitis (n=2) in the ovarian cohort and COVID-19 (n=2), keratitis (n=3) and amylase increased (n=2) in the endometrial cohort; ¶Reasons for discontinuation were pneumonitis (n=2) in the ovarian cohort and syncope (n=1), dry eye and ulcerative keratitis (n=1) and ILD (n=1) in the endometrial cohort. ILD, interstitial lung disease; TEAEs, treatment-emergent adverse events.

Most Frequent TEAEs

- The most common TEAEs in both cohorts were stomatitis* and nausea; the majority of cases were grade 1–2
- Adjudicated drug-related ILD* was reported in 1 patient in each cohort; both cases were grade 3
- Ocular surface events* were reported in 40.0% (grade 3: 0%) and 27.5% (grade 3: 5%) of patients in the ovarian and endometrial cohorts, respectively; there were no grade 4 or 5 events





*Adverse events of Special Interest. Ocular surface events and ILD are reported as group terms; †TEAEs that occurred at any grade in ≥20% of patients shown; ‡According to CTCAE v5.0; grade ≥3 AEs that occurred in ≥5 patients included; §Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
GGT, gamma-glutamyltransferase.

Conclusions

- **Dato-DXd monotherapy** demonstrated **encouraging efficacy** in patients with **advanced/metastatic ovarian and endometrial cancer** who had disease progression on prior platinum chemotherapy
  - In the ovarian cohort, ORR was 42.9% and median DoR was 5.7 (95% CI: 2.9–NC) months
    - In platinum-sensitive patients, ORR was 66.7% and median DoR was 8.5 (95% CI: 2.7–NC) months
    - In platinum-resistant patients, ORR was 34.6% and median DoR was 5.6 (95% CI: 2.9–NC) months
  - In the endometrial cohort, ORR was 27.5% and median DoR was 16.4 (95% CI: 7.1–NC) months

- The **safety profile** of Dato-DXd monotherapy was **manageable** and **consistent** with that of previous studies
  - Few TEAEs led to drug discontinuation and there were no TEAEs that led to death
  - The most common TEAEs were stomatitis and nausea; mostly grade 1/2
  - Rates of adjudicated drug-related ILD were low

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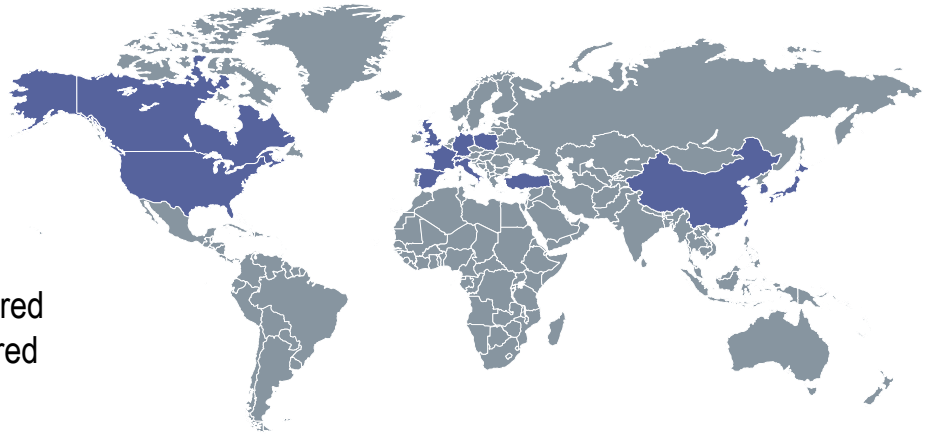

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Datopotamab deruxtecan (Dato-DXd) in patients with Ovarian or Endometrial Cancer: Results from the Phase 2 TROPION-PanTumor03 Study

Plain Language Summary

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Why did we perform this research?

- People with endometrial or ovarian cancer that has spread from its original site or is in advanced stages after treatment have poor survival rates and limited treatment options after receiving standard of care treatment
- Datopotamab deruxtecan (Dato-DXd) is an antibody-drug conjugate that consists of an antibody (datopotamab) and an anticancer drug payload (DXd), which are joined via a stable cleavable linker. Dato-DXd binds to TROP2 on the surface of cancer cells and is then taken inside the cell, where the linker detaches and releases DXd to kill the cancer cells
- Dato-DXd has shown promising antitumour activity and manageable safety in previous large studies in people with a type of breast cancer called HR+/HER2– breast cancer and with non-small cell lung cancer (NSCLC)[1,2]
- TROPION-PanTumor03 is a clinical study in which Dato-DXd is being assessed as treatment alone or in combination with other anticancer drugs, across several different cancer types
- Here, the results of the safety and efficacy analysis of Dato-DXd alone in people with ovarian or endometrial cancer are presented

How did we perform this research?

- In this study, 40 people with endometrial cancer and 35 people with ovarian cancer were included. These people had cancer that had spread to other parts of the body or was in advanced stages, and their cancers had gotten worse after receiving at least 1 line of platinum-based chemotherapy, but no more than 2 lines of other treatment for their cancer
- Within the ovarian cohort, people with tumours that had responded to platinum-based chemotherapy for at least 6 months (platinum-sensitive) and that had stopped responding within 6 months of treatment (platinum-resistant) were allowed to participate
- The participants received Dato-DXd every 3 weeks until their cancer got worse or they experienced unacceptable side effects

What were the findings of this research?

- Overall, the side effects experienced by people in this study were manageable and consistent with that known from other studies of Dato-DXd
  - Few side effects led to people stopping treatment and there were no side effects that resulted in death
  - The most common side effects reported were stomatitis (sores or inflammation in the mouth) or nausea (feeling sick); these were mostly mild or moderate in severity
- Dato-DXd demonstrated encouraging antitumour activity in patients with endometrial and ovarian cancer, including in patients with platinum-sensitive and platinum-resistant ovarian cancer
  - 27.5% and 42.9% of people in the endometrial and ovarian cohorts, respectively, had tumours that shrunk after receiving Dato-DXd
  - For people in the endometrial and ovarian cohorts, the tumours responded to treatment for a median of 16.4 and 5.7 months, respectively
  - The length of time that people survived without their cancer growing, spreading or getting worse (called progression-free survival) was 6.3 months and 5.6 months for people with endometrial and ovarian cancer, respectively

What are the implications of this research?

These results demonstrate that Dato-DXd shows encouraging efficacy and manageable safety in patients with endometrial or ovarian cancer that is in advanced stages or has spread from its original site

1. Ahn M-J, et al. Ann Oncol 2023;34:S1665–66; 2. Bardia A, et al. Ann Oncol 2023;34(suppl_2):S1264–5.