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SEOUL IGCS 2023

ADC Opportunities in Ovarian Cancer

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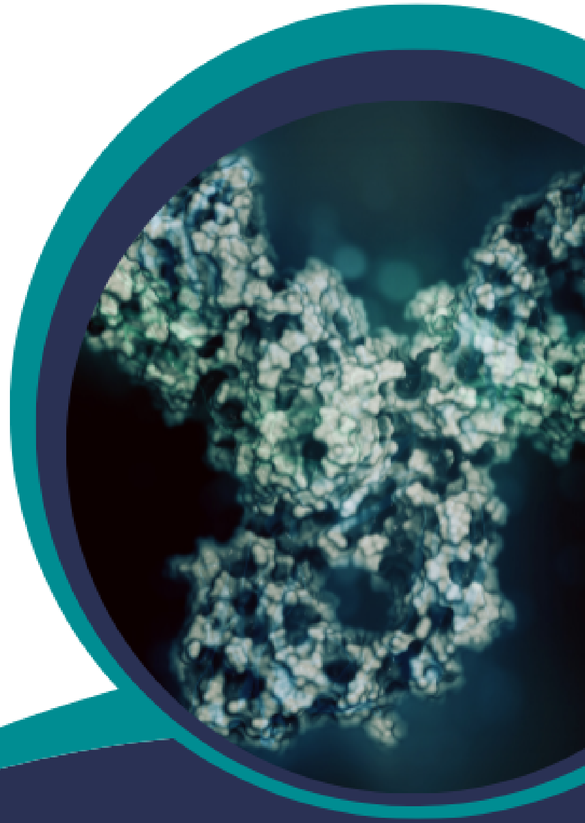
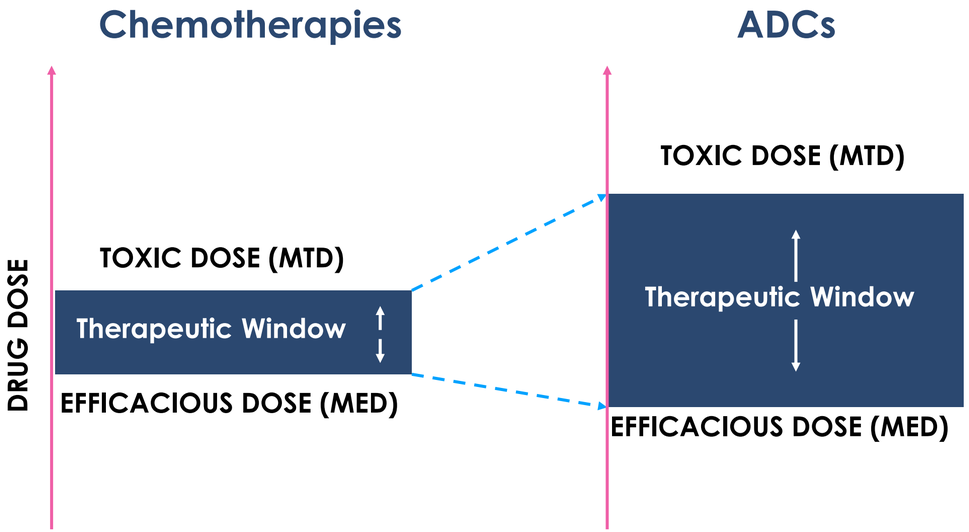


ADCs are engineered to limit systemic toxicity and improve the therapeutic index of cytotoxic agents

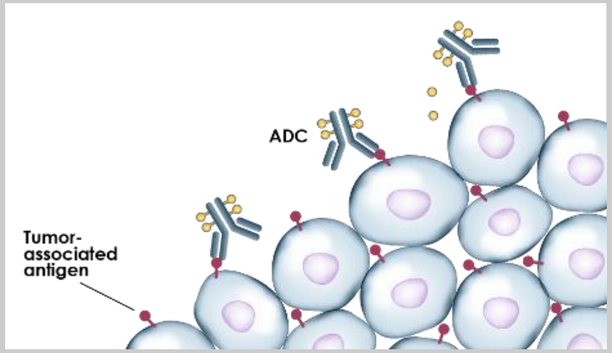
ADCs are a class of targeted therapies that are designed to selectively deliver cytotoxic drugs to cancer cells[1]

- **Systemic chemotherapies (eg, taxanes)[2]**
- Cytotoxic agents that target rapidly dividing cancerous and healthy cells
- Severe side effects limit administrable dose
- **Narrow therapeutic window** resulting from a small therapeutic index



$$\text{THERAPEUTIC INDEX} = \frac{\text{MTD}}{\text{MED}}$$

ADCs
(eg, Mirvetuximab soravtansine)[1,2]

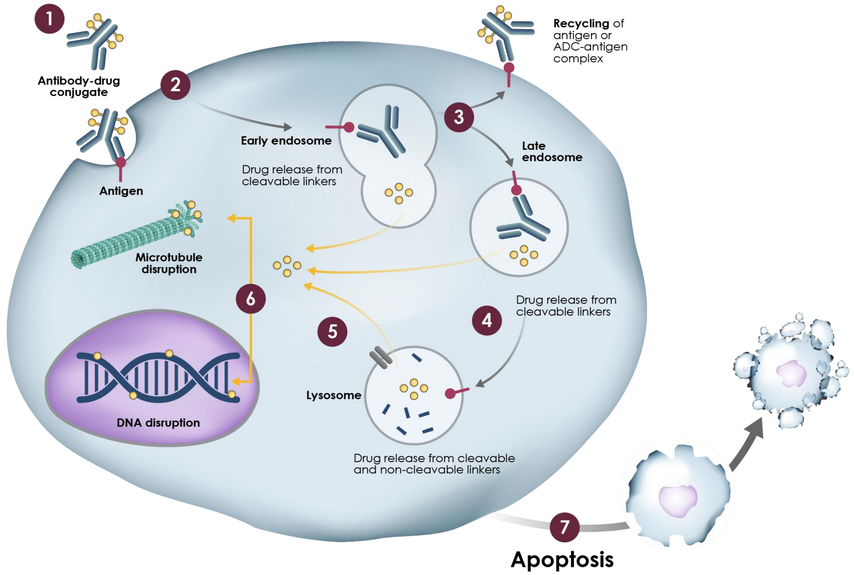


- Designed to reduce off-target toxicities of potent cytotoxic payloads
- Broader therapeutic window by limiting exposure of healthy tissue to cytotoxic drugs

ADC, antibody-drug conjugate; MED, minimum effective dose; MTD, maximum tolerated dose.

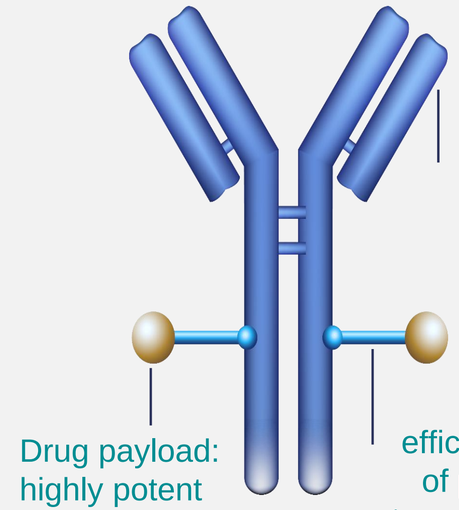
1. Criscitiello C et al. *J Hematol Oncol*. 2021;14(1):20. 2. Panowski S et al. *MAbs*. 2014;6(1):34–45.

ADCs induce cancer cell death via chemical or enzyme-mediated release of payload in lysosomes



Mechanism of action[1–3]

1. Antibody binds to the target antigen at the surface of the cancer cell
2. ADC–antigen complex is internalized by receptor-mediated endocytosis
3. An early endosome is formed whereby cargo is sent through 2 pathways:
   - Recycling, which results in trafficking back to the plasma membrane, or
   - Endolysosomal degradation
4. The payload is released by degradation of the linker in the endolysosomal compartment
5. Drug payload enters the cytoplasm
6. Drug payload acts on microtubules or DNA, resulting in apoptosis



ADC, antibody-drug conjugate; DNA, deoxyribonucleic acid.

1. Fu Z et al. *Signal Transduct Target Ther*. 2022;7(1):93. 2. Shim H. *Biomolecules*. 2020;10(3):360. 3. Hoffmann RM et al. *Oncoimmunology*. 2018;7(3):e1395127.

The linker is designed to ensure that the ADC is highly stable in circulation, yet efficiently releases the payload in the tumor

Cleavable linker[1,2]

- Uses the inherent properties of tumor cells to selectively release cytotoxic payload (protease-sensitive, pH-sensitive, glutathione-sensitive)
- Potential for premature payload release (pH-sensitive linkers)
- Examples: gemtuzumab ozogamicin, brentuximab vedotin

Noncleavable linker[1,2]

- No obvious drug release mechanism, relies on the complete lysosomal proteolytic degradation of the antibody
- More stable in circulation
- Limited diffusion to neighboring cancer (or healthy) cells
- Example: trastuzumab emtansine

Linker must be stable in serum and extracellular environment, and cleavable once in the tumor cells. Stable linkers in ADCs maintain antibody concentration in circulation, preventing premature cytotoxic drug release and reducing off-target effects[3]

ADC, antibody-drug conjugate.

1. Drago JZ et al. *Nat Rev Clin Oncol*. 2021;18(6):327–344. 2. Lu J et al. *Int J Mol Sci*. 2016;17(4):561. 3. Sau S et al. *Drug Discov Today*. 2017; 22(10):1547–1556.

Payload is the effector component of the ADC

Two classes of antitumor drugs are commonly used as payloads in ADCs[1]

Microtubule inhibitors[1–5]

DNA-damaging agents[1,2]

Considerations	Targets rapidly proliferating cells	Potent agents that may target DNA independent of cell cycle
Classes	• Auristatins (eg, MMAE, MMAF) • Eribulin • Hemiasterlin • Maytansinoids (eg, DM1, DM4) • Tubulysin	• Calicheamicin • Duocarmycin • Pyrrolobenzodiazepine • Topoisomerase inhibitor
Examples	• Mirvetuximab soravtansine • Tisotumab vedotin	• Sacituzumab govitecan • Trastuzumab deruxtecan

Bystander effect is an important characteristic, especially in tumors with heterogeneous antigen expression[6]

1. Membrane-permeable payloads diffuse from target cell into neighboring cells, leading to cell death
2. Under amenable extracellular conditions, payload may be released into the extracellular space

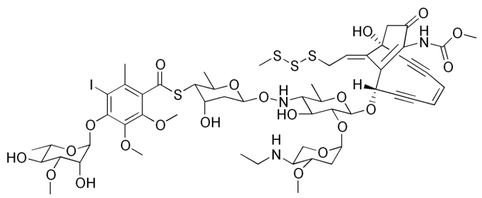
Bystander effect can be an advantage in heterogeneous tumors if the neighbor cell is a tumor cell; however, if payloads diffuse into healthy tissue or bloodstream, this can lead to off-target toxicity[6,7]

ADC, antibody-drug conjugate; DM1, maytansine 1; DM4, maytansine 4; DNA, deoxyribonucleic acid; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F.

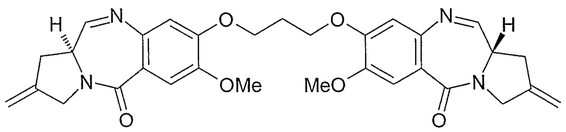
1. Fu Z et al. *Signal Transduct Target Ther*. 2022;7(1):93. 2. Donaghy H et al. *MAbs*. 2016;8(4):659–671. 3. Tang H et al. *Front Pharmacol*. 2019;10:373. 4. Cheng X et al. *Mol Cancer Ther*. 2018;17(2):2665–2675. 5. Chen H et al. *Molecules*. 2017;22(8):1281. 6. Staudacher AH et al. *Br J Cancer*. 2017;117(12):1736–1742. 7. Yurkovetskiy AV et al. *Mol Cancer Ther*. 2021;20(5):885–895.

Currently approved ADC payloads

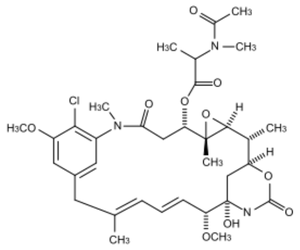
Gemtuzumab ozogamicin
Calicheamicin
DNA binders[1,2]



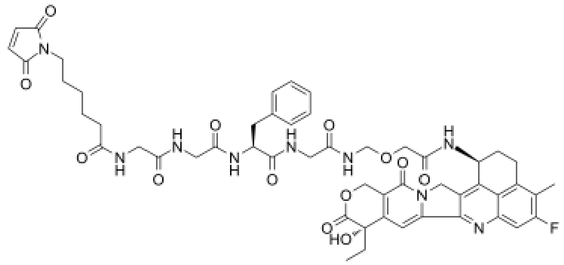
PBD: pyrrolobenzodiazepine
DNA alkylators[3]



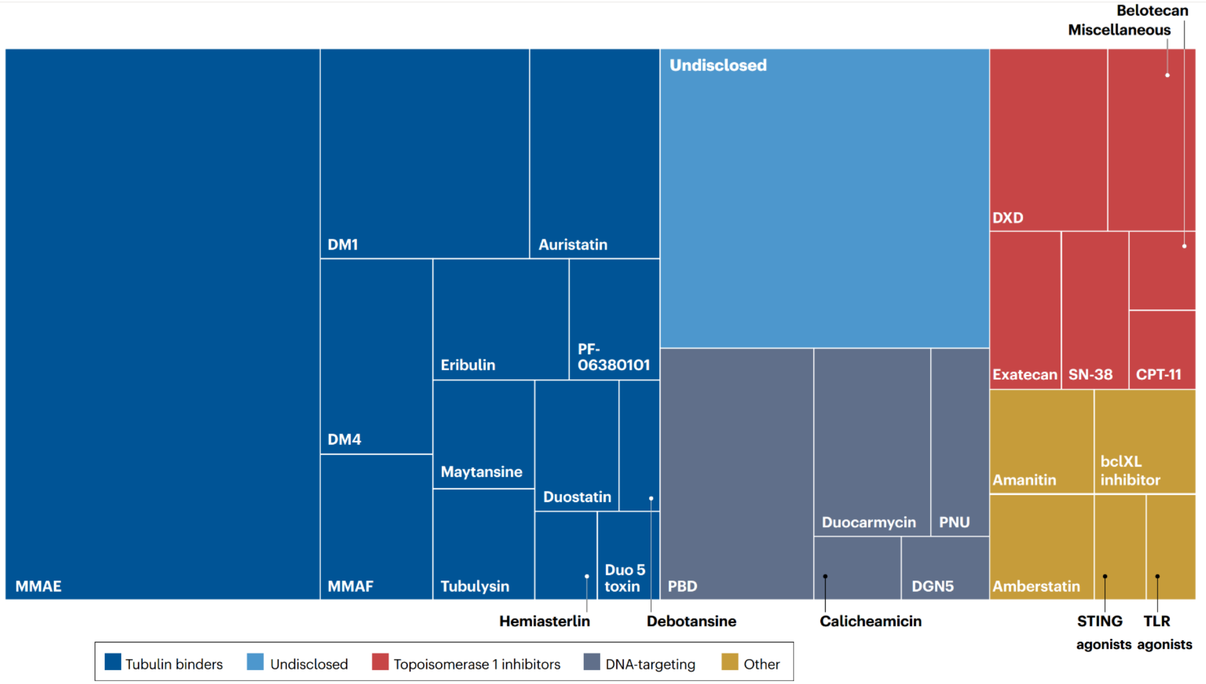
Maytansinoids
Auristatin
Tubulin binders[2]



Deruxtecan
SN-38
Topoisomerase 1 inhibitors[4]



Payload diversity in ADC pipeline[5]

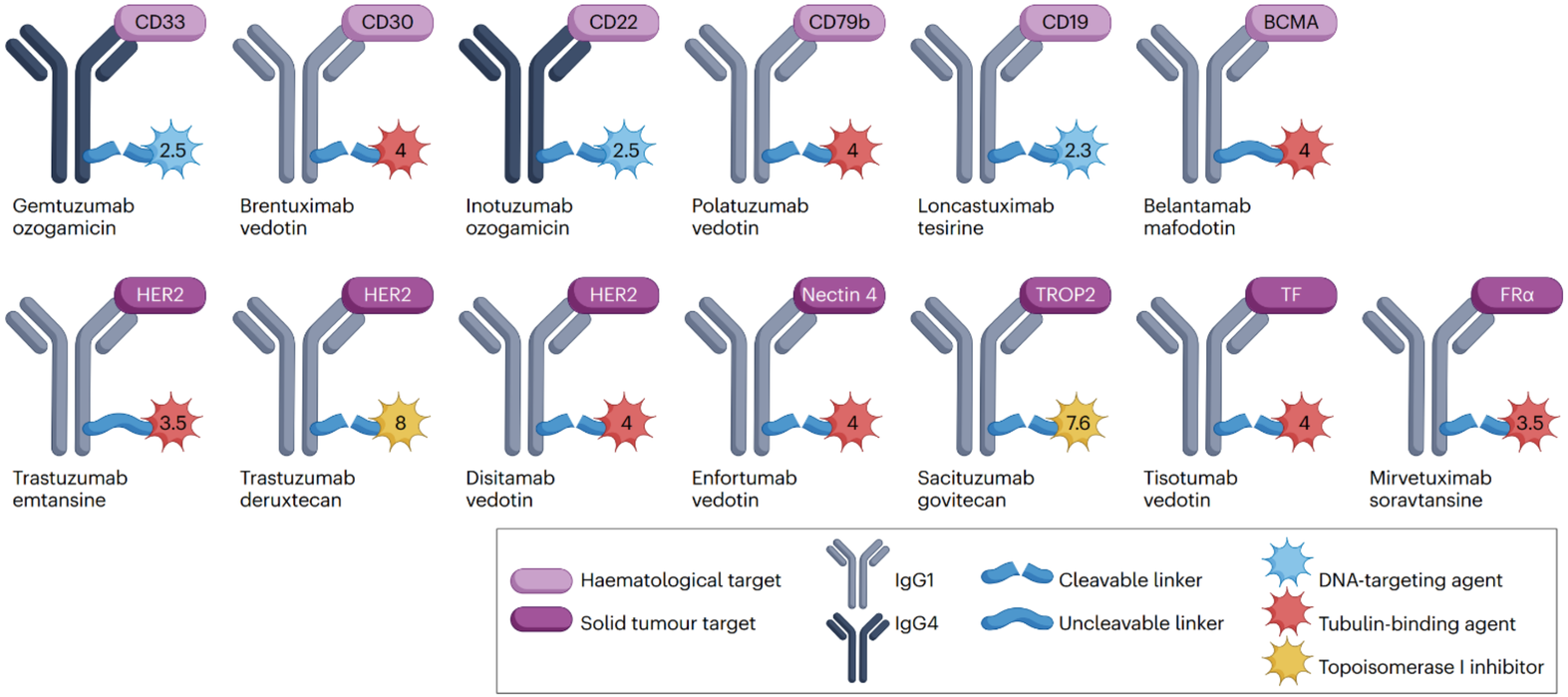


In addition to cytotoxic drugs, immune-stimulating ADCs with toll-like receptor (TLR) and stimulator of interferon gene (STING) agonists are in early phases of clinical investigation[1]

ADC, antibody-drug conjugate; bclXL; B-cell lymphoma – extra long; CPT-11, irinotecan; DM1, mertansine; DM4, ravtansine; DNA, deoxyribonucleic acid; DXD, deruxtecan; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin; PBD, pyrrolobenzodiazepine; PNU, effective metabolite of the anthracycline nemorubicin; SN-38; active metabolite of irinotecan; STING, stimulator of interferon genes; TLR, toll-like receptor.

1. Ricart AD. *Clin Cancer Res.* 2011;17(20):6417–6427. 2. Goldmacher V. Chapter Twenty-Three - Antibody–Drug Conjugates for Targeted Cancer Therapy. In: Desai CM, ed. Annual Reports in Medicinal Chemistry. Vol. 47. ImmunoGen, Inc., Waltham, MA: 2012:349-366. 3. ADC Review. Pyrrolobenzodiazepine (PBD). https://www.adcreview.com/pyrrolobenzodiazepine-pbd/. Accessed October 3, 2023. 4. Han S et al. *Pharmaceutics*. 2022;14(8):1707. 5. Dumontet C et al. *Nat Rev Drug Discov*. 2023;22(8):641-661.

Summary of currently approved ADCs for cancer treatment in the United States



13 FDA-approved ADCs
currently in the market[1–7,a,b,c,d]

2 ADCs approved for gynecologic cancers[2]:
Mirvetuximab soravtansine
(FRα+ ovarian)
Tisotumab vedotin
(Cervical [tissue factor])

Approval list as of October 2023

[a]Belantamab mafodotin was approved in 2020 for the treatment of relapsed or refractory multiple myeloma; however, withdrawal of this indication was initiated in November 2022 at the request of the US Food and Drug administration.[3,6] [b]Trastuzumab deruxtecan received accelerated approval in 2019 for HER2-positive breast cancer followed by a confirmatory trial and full approval in 2022.[2,6] [c]Sacituzumab govitecan received accelerated approval in 2020 for metastatic TNBC followed by a confirmatory trial and full approval in 2021.[2,6] [d]Tisotumab vedotin indication does not require patients to have tissue factor–expressing tumors.[1,2]

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; CD, cluster of differentiation; FDA, US Food and Drug Administration; FRα, folate receptor alpha; HER2, human epidermal growth factor receptor 2; IgG1/IgG4, immunoglobulin G1/4; TF, tissue factor; TROP2, trophoblast cell surface antigen 2.

1. Wong et al. *Moleculs*. 2021;26(19):5847. 2. US Food and Drug Administration. Hematology/Oncology (Cancer) Approvals & Safety Notifications. Published November 2022. Accessed November 16, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancer-hematologic-malignancies-approval-notifications?t=958371 3. GSK. GSK provides an update on Blenrep (belantamab mafodotin-blmf) US marketing authorization. Published November 22, 2022. Accessed December 8, 2022. https://www.gsk.com/en-gb/media/press-releases/gsk-provides-update-on-blenrep-us-marketing-authorisation/ 4. Selby C et al. *J Adv Pract Oncol*. 2019;10(1):68–82. 5. US Food and Drug Administration. 2011 Notifications. Updated September 2015. Accessed November 16, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/2011-notifications 6. US Food and Drug Administration. Hematology/Oncology (Cancer) Approvals & Safety Notifications. Published December 2020. Accessed November 16, 2022. https://wayback.archive-it.org/7993/20201219232235/https://www.fda.gov/drugs/resources-information-approved-drugs/hematologyoncology-cancer-approvals-safety-notifications 7. US Food and Drug Administration. Hematology/Oncology (Cancer) Approvals & Safety Notifications. Published December 2016. Accessed November 16, 2022. http://wayback.archive-it.org/7993/20170111064250/http://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm.

Select ADCs under clinical development in gynecologic oncology

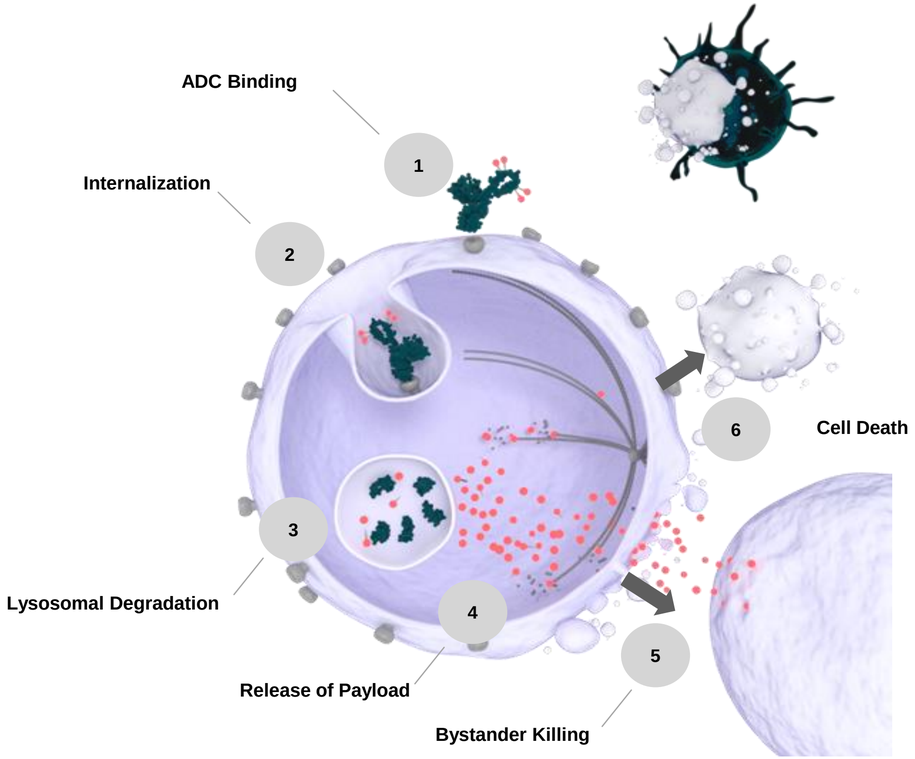
Target	Drug	DAR	Tumor type
B7-H4	XMT-1660[1]	6	Ovarian, endometrial
	SGN-B7H4V[2–4]	4	Ovarian, endometrial
	AZD8205[5,6]	8	Ovarian, endometrial
CDH6	DS-6000a[7,8]	~8	Ovarian
FRα	Luveltamab tazevibulin (STRO-002)[9,10]	4	Ovarian, endometrial
	Farletuzumab ecteribulin (MORAb-202)[11,12]	4	Ovarian, endometrial
HER2	SYD985[13,14]	2.7	Ovarian, endometrial
	T-DXd[15,16]	7–8	Cervical, ovarian, endometrial
	DB-1303/BNT323[17,18]	~8	Endometrial
Mesothelin	BMS-986148[19,20]	3	Ovarian
Tissue factor	XB002[21,22]	4	Cervical, ovarian
TROP2	Sacituzumab govitecan[23, 24]	7.5	Cervical, ovarian, endometrial
	DB-1305[25, 26]	~4	Ovarian, endometrial

ADC, antibody-drug conjugate; CDH6, cadherin 6; DAR, drug-antibody ratio; FRα, folate receptor alpha; HER2, human epidermal growth factor receptor 2; TROP2, trophoblast cell surface antigen 2.

1. Hamilton E et al. Poster presented at IGCS Annual Meeting 2022; Abstract 1420. 2. Gray E et al. *J Immunother Cancer.* 2021;9(Suppl 2):A1–A1054. 3. Patnaik A et al. Poster presented at ASCO Annual Meeting 2022; Abstract TPS3155. 4. ClinicalTrials.gov. NCT05194072. Accessed March 17, 2023. 5. Meric-Berstam F et al. Poster presented at ASCO Annual Meeting 2022; Abstract TPS3153. 6. ClinicalTrials.gov. NCT05123482. Accessed March 17, 2023. 7. Hamilton EP et al. Oral Presentation at ASCO Annual Meeting; Abstract 3002. 8. ClinicalTrials.gov. NCT04707248. Accessed March 17, 2023. 9. Li X et al. AACR Annual Meeting 2018; Poster Presentation. 10. ClinicalTrials.gov. NCT03748186. Accessed March 17, 2023. 11. Cheng X et al. *Mol Cancer Ther*. 2018;17(12):2665–2675. 12. ClinicalTrials.gov. NCT04300556. Accessed November 16, 2022. 13. Yao. *Drug Discov Today*. 2021;26(8):1857–1874. 14. ClinicalTrials.gov. NCT04602117, NCT04205630, NCT04235101. Accessed November 16, 2022. 15. Takegawa N et al. *Int J Cancer*. 2017;141(8):1682–1689. 16. ClinicalTrials.gov. NCT04585958, NCT04482309, NCT04639219. Accessed March 17, 2023. 17. Swain et al. *Nat Rev Drug Discov*. 2023;22(2):101–126. 18. ClinicalTrials.gov. NCT05150691. Accessed October 10, 2023. 19. Rottey S et al. *Clin Cancer Res.* 2022;28(1):95-105. 20. ClinicalTrials.gov. NCT02341625. Accessed October 2, 2023. 21. Tolcher A et al. Poster presentation at SGO Annual Meeting on Women's' Cancer; Poster 301. 22. Barnscher S et al. *Cancer Res*. 2017;77(13 Suppl):61. 23. Saxena A et al. Poster presentation at ASCO Annual Meeting 2020; Abstract TPS3648. 24. ClinicalTrials.gov. NCT04251416, NCT05119907, NCT03964727. Accessed March 17, 2023; 25. A Phase 1 study of DB-1305 in people with advanced ovarian, endometrial, cervical, or lung cancers. Memorial Sloan Kettering Cancer Center. Accessed October 30, 2023. https://www.mskcc.org/cancer-care/clinical-trials/23-059. 26. ClinicalTrials.gov. NCT05438329. Accessed October 30, 2023

Mirvetuximab soravtansine (Elahere), the first FRα-targeted ADC approved for treatment of PROC

Accelerated approval granted in November 2022 based on data from pivotal SORAYA trial[1]



MIRV is an ADC comprising an FRα-binding antibody, cleavable linker, and a maytansinoid DM4 payload[2]

SORAYA (NCT04296890) was a global, single-arm pivotal study evaluating mirvetuximab soravtansine in adult patients with FRα-positive platinum-resistant epithelial ovarian, primary peritoneal, or fallopian tube cancer[3–5]

Key eligibility criteria[3–5]

- Platinum-resistant ovarian cancer
- Prior bevacizumab required, prior PARPi allowed
- 1–3 prior lines of therapy
- Patients with *BRCA* mutations allowed
- FRα-positive (≥75% of cells staining positive with ≥2+ staining intensity)

Mirvetuximab soravtansine (N=106)[3]

6.0 mg/kg adjusted ideal body weight (AIBW) q3w

Primary endpoint[3]

- ORR per Investigator

Secondary endpoints[2]

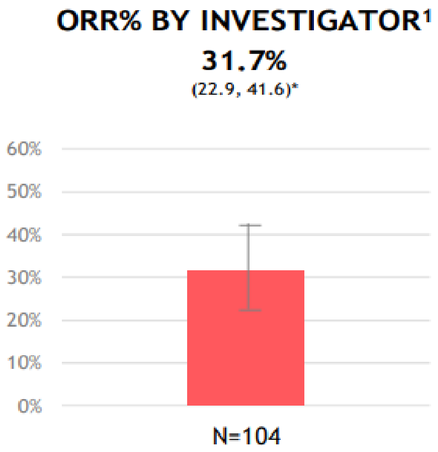
- DOR, PFS, OS, CA-125 response by GCIG criteria, safety

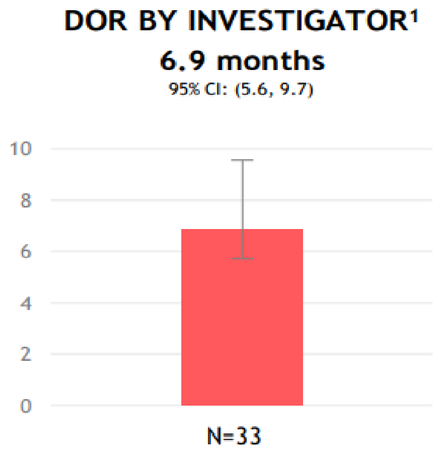
ADC, antibody-drug conjugate; BRCA breast cancer gene; CA-125, cancer antigen 125; DM4, maytansine 4; DOR, duration of response; FRα, folate receptor alpha; GCIG, Gynaecologic Cancer Intergroup; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PROC, platinum-resistant ovarian cancer; q3w, every 3 weeks.

1. FDA. Published November 14, 2022. Accessed March 3, 2023. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-mirvetuximab-soravtansine-gynx-fra-positive-platinum-resistant. 2. Moore KN et al. *Cancer*. 2017;123(16):3080–3087. 3. Matulonis UA et al. *J Clin Oncol*. 2023;JCO2201900. 4. Matulonis UA et al. Poster presentation at ASCO Annual Meeting 2022; Abstract 5512. 5. Mirvetuximab soravtansine-gynx package insert. ImmunoGen, Inc.; November 2022.

Summary of mirvetuximab soravtansine efficacy and safety

SORAYA key efficacy endpoints[1,2]





	Mirvetuximab soravtansine (n=104)
Confirmed ORR, n (%) [95% CI][a]	31.7 [22.9, 41.6]
Complete response, %	4.8
Partial response, %	26.9
mDOR, months [95% CI]	6.9 [5.6, 9.7]

TRAEs of Interest[3]

	Integrated Safety Population (N=464)		SORAYA[a] (N=106)	
Adverse event	All Grades, n (%)	Grade ≥3, n (%)	All Grades, n (%)	Grade ≥3, n (%)
Alopecia	3 (<1)	0	1 (<1)	0
Neuropathy peripheral	64 (14)	4 (<1)	14 (13)	0
Peripheral sensory neuropathy	36 (8)	4 (<1)	4 (4)	2 (2)
Peripheral motor neuropathy	4 (<1)	1 (<1)	2 (2)	1 (<1)
Paresthesia	21 (5)	0	5 (5)	0
Anemia	43 (9)	4 (<1)	8 (8)	1 (<1)
Thrombocytopenia	43 (9)	1 (<1)	10 (9)	2 (2)
Neutropenia	35 (8)	2 (<1)	14 (13)	2 (2)

[a]Data shown from SORAYA safety population are derived from a separate data cutoff of April 29, 2022.[3]

DOR, duration of response; mDOR, median duration of response; ORR, objective response rate; TRAE, treatment-related adverse event.

1. Mirvetuximab soravtansine-gynx package insert. ImmunoGen, Inc.; November 2022. 2. ImmunoGen. Accessed March 2, 2023. https://investor.immunogen.com/static-files/a614e7f6-e33d-49c0-9764-370cd55b84ee 3. Moore K et al. Poster presentation at ASCO Annual Meeting 2022. Abstract 5574.

MIRASOL (GOG-3045/ENGOT-ov55): phase 3 mirvetuximab soravtansine vs IC chemotherapy in FRα-high PROC[1,a]

Confirmatory trial designed to generate the randomized data to support full approval[2]

MIRASOL

Key inclusion criteria:

- Platinum-resistant disease (PFI ≤6 mo)
- FRα detected by IHC with PS2+ intensity among ≥75% of viable tumor cells
- High-grade serous histology
- 1º platinum-refractory disease excluded (primary PFI <3 mo)
- 1–3 prior lines of therapy
- Prior BEV and PARPi allowed
- Patients with *BRCA* mutations allowed

N=453
R 1:1

Stratified by:

- IC chemotherapy (paclitaxel, PLD, or topotecan)
- Prior therapy (1 vs 2 vs 3)

Treatment-experimental
Mirvetuximab soravtansine IV q3w
6 mg/kg, adjusted ideal body weight

Treatment regimen-control
Investigator's choice chemotherapy (paclitaxel, PLD, or topotecan)

- Paclitaxel: 80 mg/m^2 weekly
- PLD: 40 mg/m^2 q4w
- Topotecan: 4 mg/m^2 on days 1, 8, & 15 q4w or 1.25 mg/m^2 days 1–5 q3w

Endpoints

Primary
- PFS by investigator (BICR sensitivity analysis)

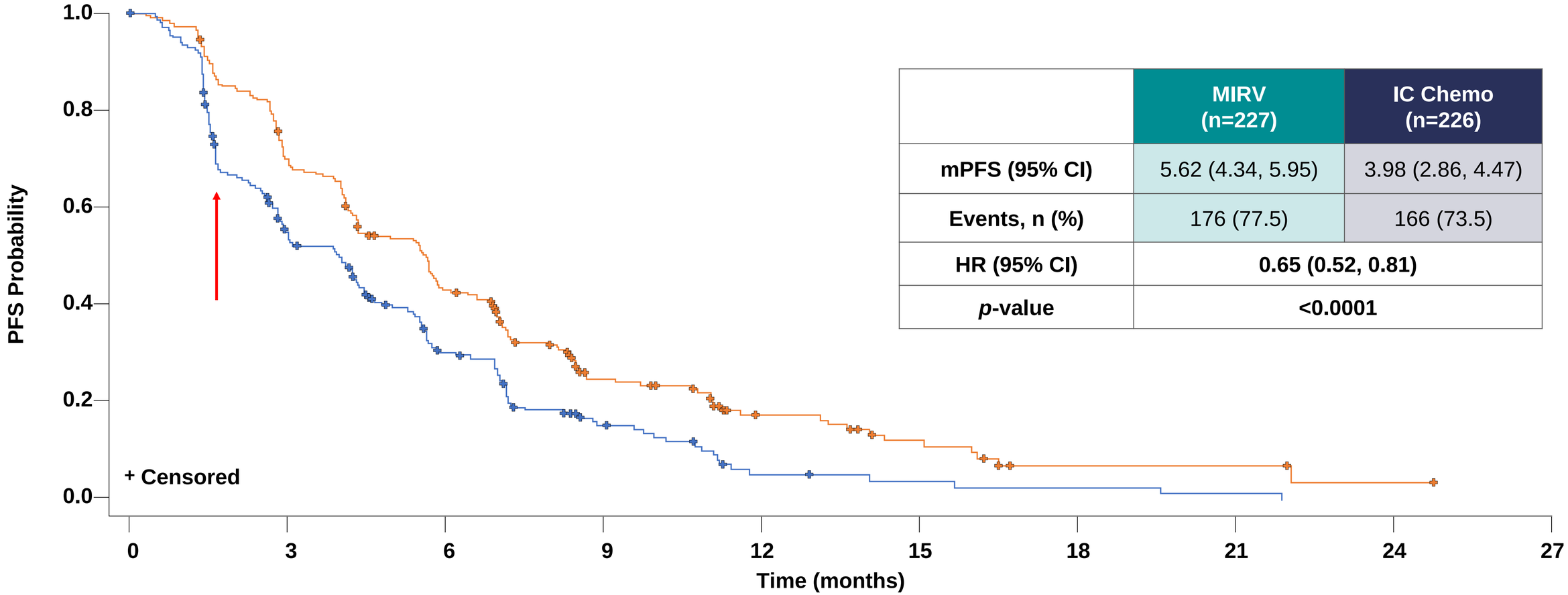
Key secondary
- ORR by inv, OS, PROs (EORTC-OV28)[a], CA-125[b]

[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (EORTC-OV28) study instrument. [b]Gynecological Cancer InterGroup (GCIG) criteria.

AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, breast cancer gene; CA-125, cancer antigen 125; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; inv, investigator; IV, intravenous; MIRV, mirvetuximab soravtansine; mo, months; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PROC, platinum-resistant ovarian cancer; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; q3w, every 3 weeks; q4w, every 4 weeks; R, randomization.

1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. 2. Moore K, et al. Presented at ASCO Annual Meeting 2020; May 29-31, 2020. Virtual Abstract TPS6103.

Primary endpoint: PFS by investigator



	MIRV (n=227)	IC Chemo (n=226)
mPFS (95% CI)	5.62 (4.34, 5.95)	3.98 (2.86, 4.47)
Events, n (%)	176 (77.5)	166 (73.5)
HR (95% CI)	**0.65 (0.52, 0.81)**	
***p*-value**	**<0.0001**	

No. Participants at Risk

MIRV — IC Chemo

MIRV	227	151	89	38	18	10	3	3	1	0
IC Chemo	226	98	48	19	5	3	2	1	0	

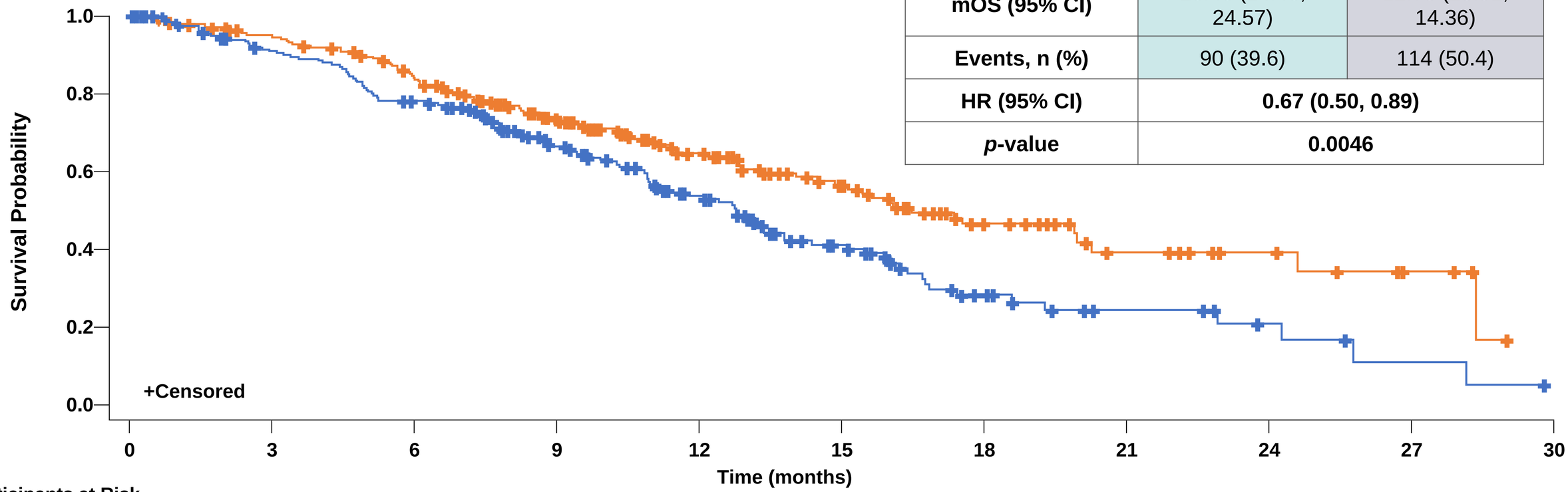
Data cutoff: March 6, 2023

IC Chemo, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine; mPFS, median progression-free survival.

Gorp TV et al. Presentation at ESGO 2023. Abstract 1015.

Key secondary endpoint: OS

	MIRV (n=227)	IC Chemo (n=226)
mOS (95% CI)	16.46 (14.46, 24.57)	12.75 (10.91, 14.36)
Events, n (%)	90 (39.6)	114 (50.4)
HR (95% CI)	**0.67 (0.50, 0.89)**	
***p*-value**	**0.0046**	



No. Participants at Risk

MIRV	227	204	175	128	82	53	28	15	9	4	0
IC Chemo	226	185	157	107	68	39	18	9	5	2	0

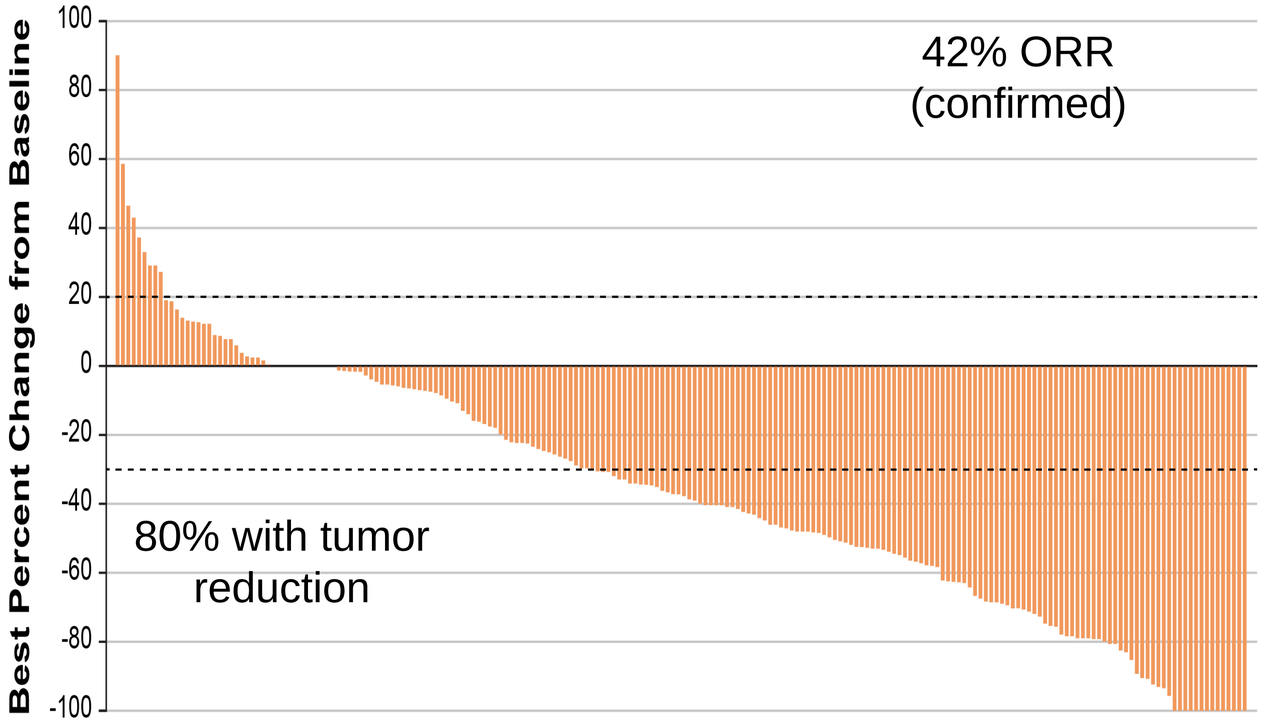
Data cutoff: March 6, 2023; median follow-up time: 13.11 months.

[a]Overall survival was statistically significant based on pre-specified boundary *p*-value at interim analysis = 0.01313.

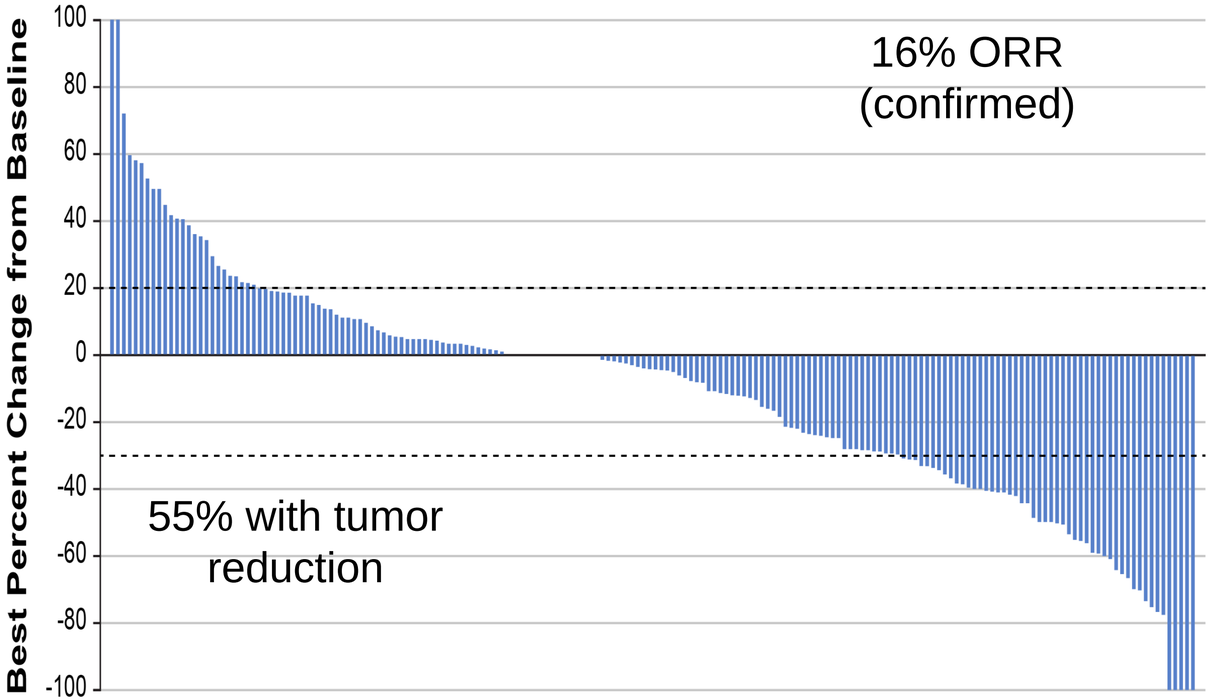
CI, confidence interval; HR, hazard ratio; IC Chemo, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine; mOS, median overall survival.

Maximum percentage change in target lesion size from baseline by investigator (N=453)

MIRV



IC Chemo



Data cutoff: March 6, 2023

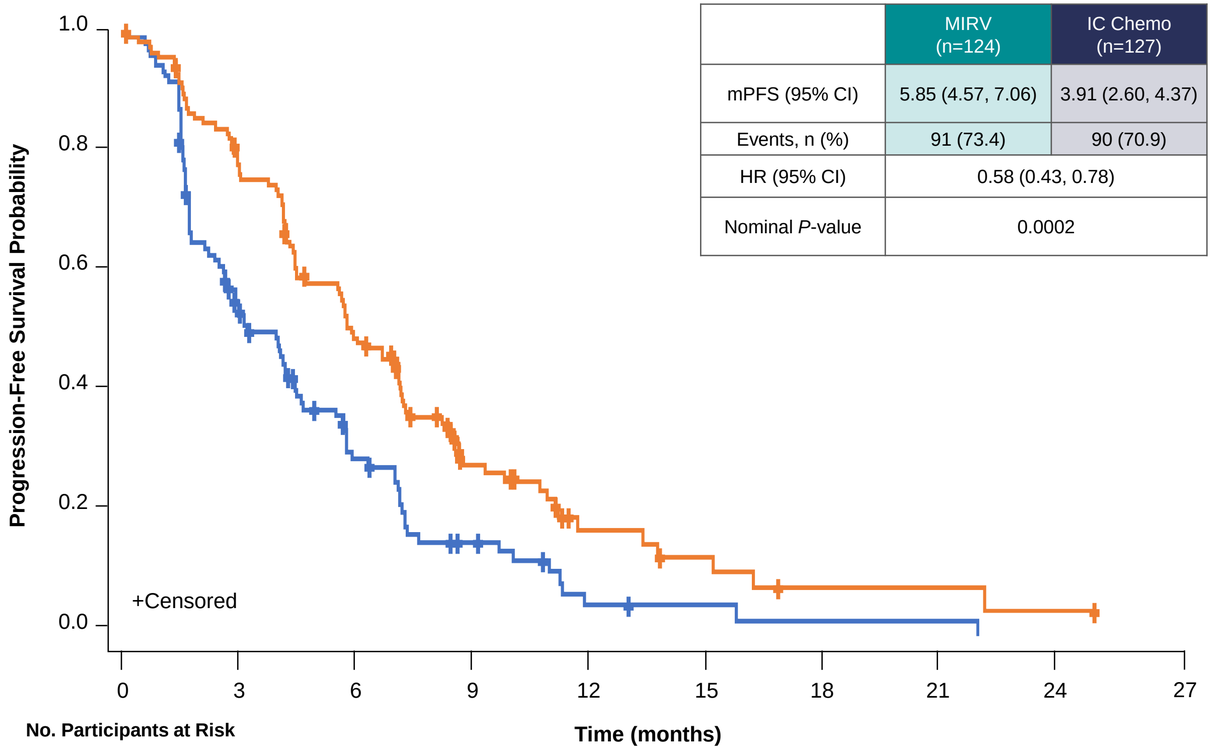
IC chemo, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine; ORR, objective response rate.

Gorp TV et al. Poster presented at ESGO 2023; Abstract 1015.

Exploratory endpoints: Activity of MIRV post PARPi treatment

PFS

	MIRV (n=124)	IC Chemo (n=127)
mPFS (95% CI)	5.85 (4.57, 7.06)	3.91 (2.60, 4.37)
Events, n (%)	91 (73.4)	90 (70.9)
HR (95% CI)	0.58 (0.43, 0.78)	
Nominal *P*-value	0.0002	



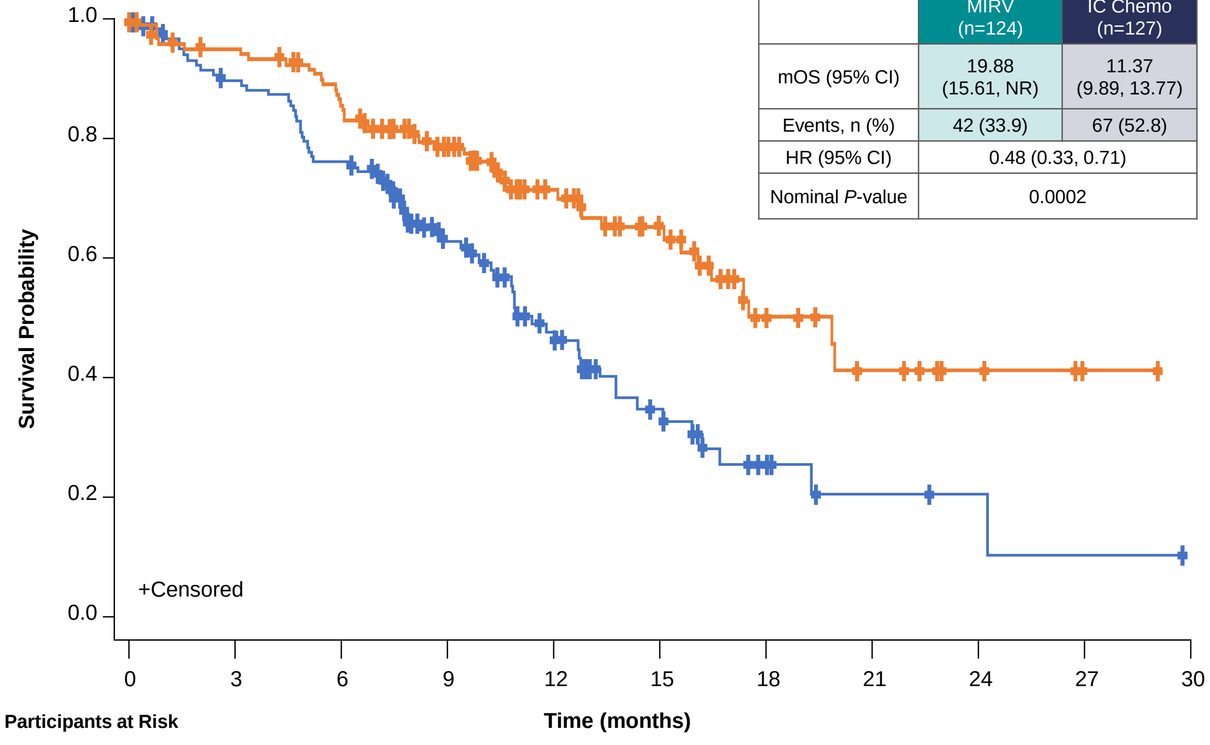
No. Participants at Risk

PARPi treated

MIRV	124	88	54	21	8	5	2	2	1	0
IC Chemo	127	52	25	11	3	2	1	1	0	

OS

	MIRV (n=124)	IC Chemo (n=127)
mOS (95% CI)	19.88 (15.61, NR)	11.37 (9.89, 13.77)
Events, n (%)	42 (33.9)	67 (52.8)
HR (95% CI)	0.48 (0.33, 0.71)	
Nominal *P*-value	0.0002	



No. Participants at Risk

PARPi treated

MIRV	124	113	99	76	47	32	13	8	4	1	0
IC Chemo	127	105	89	56	34	18	7	3	2	1	0

Data cutoff: March 6, 2023.

CI, confidence interval; HR, hazard ratio; IC Chemo, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine; PFS, median progression-free survival; OS, median overall survival; NR, not reached; PARPi, poly (adenosine diphosphate [ADP]-ribose) polymerase inhibitors.

Safety summary observed with mirvetuximab soravtansine

Characteristics	MIRV (n=218)	IC Chemo (n=207)
Any TEAE, n (%)	210 (96)	194 (94)
Grade 3+ TEAEs, n (%)	91 (42)	112 (54)
SAEs, n	52 (24)	68 (33)
Deaths on study drug or within 30 days of last dose, n (%)	5 (2)	5 (2)
Dose reductions due to TEAEs, n (%)	74 (34)	50 (24)
Dose delays due to TEAEs, n (%)	117 (54)	111 (54)
Discontinuations due to TEAEs, n (%)	20 (9)	33 (16)

Data cutoff: March 6, 2023.
The safety population comprises all patients who received at least 1 dose of MIRV or IC chemo.
IC Chemo, investigator's choice chemotherapy; MIRV, mirvetuximab soravtansine; SAE, serious adverse events; TEAE, treatment-emergent adverse events; Topo, topotecan.
Gorp TV et al. Poster presented at ESGO 2023; Abstract 1015.

Mirvetuximab soravtansine + bevacizumab in patients with PROC in the phase 1b/2 FORWARD II study

Study designed to evaluate the efficacy and safety of MIRV + bevacizumab in recurrent FRα-expressing epithelial ovarian cancer

Patient population:[1,2]

- FRα expression was assessed using immunohistochemistry PS2+ scoring, scored as the percent of viable tumor cells staining with ≥2+ intensity
  - FRα Low: ≥25% to 49%
  - FRα Medium: 50% to 74%
  - FRα High: ≥75%
- Platinum status was stratified by PFI as PFI >6 months or PFI ≤6 months
- Bev treatment status was defined as Bev-naïve or Bev-treated (defined as having received Bev in any line of therapy)

Treatment schedule: MIRV 6 mg/kg, adjusted ideal body weight +bev 15 mg/kg IV on day 1 of a 3-week cycle

Characteristics[1,2]		All patients (N=94)
Age, median (range)		62 (39–81 years)
ECOG PS, n (%)	0 1	60 (64) 34 (36)
FRα expression, n (%)	**≥75%** 50–74% 25–49%	**44 (47)** 39 (42) 11 (12)
No. of prior systemic therapies, n (%)	1–2 ≥3	45 (48) 49 (52)
Prior exposure, %	Taxanes **Bevacizumab** PARPi	91 (97) **55 (59)** 25 (27)
Primary diagnosis, n (%)	Epithelial ovarian cancer Fallopian tube cancer Primary peritoneal cancer	72 (77) 17 (18) 5 (5)

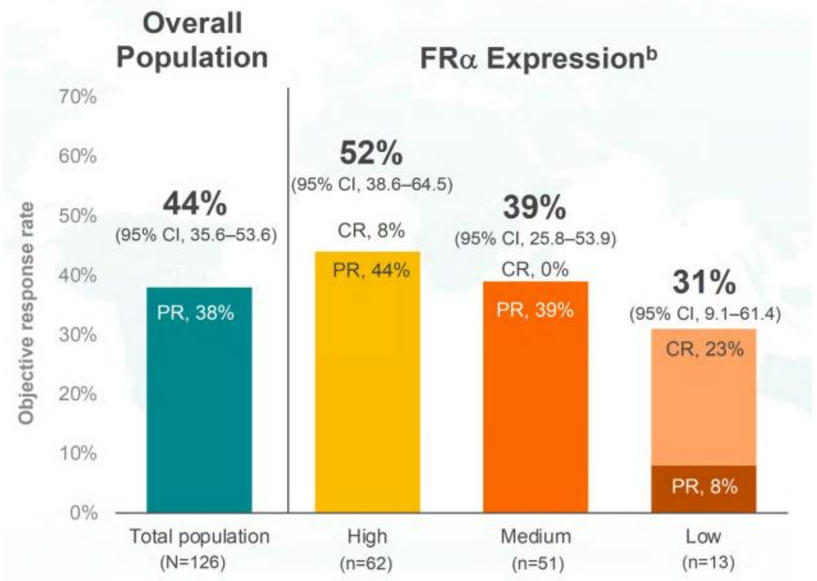
- 52% had ≥3 prior LOT
- 59% had received prior bev

Bev, bevacizumab; ECOG PS, Eastern Cooperative Oncology Group performance status; FRα, folate receptor alpha; IV, intravenous; LOT, line of therapy; PARPi, poly (ADP-ribose) polymerase inhibitor; PFI, platinum-free interval; PROC, platinum-resistant ovarian cancer; PS2+, proportion score of ≥2+ staining intensity.

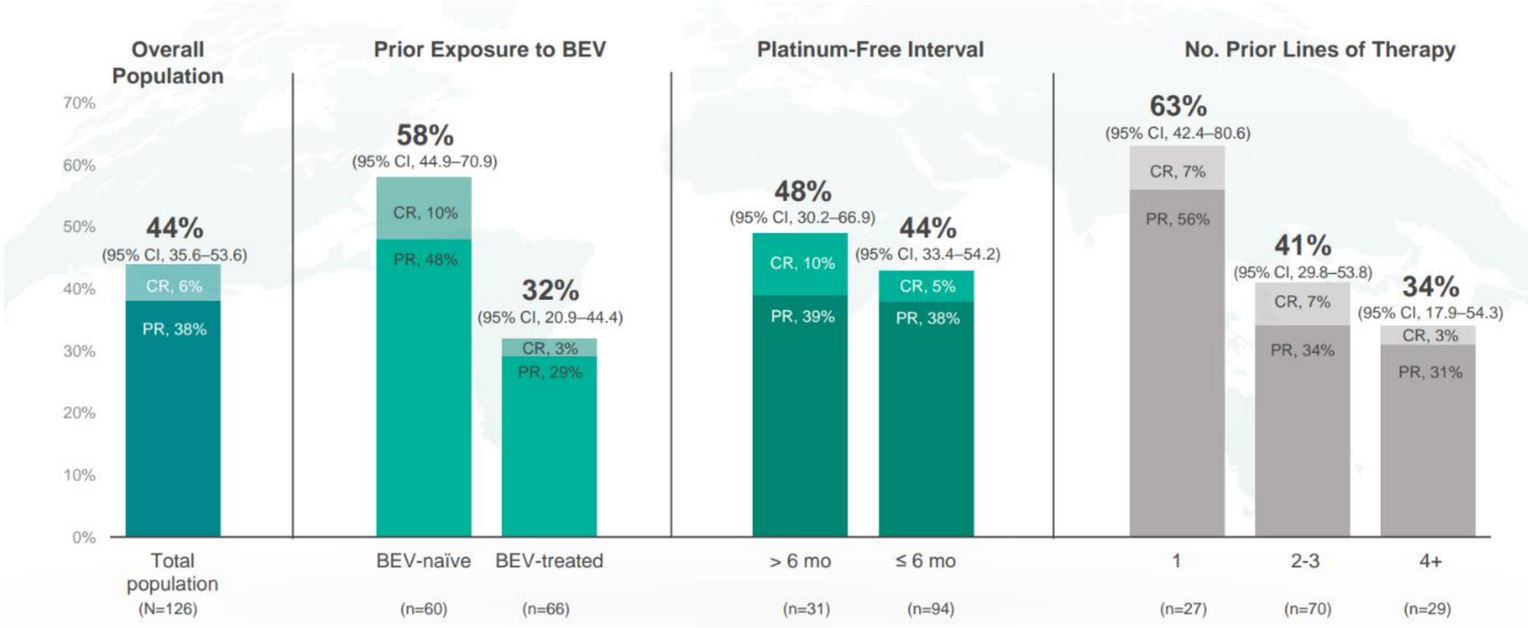
1. O'Malley et al. Poster presented at IGCS 2022; Abstract 496. 2. Gilbert L et al. *Gynecol Oncol*. 2023;170:241–247.

Phase 1b/2 FORWARD II PROC: overall response rate

ORR[a] in the overall population and by FRα expression level subgroups



ORR[a] in subgroups by bev treatment status, platinum-free interval, and prior lines of therapy



[a]DOR (a secondary endpoint) was defined as the time from the date of first response (complete or partial response) to the date of PD or death from any cause, whichever occurred first. [b]Low, 25% to 49%; medium, 50% to 74%; high ≥75% of tumor cells with ≥2+ staining intensity.

Bev, bevacizumab; CI, confidence interval; CR, complete response; DOR, duration of response; FRα, folate receptor alpha; NE, not estimable; ORR, objective response rate; PD, progressive disease; PROC, platinum-resistant ovarian cancer; PR, partial response.

O'Malley et al. Poster presentation at IGCS 2022; Abstract 496.

Phase 1b/2 FORWARD II PROC: safety summary

Treatment-related adverse events ≥20%[1,2]

TRAE, n (%)[a]	MIRV 6 mg/kg + BEV 15 mg/kg (N=126)		
	All grades	Grade 3	Grade 4
Diarrhea	74 (59)	2 (2)	0 (0)
Blurred vision	71 (56)	1 (1)	0 (0)
Fatigue	64 (51)	5 (4)	0 (0)
Nausea	64 (51)	1 (1)	0 (0)
Peripheral neuropathy[b]	50 (40)	1 (1)	0 (0)
Keratopathy[c]	43 (34)	0 (0)	0 (0)
Decreased appetite	38 (30)	0 (0)	0 (0)
Dry eye	38 (30)	3 (2)	0 (0)
Hypertension	38 (30)	20 (16)	0 (0)
Thrombocytopenia	35 (28)	4 (3)	1 (1)
AST increased	33 (26)	6 (5)	0 (0)
Headache	33 (26)	0 (0)	0 (0)
Vomiting	33 (26)	1 (1)	0 (0)
ALT increased	29 (23)	6 (5)	0 (0)

- Most TRAEs were low grade; GI, ocular, and fatigue were the most common
- 48% of patients experienced grade ≥3 events; the most common was hypertension (16%)
- Due to treatment-emergent AEs, 30% discontinued MIRV and 37% discontinued bev
  - 4 patients (3%) discontinued MIRV due to blurred vision
- Patients received a median of 8 cycles of MIRV + bev (range 1–35 cycles)
- There was 1 death, which was deemed related to a study treatment (intestinal perforation possibly related to bev)

Data cutoff: June 21, 2021.

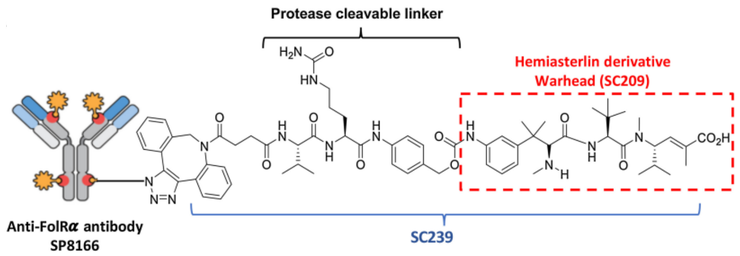
[a]Related to any study drug (either MIRV or BEV). [b]Peripheral neuropathy includes TRAEs with the following preferred terms: neuropathy peripheral, peripheral sensory neuropathy, peripheral motor neuropathy, paraesthesia, hypoaesthesia. [c]Keratopathy includes TRAES with the following preferred terms: corneal cyst, corneal disorder, corneal epithelial microcysts, keratitis, keratopathy, limbal stem cell deficiency, corneal opacity, corneal erosion, corneal pigmentation, corneal deposits, keratitis interstitial, punctate keratitis, corneal epithelium defect.

AE, adverse event; ALT, alanine transaminase; AST, aspartate aminotransferase; Bev, bevacizumab; GI, gastrointestinal; MIRV, mirvetuximab soravtansine; PROC, platinum-resistant ovarian cancer; TRAE, treatment-related adverse event.

1. O'Malley et al. Poster presentated at IGCS 2022; Abstract 496. 2. Gilbert L et al. *Gynecol Oncol*. 2023;170:241–247.

Other promising FRα ADCs: Luveltamab tazevibulin (Luvelta, STRO-002) FRα-targeted ADC

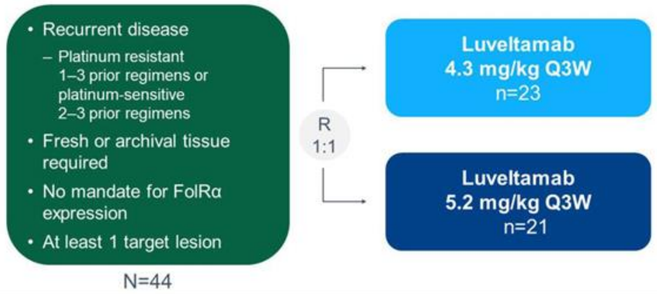
Luvelta

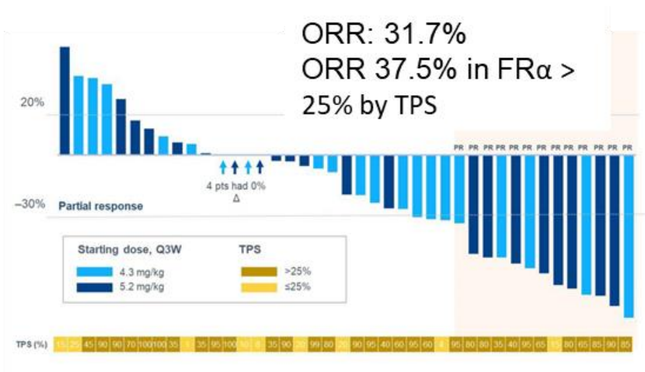


- Luvelta (STRO-002) is a homogenous ADC targeting FRα
- Cathepsin B linker, which is a stable protease-cleavable linker
- Hemiasterlin-derivative[a] cytotoxic payload
- DAR=4

Efficacy

Phase 1 dose-expansion study (NCT03748186)





Safety

Phase 1 dose-expansion study

TRAEs leading to dose reduction in 61.4%

- Neutropenia[a] in 17 patients (39%)
  - Primarily G3/4 uncomplicated (abnormal lab value only)
  - Febrile neutropenia in 2 patients (4.5%)
  - Resolved without growth factor support in most patients
  - Median duration of G3+ AEs, 8 days
- Arthralgia in 8 patients (18%)
- Peripheral neuropathy in 3 patients (6.8%)
  - Most G1/2

TEAEs leading to dose discontinuation in 3 patients (6.8%)

- G3 fatigue
- G2 neuropathy
- G5 Sepsis

Currently moving to late phase trial

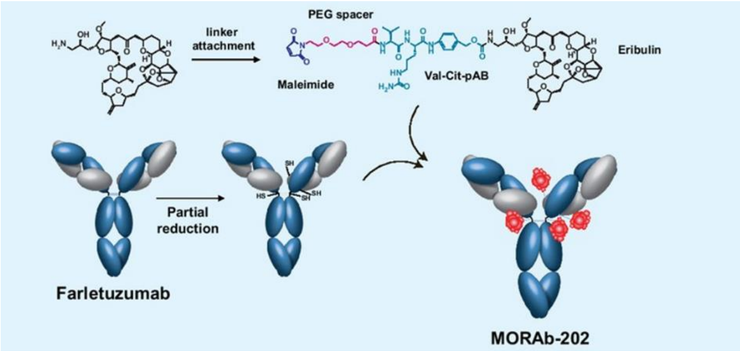
[a]Sutro-proprietary tubulin-targeting 3-aminophenol hemiasterlin warhead, SC209.

ADC, antibody-drug conjugate; AE, adverse event; DAR, drug-to-antibody ratio; FRα, folate receptor alpha; G, grade; ORR, objective response rate; PD, progressive disease; PR, partial response; R, randomization; TPS, tumor proportion score; Q3W, every 3 weeks; TEAE, treatment-emergent adverse event.

1. Oaknin et al. Poster presented at ASCO 2023; Abstract 5508. 2. Sutro Biopharma. Accessed March 2, 2023. https://www.sutrobio.com/wp-content/uploads/2023/01/Sutro-STRO-002-Luvelta-update-Jan-9-2023-FINAL.pdf

Other promising FRα ADCs: Farletuzumab ecteribulin (MORAb-202) FRα-targeted ADC

MORAb-202[1,2]

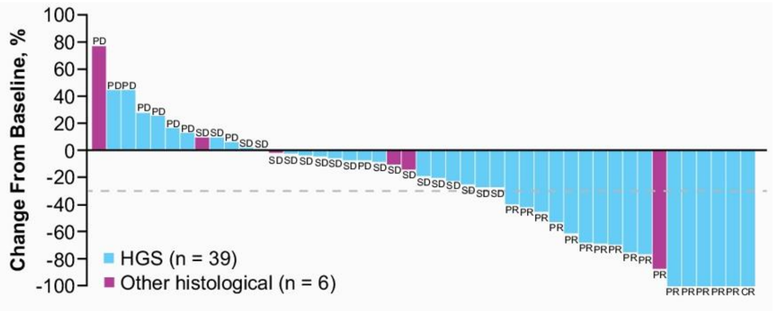


MORAb-202 is an ADC consisting of:

- Antibody: farletuzumab
- Linker: cathepsin B cleavable linker
- Payload: eribulin, microtubule inhibitor
- DAR=4

Efficacy[1,2]

Phase 1 dose-expansion study (NCT03386942)



Data cutoff date: October 31, 2021.

Parameter	Cohort 1: MORAb-202 0.9 mg/kg (n=24)	Cohort 2: MORAb-202 1.2 mg/kg (n=21)
CR, n (%)	1 (4.2)	0
PR, n (%)	5 (20.8)	11 (52.4)
SD, n (%)	10 (41.7)	9 (42.9)
PD, n (%)	8 (33.3)	1 (4.8)
ORR, n (5), (95% CI)[a]	**6 (25.0), (9.8–46.7)**	**11 (52.4), (29.8–74.3)**
DCR, n (5), (95% CI)[a]	**16 (66.7), (44.7–84**	**20 (95.2), (76.2–99.9)**
mPFS, mo (95% CI)[a]	**6.7 (1.5–12)**	**8.2 (4.2–10.4)**
mOS, mo (95% CI)[a]	10.5 (6.4–15.1)	NE (12.5–NE)

Safety[1]

Phase 1 dose-expansion study

- The most common TEAE was interstitial lung disease (ILD)/pneumonitis at both dose levels
  - Cohort 1: 37.5% (n=9; 8 with Gr 1; 1 with Gr 2)
  - Cohort 2: 66.7% (n=14; 6 with Gr 1; 7 with Gr 2, 1 with Gr 3)
- Other common TEAEs of any grade, in Cohorts 1 and 2, respectively, were:
  - Nausea (25.0%; 33.3%)
  - Pyrexia (33.3%; 42.9%)
  - Malaise (16.7%; 28.6%)
  - Headache (12.5%; 47.6%)

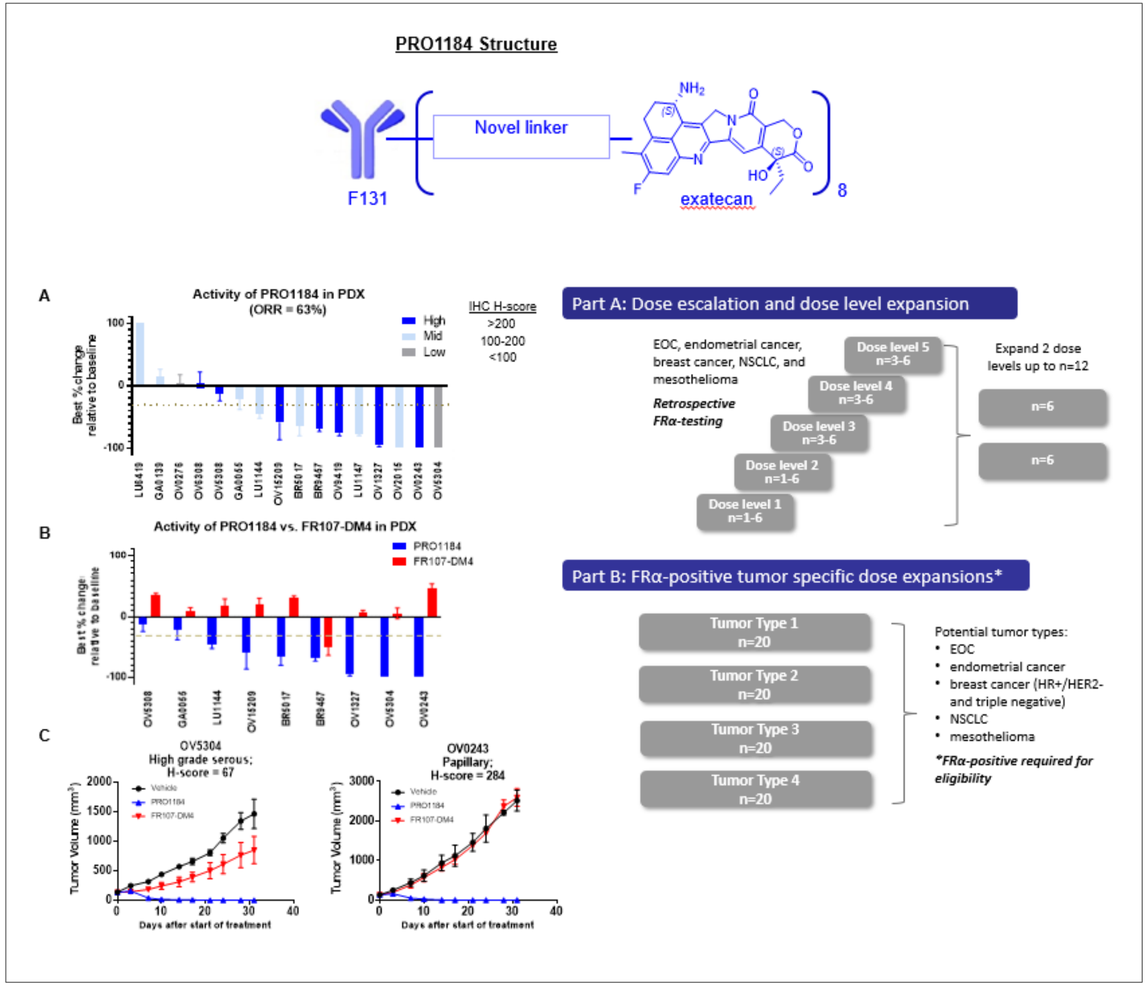
[a]CI calculations: ORR, DRC–Clopper-Pearson's exact method; PFS, OS–Kaplan-Meier estimate and Greenwood formula.

ADC, antibody-drug conjugate; CI, confidence interval; CR, complete response; DAR, drug-to-antibody ratio; DCR, disease control rate; FRα, folate receptor alpha; Gr, grade; HGS, high-grade serous; ILD, interstitial lung disease; mOS, median overall survival; mPFS, median progression-free survival; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; TEAE, treatment-emergent adverse event.

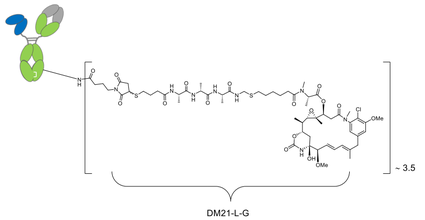
1. Nishio S et al. Poster presented at ASCO 2022; Abstract 5513. 2. Shimizu T et al. Poster presented at ASCO 2019; Abstract 5544.

Other promising FRα ADCs: PRO1184 & IMGN1511 in phase 1/2 Studies

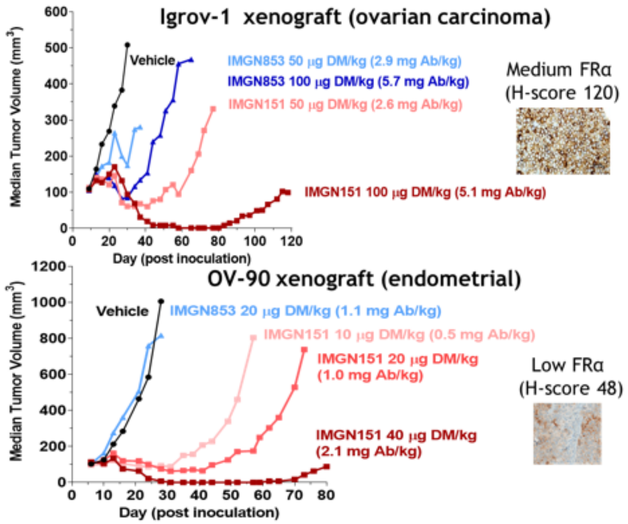
PRO1184 (NCT05579366)[1,2] – Phase 1/2

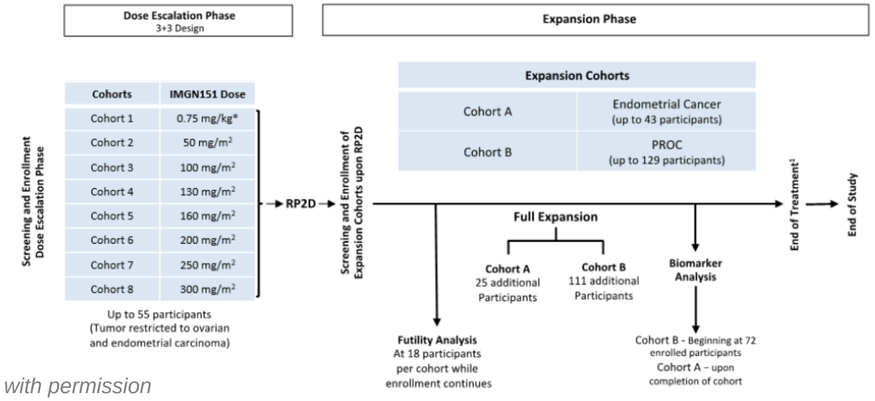


IMGN 151 (NCT04209855)[3,4] – Phase 1/2



- B5327A: asymmetric biparatopic anti-FRα antibody comprised of IMGN853 arm and a scFv-arm targeting an independent epitope of FRα
- DM21-L-G: new more potent maytansine-derived payload/linker





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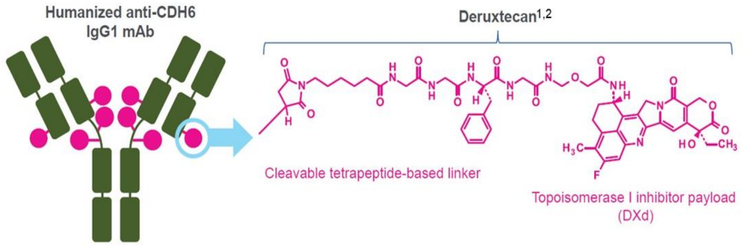
ADC, antibody-drug conjugate; FRα, folate receptor alpha; Gr, grade; HGS, high-grade serous; HER, human epidermal receptor; IHC, immunohistochemistry; mPFS, median progression-free survival; mOS, median overall survival; EOC, epithelial ovarian cancer; ORR, objective response rate; PDX, patient derived xenograft; NSCLC, non-small cell lung cancer; PROC, platinum-resistant ovarian cancer; RP2D, recommended phase 2 dose; scFV, single-chain fragment variable;

1. Call J, et al. AACR 2023 Abstract #CT244. 2. ClinicalTrials.gov NCT05579366. Accessed September 29, 2023. 3. Olga Ab. Poster presented at AACR 2020; Abstract #2890. 4. ClinicalTrials.gov NCT05527184.Accessed October 02, 2023.

Raludotatug deruxtecan (DS-6000a), CDH6-directed ADC[1,2]

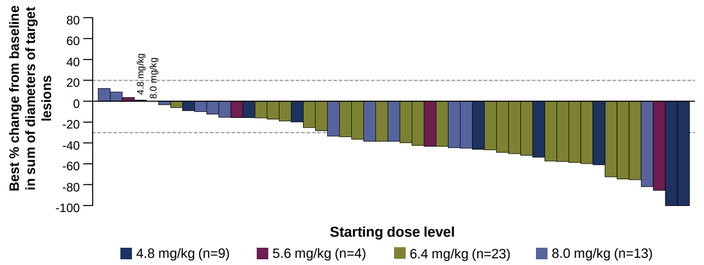
DS-6000[1,2]

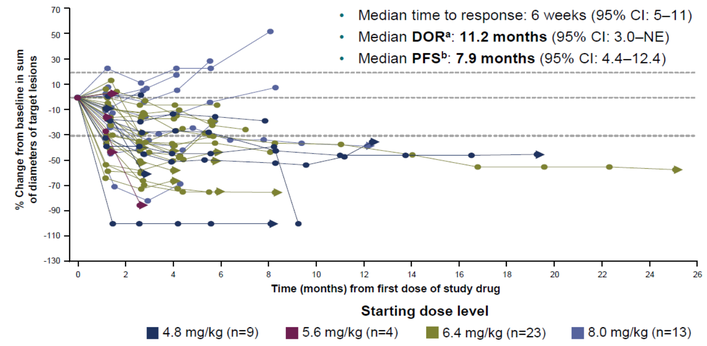


- A humanized anti-CDH6 IgG1 monoclonal antibody
- A topoisomerase I inhibitor payload, an exatecan derivative
- A tetrapeptide-based cleavable linker
- DAR ~8

Efficacy

- **Confirmed ORR**: 53%; unconfirmed ORR: 57% % in the 4.8–8.0 mg/kg OVC cohort
- **DCR:** 98%





Safety

Most common (≥10%)TEAEs

	All grades	Grade ≥3
Nausea	35 (58.3)	1 (1.7)
Fatigue	27 (45.0)	2 (3.3)
Vomiting	20 (33.3)	1 (1.7)
Anemia	17 (28.3)	11 (18.3)
Decreased neutrophil count	15 (25.0)	7 (11.7)
Diarrhea	16 (26.7)	1 (1.7)
Decreased appetite	15 (25.0)	1 (1.7)
Decreased platelet count	10 (16.7)	3 (5.0)
Alopecia	7 (11.7)	0
Malaise	6 (10.0)	0

NCT04707248: Recruiting

- Estimated enrollment: 140 participants
- Estimated primary completion date: October 31, 2024

Data cutoff: July 14, 2023

The efficacy evaluable population included patients who received ≥1 dose of study treatment and completed ≥1 post-baseline tumor assessment or discontinued treatment for any reason. Change from baseline in target tumor size was assessed per RECIST v1.1. Two patients with no measurable lesions at baseline and one patient who discontinued and did not have a post-baseline tumor assessment were not included in the waterfall or spider plots. DCR: CR + PR + stable disease.

[a]Median f/u for DOR: 5.8 months (range: 1.4-16.8). [b]Median f/u for PFS: 5.6 months (range 0.03-25.1)

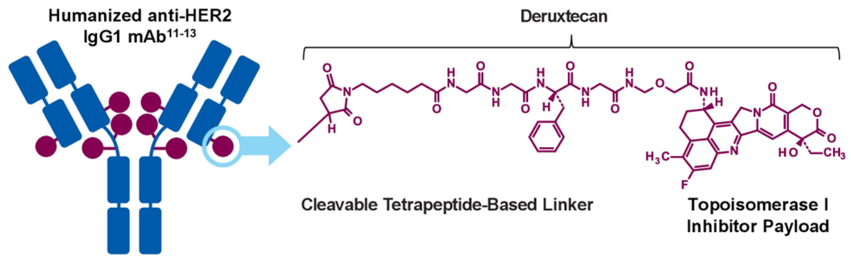
ADC, antibody-drug conjugate; CDH6, cadherin-6; cORR, confirmed overall response rate; CR, complete response; DAR, drug-to-antibody ratio; DCR, disease control rate; DOR, duration of response; f/u, follow-up; IgG1, immunoglobulin G1; NE, not estimable; ORR, overall response rate; OVC, serous ovarian cancer; PFS, progression-free survival; PR, partial response; PROC, platinum-resistant ovarian cancer; RCC, renal cell carcinoma; TEAE, treatment-emergent adverse event.

1. Moore KN et al. Poster presented at ESMO 2023; Abstract 3002. 2. ClinicalTrials.gov. NCT04707248. Accessed March 1, 2023.

Trastuzumab deruxtecan (T-DXd), HER2-targeted ADC under clinical investigation for patients with HER2-expressing tumors including OC

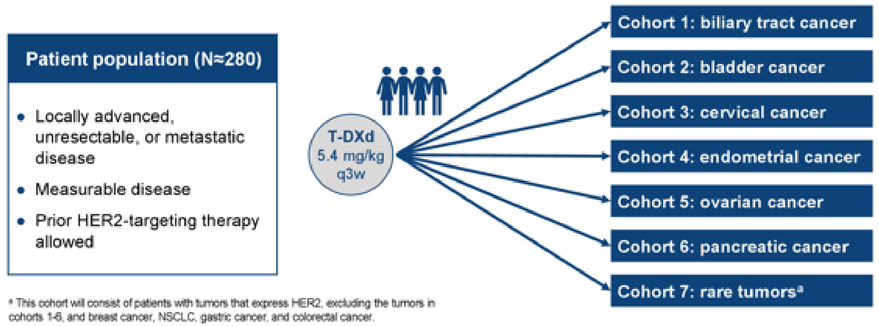
DESTINY-PanTumor02 (NCT04482309), phase 2, T-DXd in select advanced HER2-expressing tumors (including GYN tumors)[1,2]

Trastuzumab deruxtecan (T-DXd)[1]



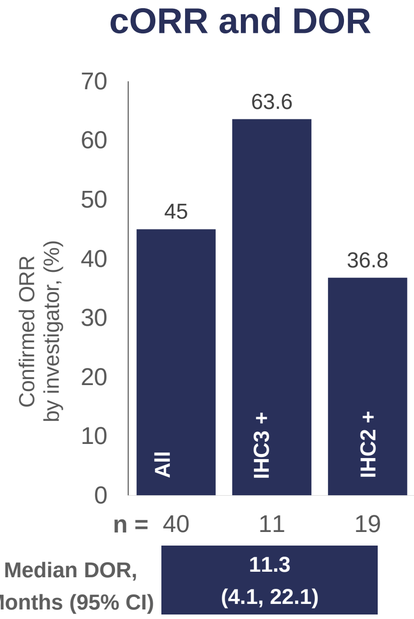
- ADC targeting ERBB2 (HER2)
- Conjugated to a topoisomerase inhibitor
- DAR=8

Study design and population



NCT04482309: Active, not recruiting
- Actual enrollment: 468 participants
- Estimated primary completion date: March 2027

Objective response and duration of response in ovarian cancer cohort



ADC, antibody-drug conjugate; cORR, confirmed overall response rate; DAR, drug-to-antibody ratio; DOR, duration of response; ERBB2, erb-b2 receptor tyrosine kinase 2; GYN, gynecologic; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; OC, ovarian cancer; q3w, every 3 weeks.

1. ClinicalTrials.gov. NCT04482309. Accessed March 1, 2023; 2. Meric-Bernstam F et al. Poster presented at ESMO Annual Meeting 2023. LBA 34.