THE ABC'S OF ADC'S IN OVARIAN CANCER

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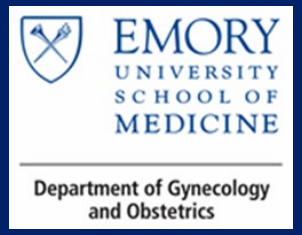
DISCLOSURES



I receive a stipend as Editor-in-Chief for *Gynecologic Oncology Reports*

I borrowed and edited (with permission) some slides from my colleague, Dr. Rob Coleman, on ADC's

U.S. FEMALE CANCER STATISTICS 2023

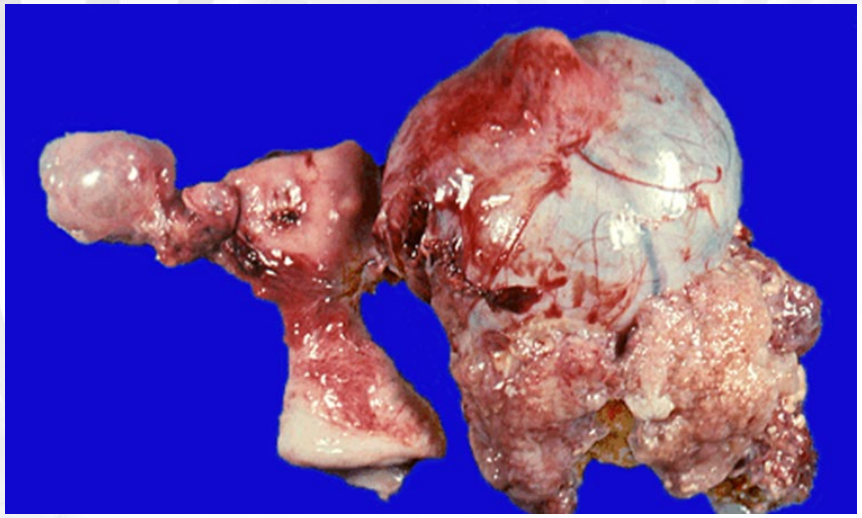
Site	Number	Deaths
Breast	297,790	43,170
Uterus	66,200	13,030
Ovary	19,710	13,270
Cervix	13,960	4,310
Vulva	6,470	1,670

American Cancer Society. Cancer Facts and Figures 2023

WHY DO WE CARE?

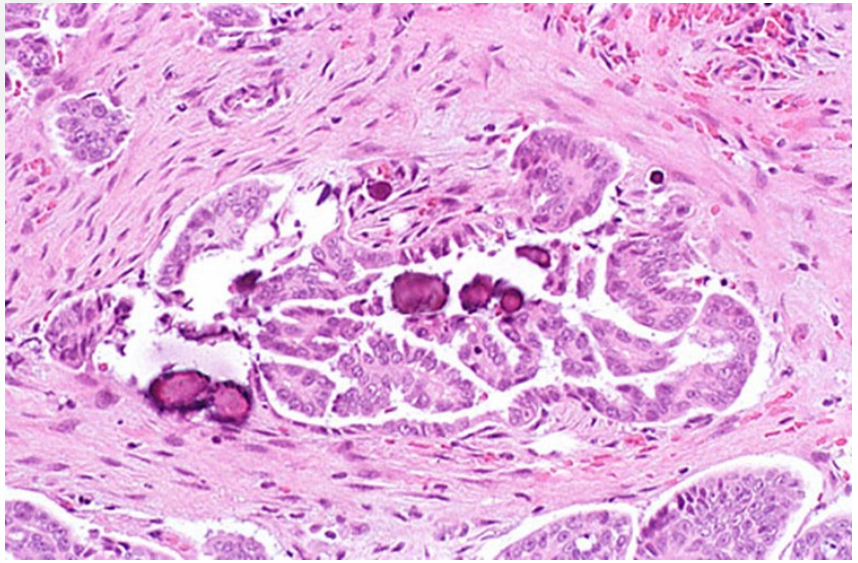
Epithelial Ovarian cancer is expected to be the 5th leading cause of cancer death in U.S. women in 2023

- 3% of all female cancers but 5% of all deaths



Most women recur and will develop platinum resistant disease with dismal response rates to treatment

Phase III studies (AURELIA, CORAIL, NINJA, FORWARD I, and JAVELIN, Ovarian 200) in patients with platinum resistant disease show overall response rates from 4-13%



NCCN Guidelines Version 1.2023
Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer

NCCN Guidelines Index
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Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Acceptable Recurrence Therapies for Epithelial Ovarian (including LCOC)[n]/Fallopian Tube/Primary Peritoneal Cancer[o]

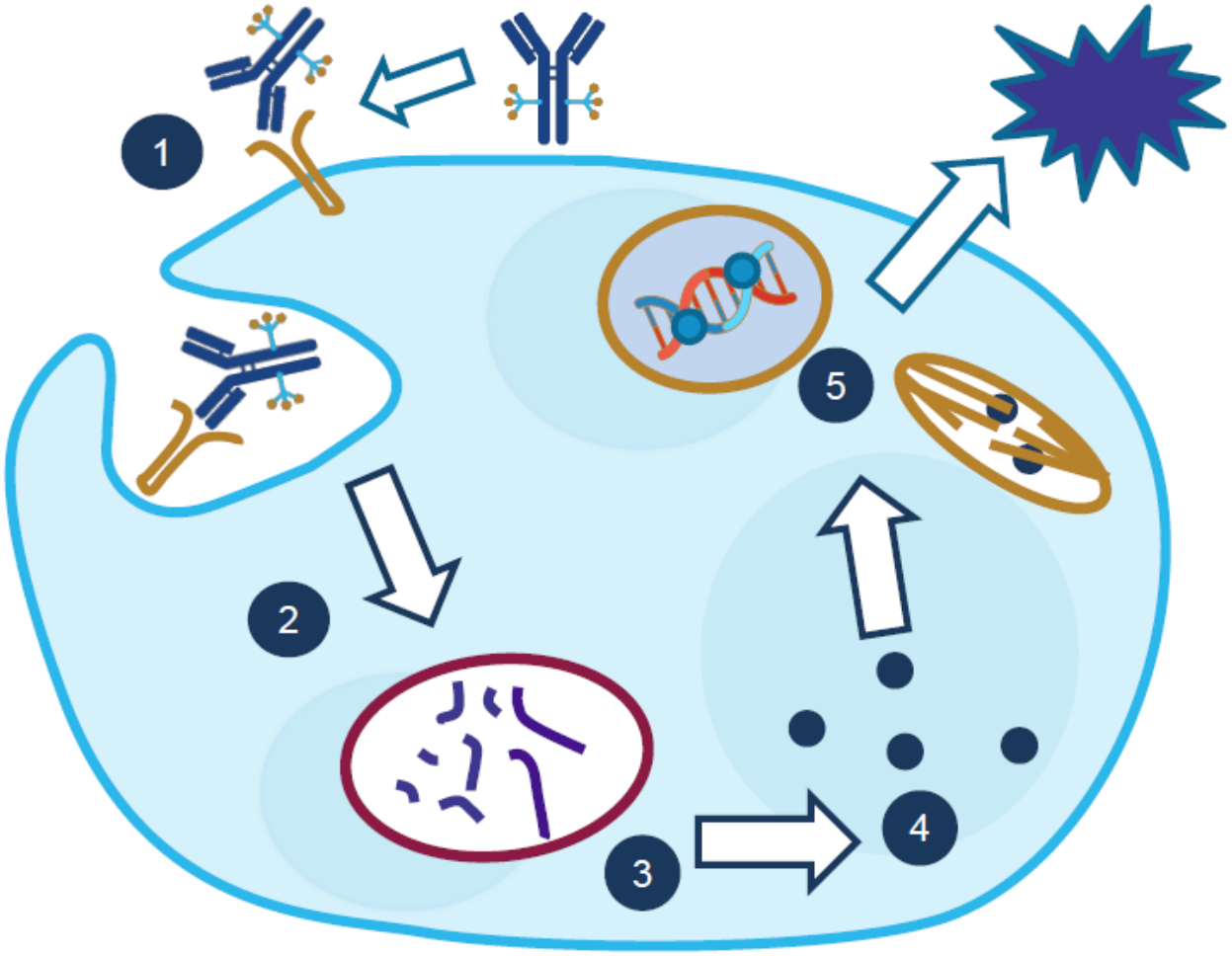
Recurrence Therapy for Platinum-Resistant Disease (alphabetical order)

Preferred Regimens	Other Recommended Regimens	Useful in Certain Circumstances
Cytotoxic Therapy Cyclophosphamide (oral)/ bevacizumab[i,35] Docetaxel[36] Etoposide, oral[37] Gemcitabine[38,39] Liposomal doxorubicin[38,39] Liposomal doxorubicin/ bevacizumab[i,q,40] Paclitaxel (weekly)[f,41] Paclitaxel (weekly)/ bevacizumab[f,i,q,40] Topotecan[42,43] Topotecan/bevacizumab[i,q,40] Targeted Therapy (single agents) Bevacizumab[i,q,17,18] Mirvetuximab soravtansine-gynx (for *FRα*-expressing tumors)[x,44]	Cytotoxic Therapy[s] Capecitabine Carboplatin[*] Carboplatin/docetaxel[*] Carboplatin/paclitaxel (weekly)[f,*] Carboplatin/gemcitabine[10] ± bevacizumab[i,q,r,11,*] Carboplatin/liposomal doxorubicin[12] ± bevacizumab[i,q,13,*] Carboplatin/paclitaxel[f,14] ± bevacizumab[i,q,r,15,*] Cyclophosphamide Doxorubicin Gemcitabine/cisplatin[16,*] Ifosfamide Irinotecan Ixabepilone/bevacizumab (category 2B)[i,y,46] Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound Pemetrexed Sorafenib/topotecan[45] Vinorelbine Targeted Therapy (single agents) Niraparib (category 3)[u,23] Olaparib (category 3)[v,24] Pazopanib (category 2B)[25] Rucaparib (category 3)[w,26] Hormone Therapy Aromatase inhibitors (anastrozole, exemestane, letrozole) Leuprolide acetate Megestrol acetate Tamoxifen	Carboplatin/paclitaxel (for age >70)[f,t,*] Carboplatin/paclitaxel, albumin bound (for confirmed taxane hypersensitivity)[*] Immunotherapy Dostarlimab-gxly (for dMMR/MSI-H recurrent or advanced tumors)[x,32] Pembrolizumab (for patients with MSI-H or dMMR solid tumors, or TMB-H tumors ≥10 mutations/ megabase)[x,33] Hormone Therapy Fulvestrant (for low-grade serous carcinoma) Targeted Therapy Dabrafenib + trametinib (for *BRAF* V600E-positive tumors)[x,28] Entrectinib or larotrectinib (for *NTRK* gene fusion positive tumors)[x] Mirvetuximab soravtansine-gynx/bevacizumab (for *FRα*-expressing tumors) (category 2B)[i,x,47, 48] Selpercatinib (for *RET* gene fusion-positive tumors)[x,29] For low-grade serous carcinoma: • Trametinib[30] • Binimetinib (category 2B)[31,32]

* Do not use in platinum-refractory disease.

NEW AGENTS ARE NEEDED

Mechanism of action of ADCs[1,2]



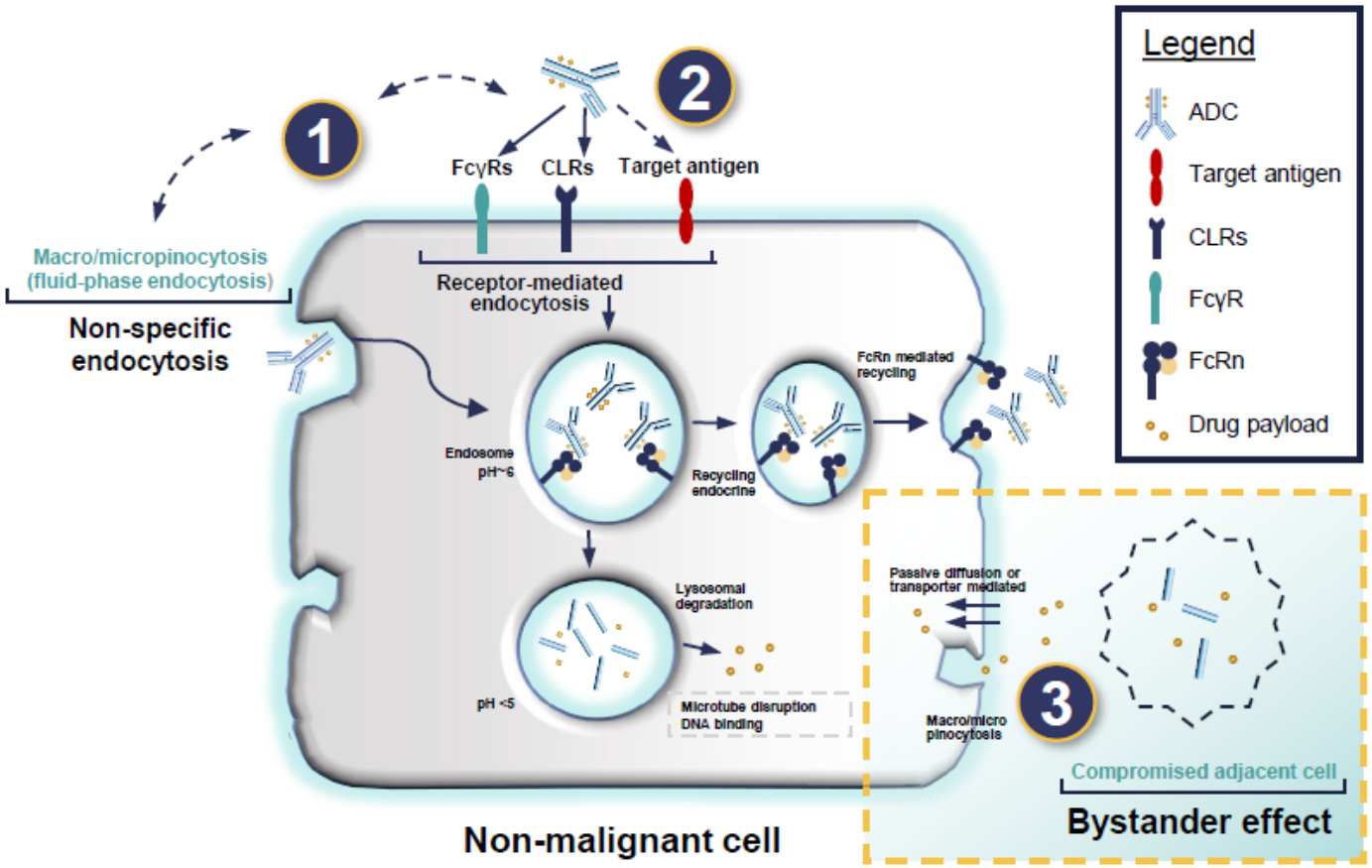
Mechanism of action

1. Antibody binds to the target antigen at the surface of the cancer cell
2. ADC–antigen complex is internalized and trafficked through the endolysosomal compartment
3. Payload is released in the lysosome
4. Drug payload enters the cytoplasm
5. Drug payload acts on microtubules or DNA, resulting in cell death

ADC, antibody-drug conjugate.

1. Drago JZ et al. *Nat Rev Clin Oncol*. 2021;18(6):327–344. 2. Shim H. *Biomolecules*. 2020;10(3):360.

Antibody-drug conjugates: potential mechanisms of toxicity



1. **Target-independent toxicity:** ADC uptake into non-malignant cells
   - Non-specific endocytosis
   - Macropinocytosis and micropinocytosis
   - Binding to Fc receptors
2. **On-target, off-tumor toxicity:** target antigen may be expressed on normal cells and contribute to target antigen–dependent uptake of ADCs
3. **Bystander effect (off-target, off-tissue toxicity):** membrane-permeable drug payloads diffuse from target cell into neighboring cells
   - May be beneficial if the neighboring cell is cancerous, or detrimental if neighboring cell is healthy

Microtubule inhibitor	Commonly reported clinical toxicity
MMAE	Anemia, neutropenia, and peripheral neuropathy
DM1	Thrombocytopenia and hepatotoxicity
MMAF and DM4	Ocular toxicity

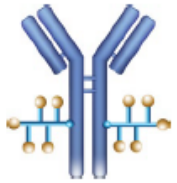
ADC, antibody-drug conjugate; CLR, C-type leptin receptor; DM1, maytansinoid DM1; DM4, maytansinoid DM4; FcRn, neonatal FC receptor; FcγR, Fc gamma receptor; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F.

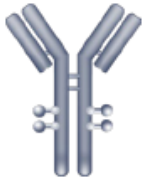
Mahalingaiah PK et al. *Pharmacol Ther*. 2019;200:110–125.

Table 2. FDA-approved ADCs (as of November 2022)

	Initial FDA Approval	Target	Payload	Linker
Solid tumors				
Ado-trastuzumab emtansine	2013	HER2	DM-1	Non-cleavable
Fam-trastuzumab deruxtecan	2019	HER2	DXd	Cleavable
Enfortumab vedotin	2019	Nectin-4	MMAE	Cleavable
Sacituzumab govitecan	2021	Trop-2	SN38	Cleavable
Tisotumab vedotin	2021	TF	MMAE	Cleavable
Mirvetuximab soravtansine	2022	FRα	DM-4	Cleavable

Properties of select ADCs in gynecologic oncology



	Upifitamab rilsodotin[1,2]	Mirvetuximab soravtansine[3–5]	STRO-002[6,7]	Tisotumab vedotin[8–10]
Target	NaPi2b	Folate receptor α	Folate receptor α	Tissue factor (CD142)
Linker	Polymer scaffold conjugated (cleavable)	Sulfo-SPDB (cleavable)	Valine-citrulline (cleavable)	Valine-citrulline (cleavable)
DAR	~10	3–4	4	4
Payload	AF-HPA/AF	DM4	SC209 (hemiasterlin)	MMAE
Bystander effect	Controlled bystander effect	Yes	Yes	Yes
Disease of interest or approved	Ovarian cancer	Ovarian and endometrial cancer	Ovarian and endometrial cancer	Cervical[a] and ovarian cancer

[a] Tisotumab vedotin (TIVDAK) is indicated for treatment of adult patients with recurrent or metastatic cervical cancer with disease progression on or after chemotherapy. Accelerated FDA approved in September 2021 with boxed warning for ocular toxicity.[11]

ADC, antibody-drug conjugate; AF, auristatin F; AF-HPA, auristatin F-hydroxypropylamide; CD, cluster of differentiation; DAR, drug-to-antibody ratio; DM4, maytansinoid DM4; FDA, US Food and Drug Administration; MMAE, monomethyl auristatin E; NaPi2b, sodium-dependent phosphate transport protein 2B.

1. Richardson DL et al. SGO Annual Meeting on Women's Cancer 2022; Abstract 76. 2. ClinicalTrials.gov. NCT03319628, NCT05329545, NCT04907968. Accessed Sep 27, 2022. 3. Calo CA et al. *Expert Opin Biol Ther*. 2021;21(7):875–887. 4. Manzano A et al. *Cancers (Basel)*. 2020;12(8):2223. 5. ClinicalTrials.gov. NCT03832361, NCT04296890, NCT04209855. Accessed Sep 27, 2022. 6. Li X et al. AACR Annual Meeting 2018; Abstract 1782. 7. ClinicalTrials.gov. NCT03748186. Accessed Sep 27, 2022. 8. de Bono JS et al. *Lancet Oncol*. 2019;20(3):383–393. 9. Fu X et al. *Signal Transduct Target Ther*. 2022;7(1):93. 10. ClinicalTrials.gov. NCT03438396, NCT03657043. Accessed Sep 27, 2022. 11. US Food and Drug Administration. Published September 20, 2021. Accessed Sep 27, 2022. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tisotumab-vedotin-tftv-recurrent-or-metastatic-cervical-cancer

MIRVETUXIMAB: CURRENT STATUS

- FDA approval for platinum resistant epithelial ovarian cancer in 2022
  - Based on Mirasol and Soraya trials, others ongoing
- Requires high folate receptor expression
- Ongoing trials in platinum sensitive ovarian cancer
  - Piccolo completed
  - Gloriosa and other trials currently enrolling

Mirvetuximab soravtansine (FRα-targeting, DM4)[1,2]

Single-arm Phase 3 trial, N=106 patients

SORAYA

Key eligibility criteria

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

Mirvetuximab soravtansine q3w
6 mg/kg, adjusted ideal body weight

Primary endpoint

- Investigator-assessed ORR

Secondary endpoints

- DOR
- Safety and tolerability
- PFS
- OS
- ORR, DOR, and PFS by BICR as sensitivity analyses
- CA-125 response by GCIG criteria

[a] PS2+ scoring method, sum of staining of 2+ and 3+ intensity.

ADC, antibody-drug conjugate; BICR, blinded independent central review; *BRCA*, BRCA DNA repair associated gene; CA-125, cancer antigen 125; DM4, maytansinoid DM4; DOR, duration of response; FRα, folate receptor alpha; GCIG, Gynecologic Cancer InterGroup; ORR, overall response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; q3w, every 3 weeks.

1. Matulonis UA et al. ASCO Annual Meeting 2022; Abstract 5512. 2. ClinicalTrials.gov. NCT04296890. Accessed Sep 27, 2022.

Mirvetuximab soravtansine is an investigational drug not currently approved for use by any health authority in any indication.

SORAYA

POSITIVE TOP-LINE RESULTS
POTENTIAL FOR ACCELERATED APPROVAL

SINGLE-ARM PIVOTAL TRIAL OF MIRVETUXIMAB IN FRα-HIGH PATIENTS WITH PLATINUM-RESISTANT OVARIAN CANCER

INCLUSION CRITERIA

106 PATIENTS

- Platinum-resistant disease (PFI < 6 months)
- FRα-high only
- Prior bevacizumab required
- Prior PARPi allowed
- 1 to 3 prior lines allowed
- Patients with BRCA mutations allowed

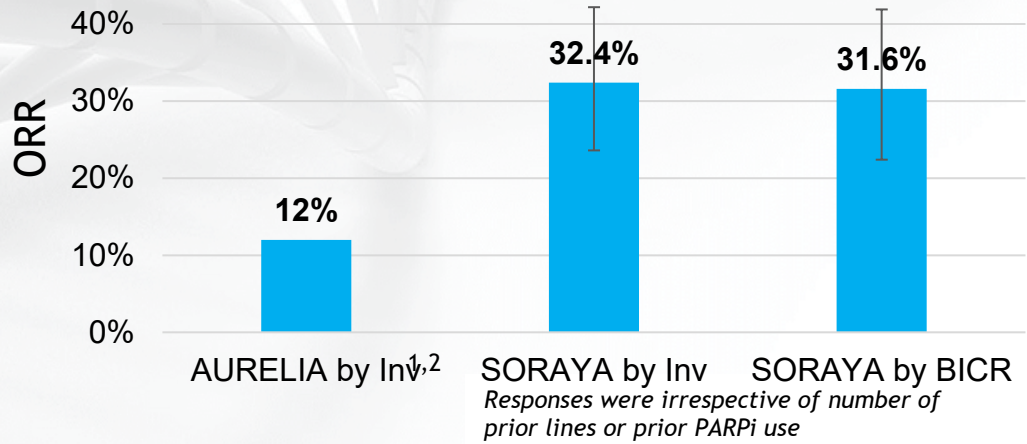
PRIOR TREATMENT

51%	100%	48%
3 prior lines of therapy	Received prior bevacizumab	Received prior PARPi

SAFETY AND TOLERABILITY

- Favorable tolerability data
- >700 patients treated to date
- The most common AEs were low-grade gastrointestinal and ocular events, including blurred vision, keratopathy, and nausea; 7% of patients discontinued due to treatment-related AEs, including one patient due to ocular AE

MET PRIMARY ENDPOINT



Responses were irrespective of number of prior lines or prior PARPi use

KEY SECONDARY ENDPOINT

5.9 months mDOR

By Investigator at Data Cutoff *(95% CI: 5.6, 7.7)*

Nearly half of responders still receiving mirvetuximab at data cutoff; with longer follow-up, mDOR could range from 5.7 to above 7 months

FDA Accelerated Approval in November 2022

[1]AURELIA Study, JCO 2014, Pujade-Lauraine, E., et al.
[2]Disclaimer: These comparisons are not based on head-to-head clinical studies. The results from these two studies are not directly comparable and do not imply a clinical benefit of mirvetuximab over bevacizumab.
FRα: folate receptor alpha; PFI: platinum-free interval; PARPi: poly ADP-ribose polymerase inhibitor; BRCA: BReast CAncer gene; AE: adverse event; ORR: confirmed objective response rate Inv: Investigator; BICR: blinded independent central review; mDOR: median duration of response; BLA: Biologics License Application; FDA: US Food and Drug Administration

SORAYA TRIAL: PUBLISHED 2023

original reports

Efficacy and Safety of Mirvetuximab Soravtansine in Patients With Platinum-Resistant Ovarian Cancer With High Folate Receptor Alpha Expression: Results From the SORAYA Study

Ursula A. Matulonis, MD[1]; Domenica Lorusso, MD, PhD[2]; Ana Oaknin, MD, PhD[3]; Sandro Pignata, MD, PhD[4]; Andrew Dean, MBChB, MRCP, FRACP[5]; Hannelore Denys, MD, PhD[6]; Nicoletta Colombo, MD, PhD[7,8]; Toon Van Gorp, MD, PhD[9]; Jason A. Konner, MD[10]; Margarita Romeo Marin, MD, PhD[11]; Philipp Harter, MD, PhD[12]; Conleth G. Murphy, MD[13]; Jiuzhou Wang, PhD[14]; Elizabeth Noble, BS[14]; Brooke Esteves, BSN[14]; Michael Method, MD, MPH, MBA[14]; and Robert L. Coleman, MD[15]

- ORR was 32.4% (95% CI, 23.6 to 42.2), including five complete and 29 partial responses
- The median duration of response was 6.9 months (95% CI, 5.6 to 9.7)

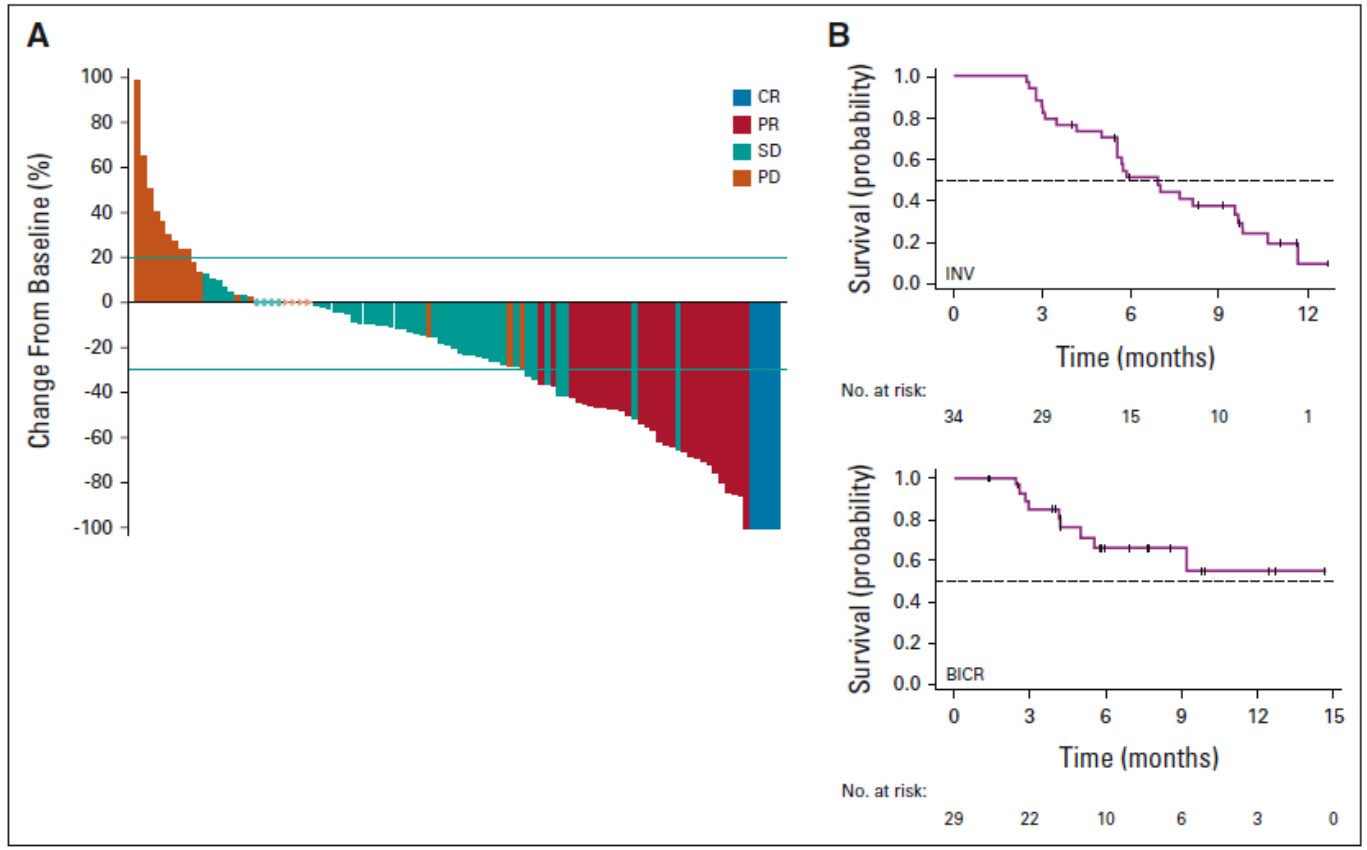


FIG 1. Antitumor activity of mirvetuximab soravtansine. (A) Maximum percentage change in target lesion size from baseline. Best response according to RECIST is indicated by color coding of bars. (B) Kaplan-Meier plot of DOR in patients with confirmed complete or partial response as assessed by INV (upper panel) and BICR (lower panel). Median DOR by INV was 6.9 months and NR by BICR. BICR, blinded independent central review; CR, complete response; DOR, duration of response; INV, investigator; NR, not reached; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

J Clin Oncol 41:2436-2445.

TOXICITY

TABLE 5. Most Common (≥ 10%) TRAEs in the Safety Population

TRAEs	All Grades, No. (%)	Grades 3-4, No. (%)
Patients with any event	91 (86)	31 (29)
Blurred vision	43 (41)	6 (6)
Keratopathy[a]	31 (29)	9 (9)
Nausea	31 (29)	0 (0)
Dry eye	26 (25)	2 (2)
Fatigue	25 (24)	1 (1)
Diarrhea	23 (22)	2 (2)
Asthenia	16 (15)	1 (1)
Photophobia	14 (13)	0 (0)
Peripheral neuropathy	14 (13)	0 (0)
Decreased appetite	14 (13)	1 (1)
Neutropenia	14 (13)	2 (2)
Vomiting	12 (11)	0 (0)

2023 ASCO® ANNUAL MEETING

PHASE III MIRASOL (GOG 3045/ENGOT-OV55) STUDY: MIRVETUXIMAB SORAVTANSINE VS. INVESTIGATOR'S CHOICE OF CHEMOTHERAPY IN PLATINUM-RESISTANT, ADVANCED HIGH-GRADE EPITHELIAL OVARIAN, PRIMARY PERITONEAL OR FALLOPIAN TUBE CANCERS WITH HIGH FOLATE RECEPTOR-ALPHA (FRα) EXPRESSION

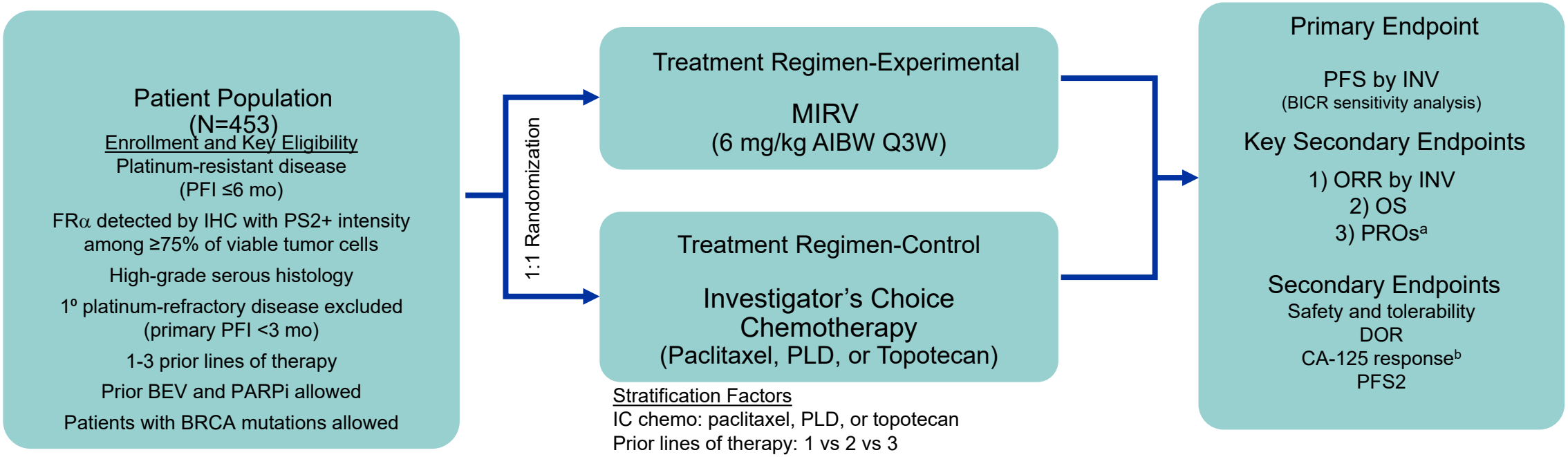
Kathleen N. Moore[1], Antoine Angelergues[2], Gottfried E. Konecny[3], Susana Banerjee[4], Sandro Pignata[5], Nicoletta Colombo[6], John Moroney[7], Casey Cosgrove[8], Jung-Yun Lee[9], Andrzej Roszak[10], Shani Breuer[11], Jacqueline Tromp[12], Diana Bello Roufai[13], Lucy Gilbert[14], Rowan Miller[15], Tashanna Myers[16], Yuemei Wang[17], Anna Berkenblit[17], Domenica Lorusso[18], Toon Van Gorp[19]

ENGOT European Network of Gynaecological Oncological Trial groups

GOG FOUNDATION® Transforming the standard of care™

Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

MIRASOL – STUDY DESIGN[1,2]



AIBW, adjusted ideal body weight; BEV; bevacizumab; BICR, blinded independent central review; BRCA, BReast CAncer gene; CA-125, cancer antigen 125; chemo, chemotherapy; DOR, duration of response; FRα, folate receptor alpha; IC, investigator's choice; IHC, immunohistochemistry; INV, investigator; MIRV, mirvetuximab soravtansine; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitors; PFI, platinum-free interval; PFS, progression-free survival; PFS2, time from randomization until second disease progression; PLD, pegylated liposomal doxorubicin; PROs, patient-reported outcomes; PS2+, positive staining intensity ≥2; Q3W, every 3 weeks.

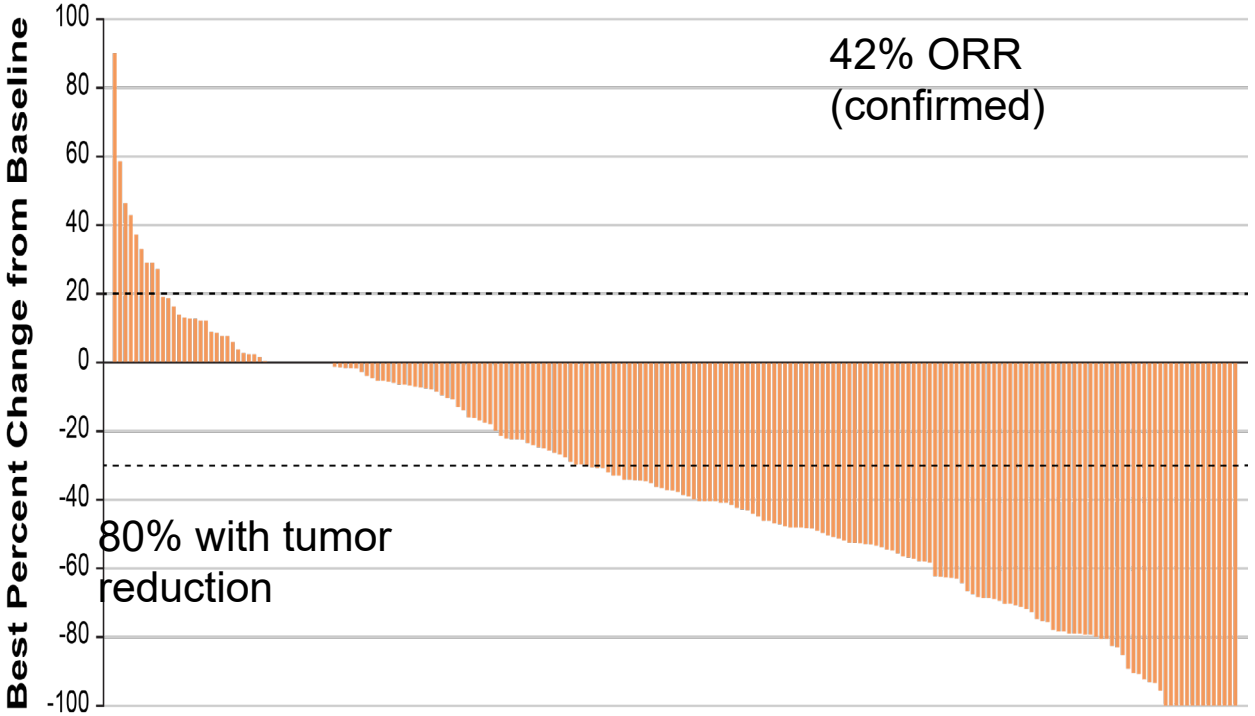
[a]PROs will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire, 28-item Ovarian Cancer Module (OV28) study instrument.

[b]Gynecological Cancer InterGroup (GCIG) criteria.

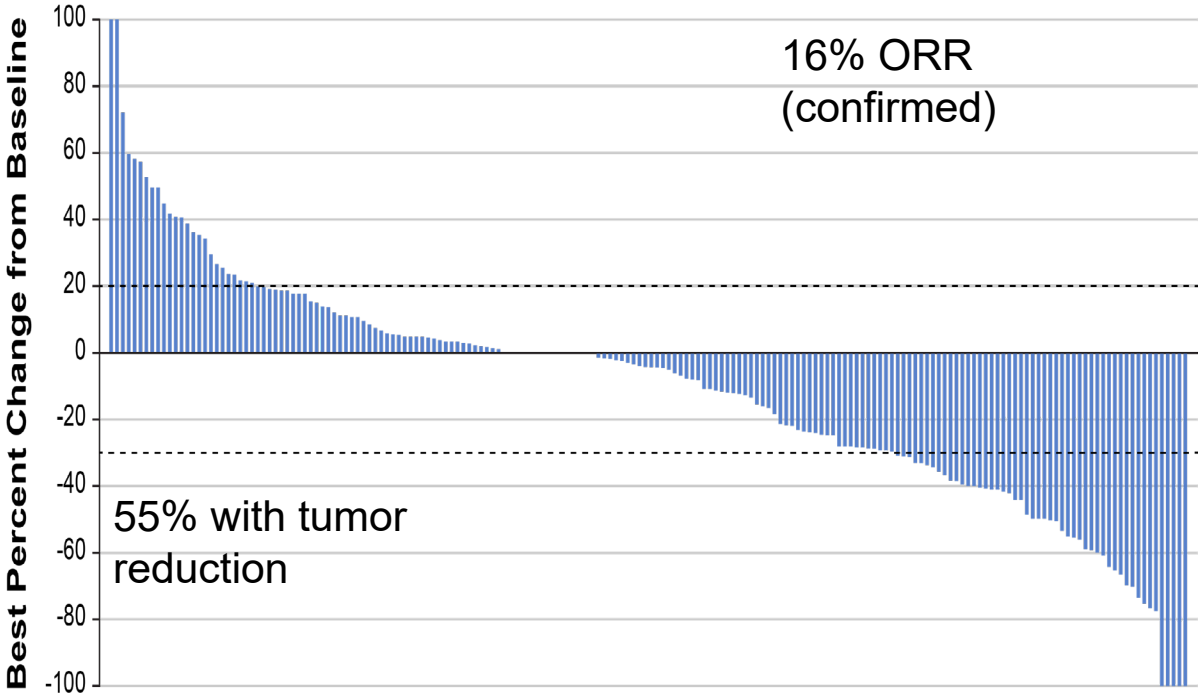
1. ClinicalTrials.gov identifier: NCT04209855. Updated June 16, 2022. Accessed October 5, 2022. https://clinicaltrials.gov/ct2/show/NCT04209855
2. Moore K, et al. Presented at: 2020 American Society of Clinical Oncology Annual Meeting; May 29-31, 2020; Virtual. Abstract TPS6103.

Maximum Percentage Change in Target Lesion Size from Baseline by Investigator (N=453)

MIRV



IC Chemo



Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC chemo, investigator's choice chemotherapy; ORR, objective response rate.

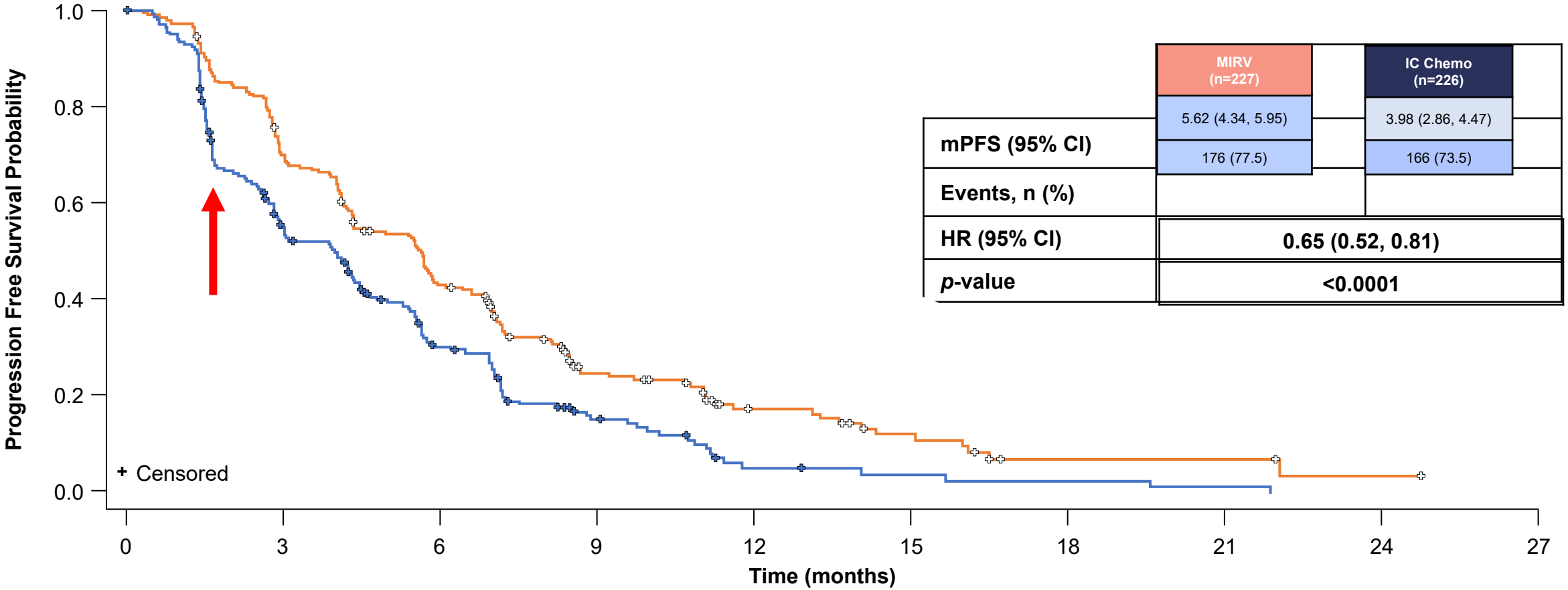
OVERALL RESPONSE RATE BY INVESTIGATOR (N=453)

	MIRV (n=227)	IC Chemo (n=226)
ORR **n, 95% CI**	**42%** 96, (35.8, 49.0)	**16%** 36, (11.4, 21.4)
Best overall response, n (%)		
CR	12 (5%)	0
PR	84 (37%)	36 (16%)
SD	86 (38%)	91 (40%)
PD	31 (14%)	62 (27%)
Not evaluable	14 (6%)	37 (16%)

ORR Difference 26.4% (18.4, 34.4)
OR 3.81 (2.44, 5.94)
p<0.0001

Data cutoff: March 6, 2023
MIRV, mirvetuximab soravtansine; IC chemo, investigator's choice chemotherapy; ORR, objective response rate; CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OR, odds ratio.

PRIMARY ENDPOINT: PROGRESSION-FREE SURVIVAL 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	

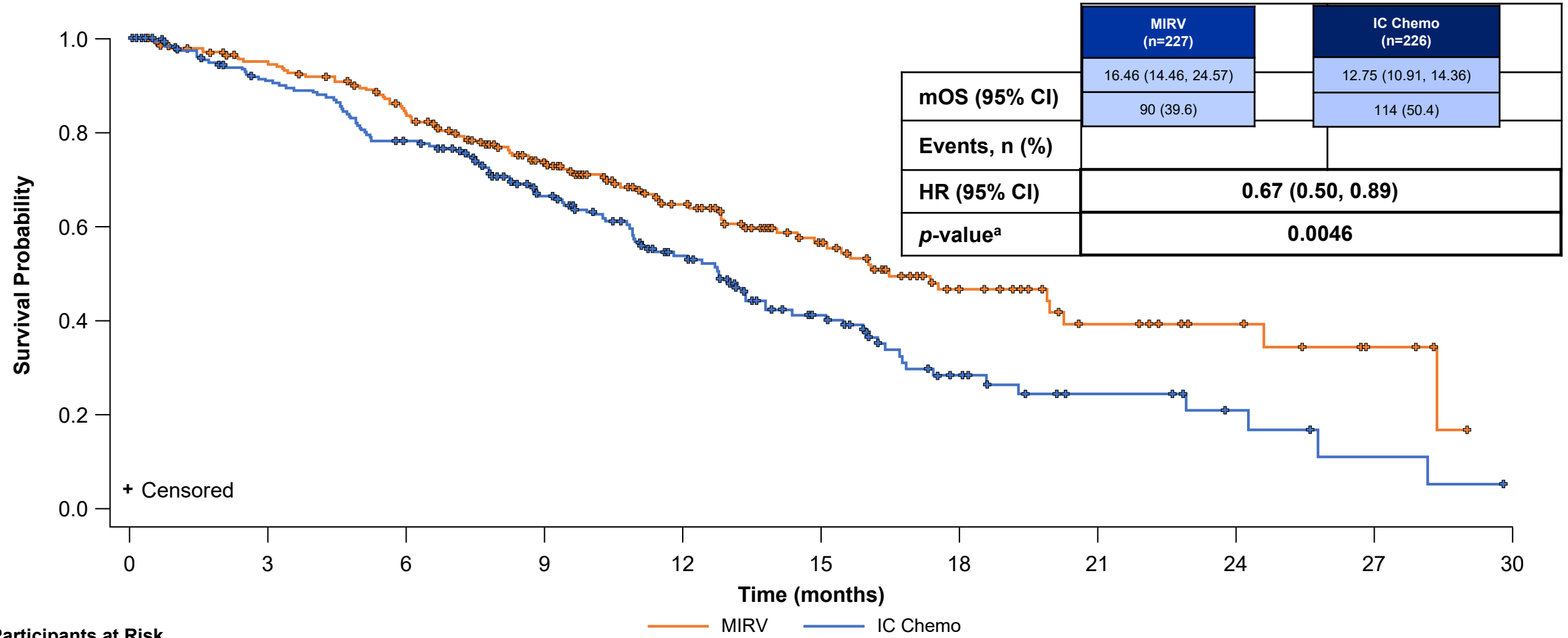
No. Participants at Risk

MIRV	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

MIRV, mirvetuximab soravtansine; IC Chemo, investigator's choice chemotherapy; mPFS, median progression-free survival; CI, confidence interval; HR, hazard ratio.

OVERALL SURVIVAL



	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[a]	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

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

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

SAFETY SUMMARY (N=425)

	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 one dose of MIRV or IC Chemo

TEAEs, treatment-emergent adverse events; SAEs, serious adverse events; MIRV, mirvetuximab soravtansine; IC, investigator's choice chemotherapy.

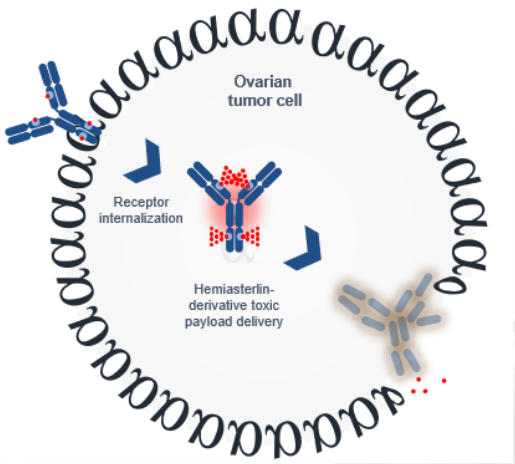
Ocular Care and Pre-Medications

- Ophthalmic care
  - Eye exam: at baseline, every other cycle for the first 8 cycles, and as clinically indicated
  - Corticosteroid: dexamethasone 0.1% to use 1 drop in each eye 6 times daily starting the day prior to infusion until day 4, then administer 1 drop in each eye 4 times daily for days 5-8 of each cycle
  - Lubricating ophthalmic drops: preservative free OTC artificial tears at least 4x daily for duration of therapy, waiting at least 10 minutes after steroid administration
  - Contact lens use: should be avoided for duration of treatment

LUVELTAMAB TAZEVIBULIN (STRO-002)

ANTI-FOLATE RECEPTOR ALPHA ANTIBODY DRUG CONJUGATE

LUVELTAMAB TAZEVIBULIN (STRO-002), AN ANTI-FOLATE RECEPTOR ALPHA ANTIBODY DRUG CONJUGATE, SAFETY AND EFFICACY IN A BROAD DISTRIBUTION OF FOLRA EXPRESSION IN PATIENTS WITH RECURRENT EPITHELIAL OVARIAN CANCER: UPDATE OF STRO-002-GM1 PHASE 1 DOSE EXPANSION COHORT



Luveltamab tazevibulin (luvelta) is a FolRα targeting antibody drug conjugate designed using site specific conjugation and a cell-free synthesis platform to induce cytotoxic and immunogenic cell death to target a broad range of FolRα expressing tumors

NCT03748186

- Recurrent disease
  - Platinum resistant 1–3 prior regimens or platinum-sensitive 2–3 prior regimens
- Fresh or archival tissue required
- No mandate for FolRα expression
- At least 1 target lesion

R 1:1

Luveltamab 4.3 mg/kg Q3W n=23

Luveltamab 5.2 mg/kg Q3W n=21

- Primary endpoint: ORR by RECIST v1.1
- Secondary endpoints: Safety, PK, PFS, DOR

- FolRα expression retrospectively determined using IHC* on fresh or archival tissue required
- TPS is the percentage of cells stained positive at any intensity
  - Established in multiple approvals and tumor indications
  - Does not require differentiation between staining intensity
  - Simple and straightforward for pathology read
- **Enriched population defined as TPS >25%**
- **TPS >25% in 35/44 (80%) of all enrolled patients**

Patients enrolled unselected for FolRα N=44

FolRα >25% by TPS (TPS >25%) n=35

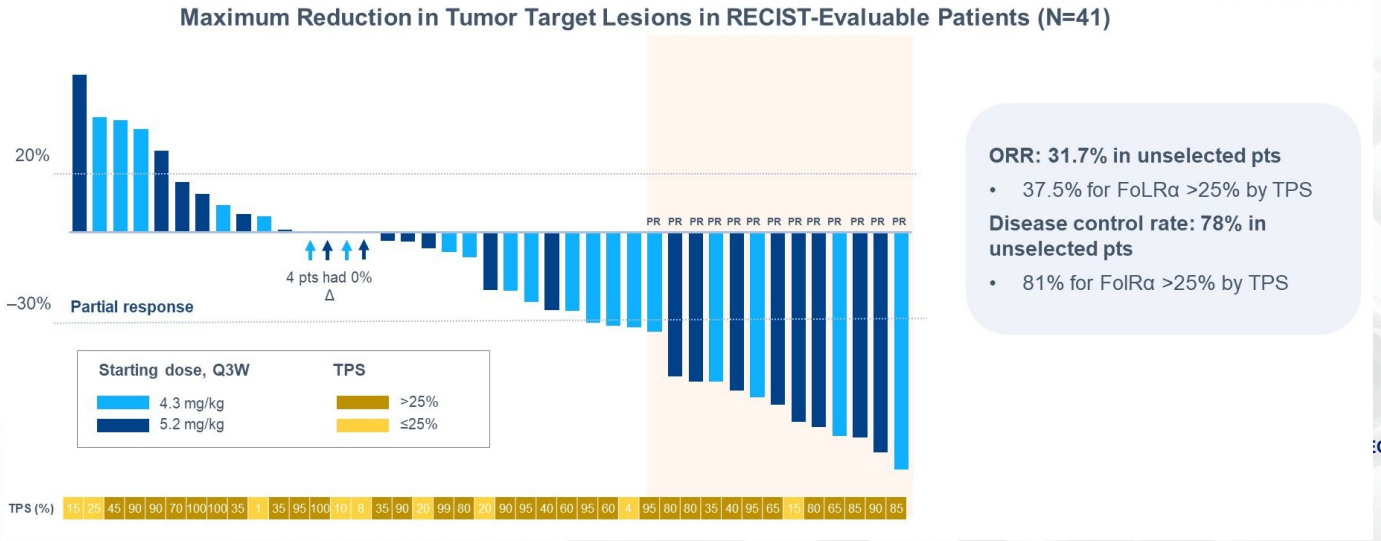
- **RECIST v1.1 evaluable** At least 1 post-baseline scan n=32
- **Not RECIST evaluable** Discontinued prior to receiving any post-baseline scan n=3†

FolRα ≤25% by TPS (TPS ≤25%) n=9

- **RECIST v1.1 evaluable** At least 1 post-baseline scan n=9
- **Not RECIST evaluable** Discontinued prior to receiving any post-baseline scan n=0

A Oaknin, **ASCO 2023**

Efficacy

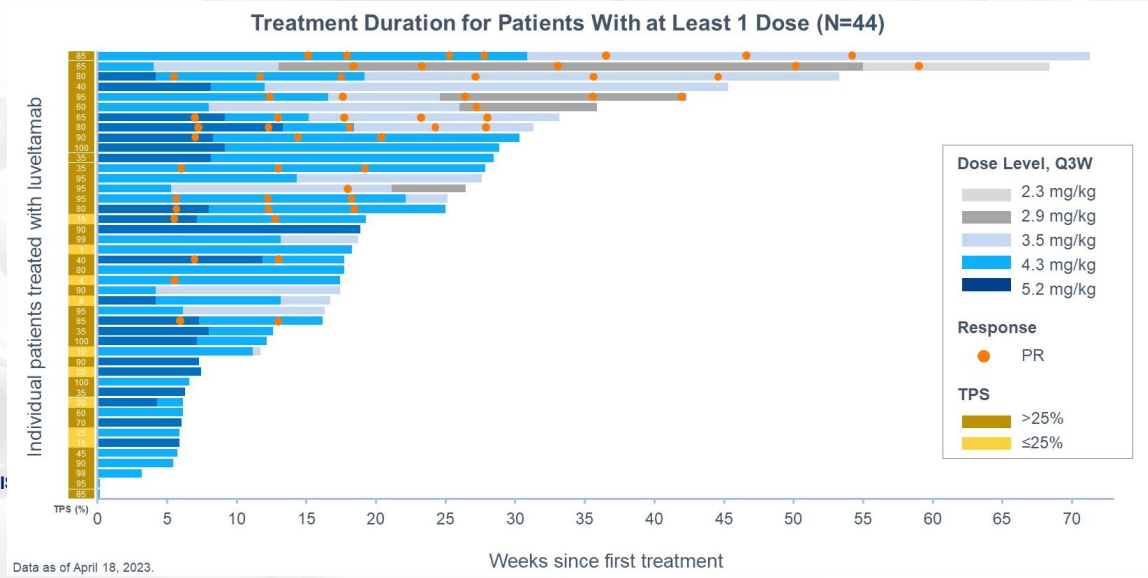


ORR: 31.7% in unselected pts

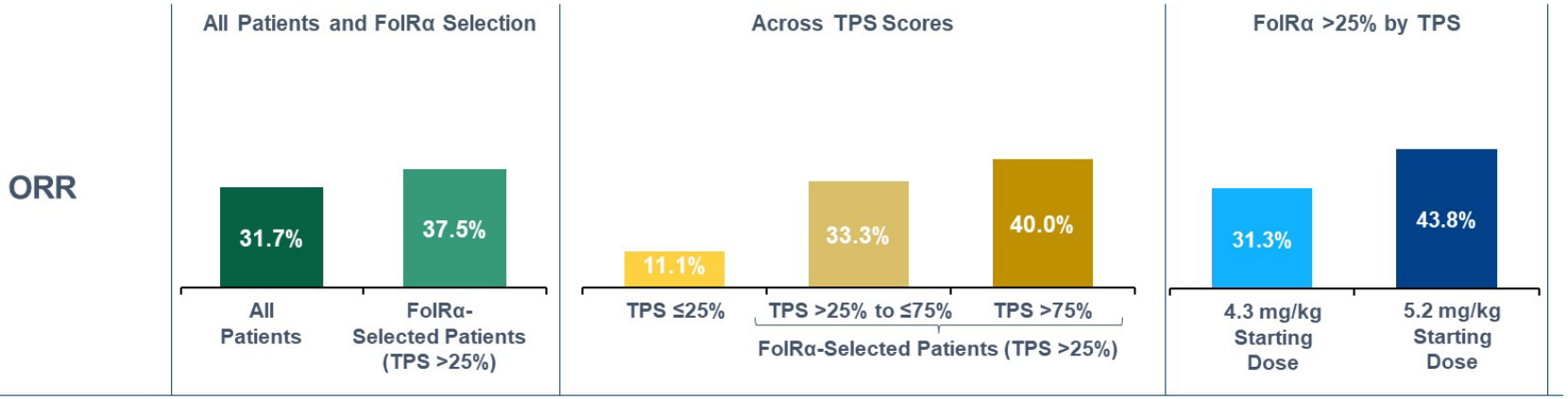
- 37.5% for FoLRα >25% by TPS

Disease control rate: 78% in unselected pts

- 81% for FolRα >25% by TPS



Treatment Response in RECIST-Evaluable Patients (N=41)



RECIST-evaluable patients	N=41	n=32	n=9	n=12	n=20	n=16	n=16
PR	13	12	1	4	8	5	7
ORR (95% CI), %	31.7 (18.1, 48.1)	37.5 (21.1, 56.3)	11.1 (0.3, 48.3)	33.3 (9.9, 65.1)	40.0 (19.1, 63.9)	31.3 (11.0, 58.7)	43.8 (19.8, 70.1)

A Oaknin, et al.
ASCO 2023

TRAZTUZUMAB DERUXTECAN

ANTI HER-2-NEU ANTIBODY DRUG CONJUGATE

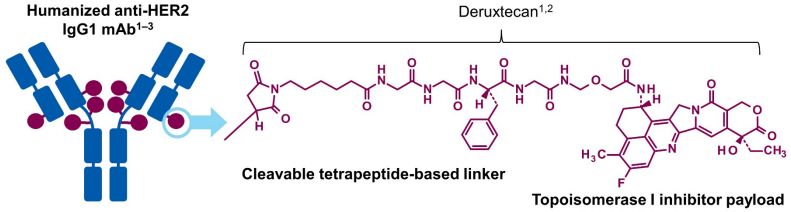
DESTINY-PanTumor02

Efficacy and safety of trastuzumab deruxtecan in patients with HER2-expressing solid tumors: DESTINY-PanTumor02 interim results

Funda Meric-Bernstam

T-DXd is an ADC with three components:

1. A humanized anti-HER2 IgG1 mAb with the same amino acid sequence as trastuzumab
2. A topoisomerase I inhibitor payload, an exatecan derivative
3. A tetrapeptide-based cleavable linker



Seven Key Attributes[a,1–5]
Payload mechanism of action: topoisomerase I inhibitor
High potency of payload
High drug-to-antibody ratio ≈8
Payload with short systemic half-life
Stable linker payload
Tumor-selective cleavable linker
Bystander antitumor effect

[a]The clinical relevance of these features is under investigation.

ADC, antibody–drug conjugate; HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.
1. Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173–185. 2. Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097–5108. 3. Trail PA, et al. *Pharmacol Ther*. 2018;181:126–142. 4. Okamoto H, et al. *Xenobiotica*. 2020;50(10):1242–1250. 5. Nagai Y, et al. *Xenobiotica*. 2019;49(9):1086–1096.

- Advanced solid tumors not eligible for curative therapy
- 2L+ patient population
- HER2 expression (IHC 3+ or 2+)
  - Local test or central test by HercepTest if local test not feasible (ASCO/CAP gastric cancer guidelines[1])[a]
- Prior HER2-targeting therapy allowed
- ECOG/WHO PS 0–1

T-DXd
5.4 mg/kg
q3w

n≈40 per cohort planned

(*Cohorts with no objective responses in the first 15 patients were to be closed*)

- Cervical cancer
- Endometrial cancer
- Ovarian cancer
- Biliary tract cancer
- Pancreatic cancer
- Bladder cancer
- Other tumors[b]

Primary endpoint

- Confirmed ORR (investigator)[c]

Secondary endpoints

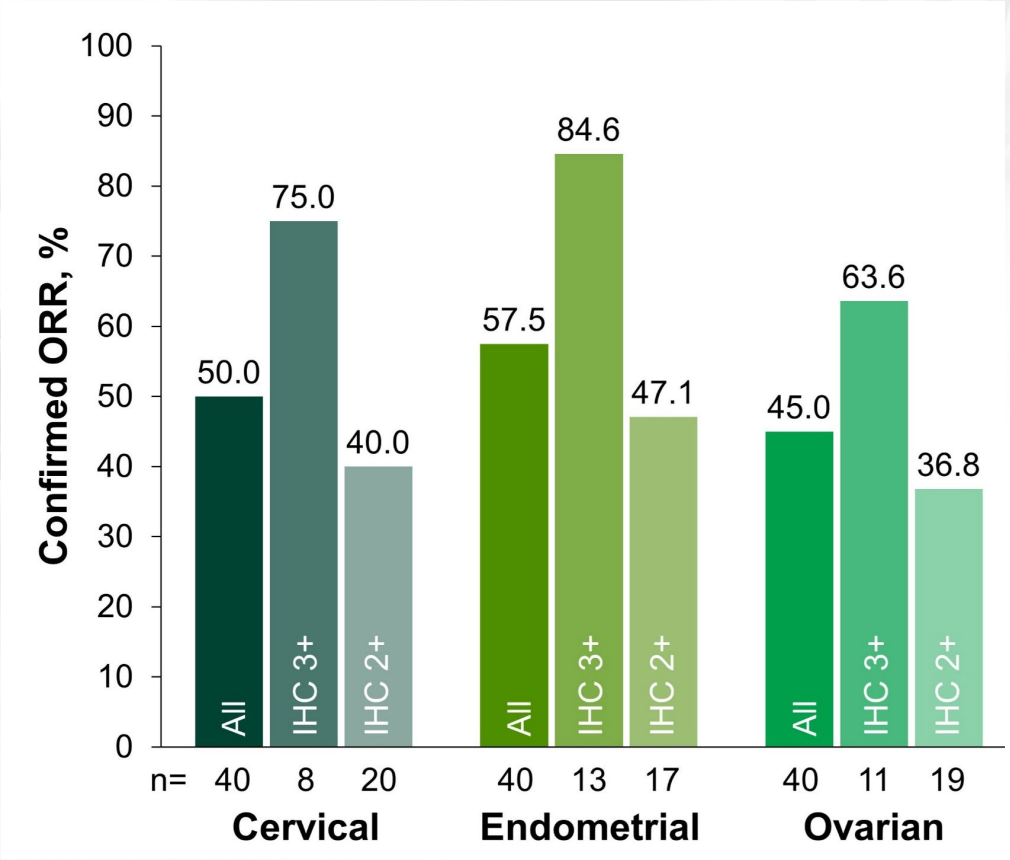
- DOR[c]
- DCR[c]
- PFS[c]
- OS
- Safety

Data cut-off for analysis:

- Nov 16, 2022

Efficacy

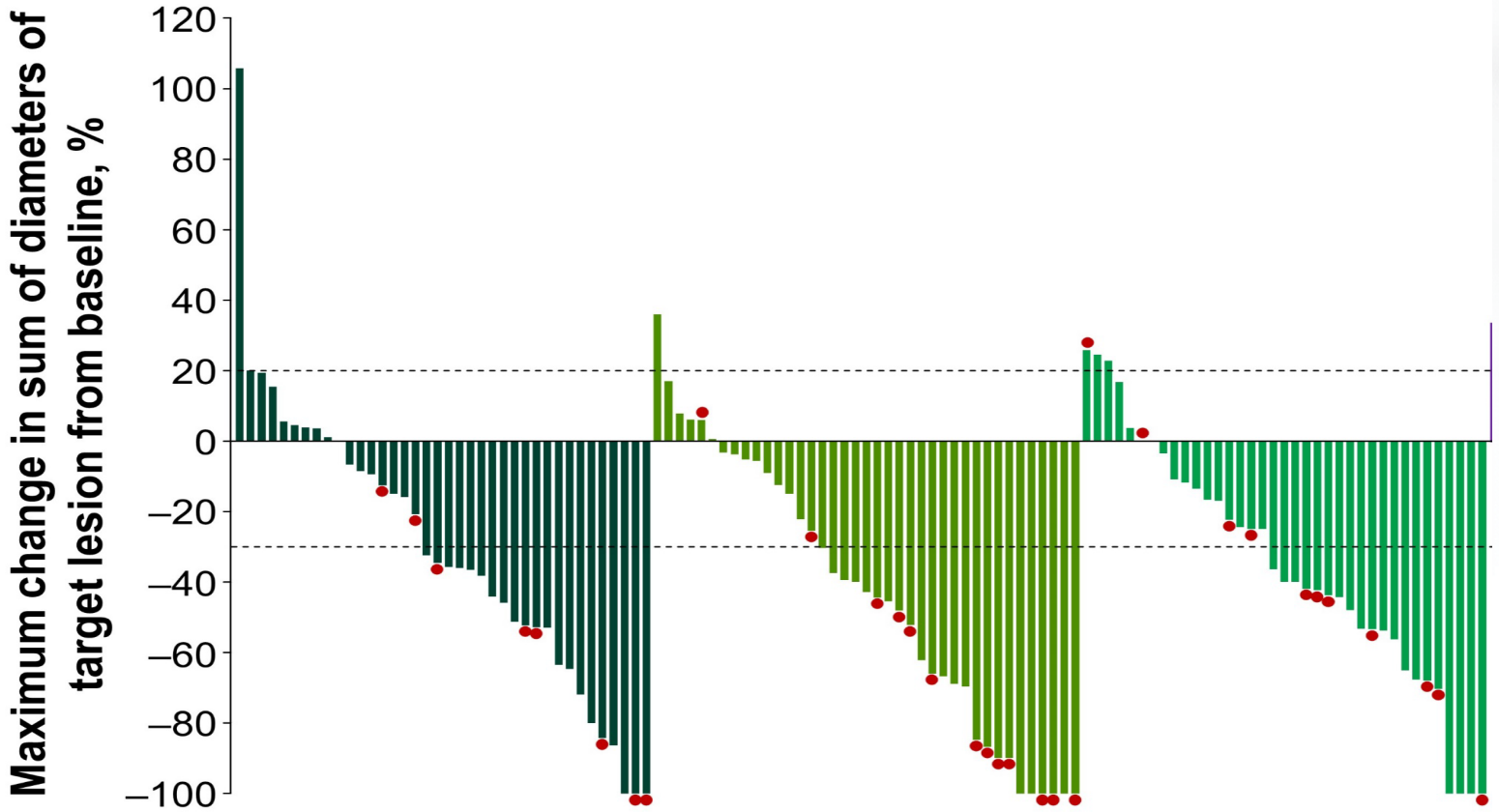
		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)
Investigator assessment				
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)
	PD	7 (17.5)	4 (10.0)	7 (17.5)
	Not evaluable	1 (2.5)	0	1 (2.5)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)



	All patients (N=99)	IHC 3+ (n=46)	IHC 2+ (n=34)
Median DOR, months (95% CI)	11.8 (9.8–NE)	22.1 (9.3–NE)	9.8 (4.2–12.6)

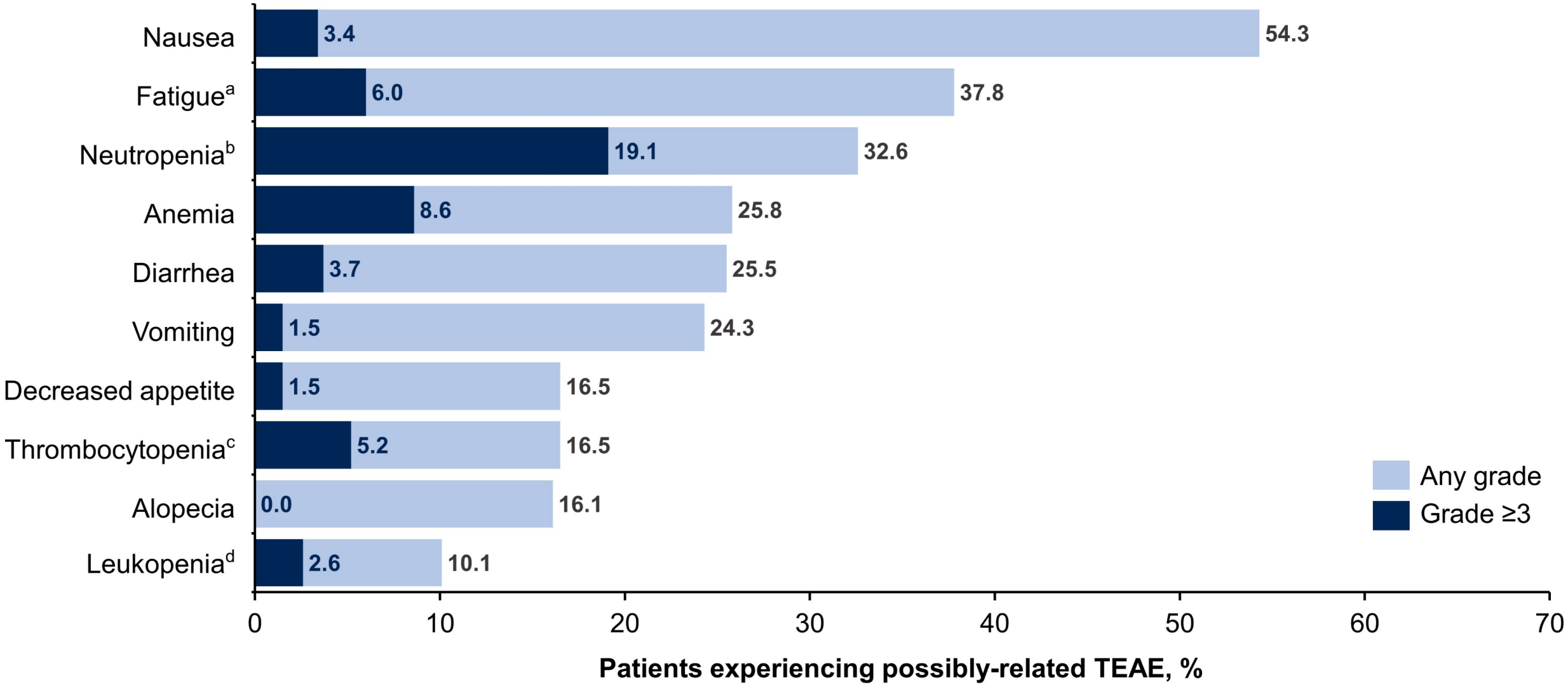
Analysis of ORR was performed in patients who received ≥1 dose of T-DXd; all patients (n=267; including 67 patients with IHC 1+ [n=25], IHC 0 [n=30], or unknown IHC status [n=12] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=75) or IHC 2+ (n=125) status. Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd; all patients (n=99; including 19 patients with IHC 1+ [n=6], IHC 0 [n=9], or unknown IHC status [n=4] by central testing) and patients with centrally confirmed HER2 IHC 3+ (n=46) or IHC 2+ (n=34) status. [a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; CI, confidence interval; DOR, duration of response; IHC, immunohistochemistry; NE, non-estimable; ORR, objective response rate.

TRAZTUZUMAB-DXD: GYN TUMORS



ORR in IHC 3+ n (%)	Cervical (n=8)	Endometrial (n=13)	Ovarian (n=11)
	6 (75.0)	11 (84.6)	7 (63.6)

TOXICITY

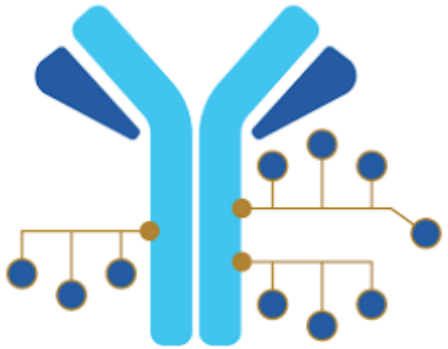


Meric-Berstam, ASCO 2023

UPFITINIMAB

ANTI NAPIB2

Upifitamab rilsodotin (UpRi): investigational first-in-class ADC targeting NaPi2b



UpRi

Antibody[1]: Humanized monoclonal anti-*SLC34A2* (NaPi2b)

Linker[2]: Fleximer polymer scaffold; cleavable ester linker stable in circulation

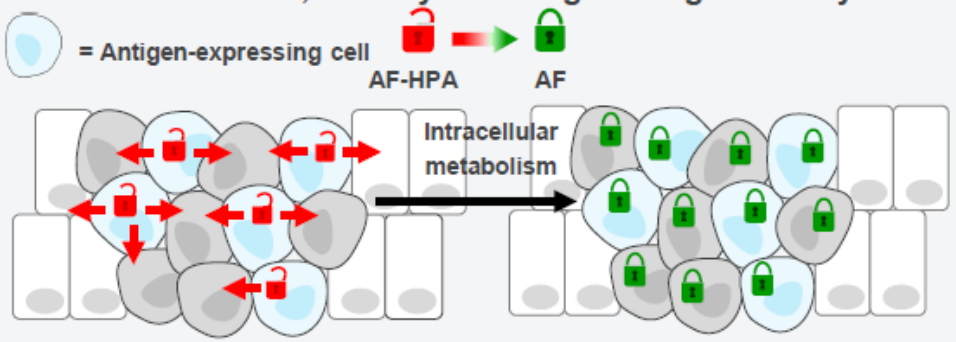
Payload[1]: AF-HPA (*DolaLock-controlled bystander effect*); selectively toxic to rapidly dividing cells

DAR[1]: ~10 while maintaining drug-like properties

NaPi2b is a sodium-dependent phosphate transporter broadly expressed in ovarian cancer with limited expression in healthy tissues[3]

- It is believed that approximately **two-thirds of patients with HGSOC have NaPi2b-positive tumors** based on an IHC tumor proportion score (TPS) of at least 75%[4]
- NaPi2b is a lineage marker; its expression appears to remain consistent throughout the course of disease[1,5]

Controlled bystander effect is designed to lock the payload in tumor cells, limit diffusion, thereby reducing off-target toxicity[3]



Upon UpRi internalization into tumor cells and efficient release of payload, AF-HPA payload is metabolized to AF that remains highly potent but loses the ability to cross the cell membrane, locking it in the tumor, controlling the bystander effect, and consequently limiting impact on adjacent healthy cells[6]

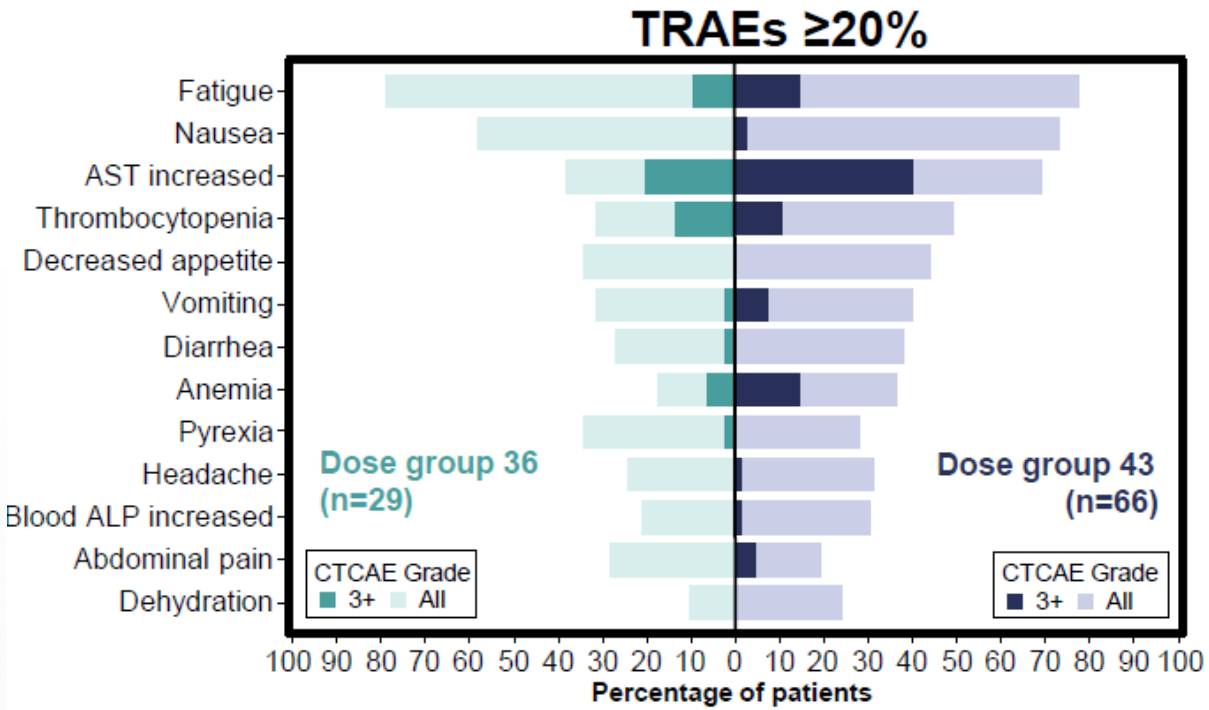
ADC, antibody-drug conjugate; AF-HPA, auristatin F-hydroxypropylamide; DAR, drug-to-antibody ratio; HGSOC, high-grade serous ovarian cancer; IHC, immunohistochemistry; NaPi2b, sodium-dependent phosphate transport protein 2B; *SLC34A2*, solute carrier family 34 member 2 gene.

1. Bodyak ND et al. *Mol Cancer Ther*. 2021;20(5):896–905. 2. Mersana Therapeutics. Accessed Sep 27, 2022. https://www.mersana.com/our-technology-platforms/dolaflexin 3. Yurkovetskiy AV et al. *Mol Cancer Ther*. 2021;20(5):885–895. 4. Drapkin R et al. IGCS Annual Global Meeting 2022; Abstract 408. 5. Richardson DL et al. IGCS Annual Global Meeting 2022; Abstract 425. 6. Lin K et al. *Clin Cancer Res*. 2015;21(22):5139–5150

UpRi is an investigational drug not currently approved for use by any health authority in any indication

Key safety and antitumor activity of UpRi Phase 1b EXP cohort

UpRi (NaPi2b-targeting, AF-HPA controlled bystander effect)



		All dose levels	Dose group 36	Dose group 43
NaPi2b-positive (TPS ≥75%)	N	38	16	22
	ORR, n (%)	**13 (34)**	**7 (44)**	**6 (27)**
	CR, n (%)	2 (5)	2 (13)	0
	PR, n (%)	11 (29)	5 (31)	6 (27)
	DCR, n (%)	33 (87)	12 (75)	21 (95)
All NaPi2b levels	N	75	25	48
	ORR, n (%)	**17 (23)**	**9 (36)**	**8 (17)**
	CR, n (%)	2 (3)	2 (8)	0
	PR, n (%)	15 (20)	7 (28)	8 (17)
	DCR, n (%)	54 (72)	18 (72)	35 (73)

- **No severe (Grade 3+) ocular toxicity, neutropenia, or peripheral neuropathy occurred in either dose group**
- **2 (7%) patients discontinued treatment in dose group 36 vs 8 (12%) in dose group 43**

Data cut: June 10, 2021. Two patients received <30 mg/m² and were therefore not included in either dose group. All responses are confirmed. There were 75 evaluable patients. There were 22 unevaluable patients: 4 in dose group 36, 2 patient withdrawals (1 enrolled in hospice), 2 patient deaths; 18 in dose group 43, 5 patient withdrawals, 1 clinical progression, 3 due to adverse events, 8 deaths, 1 had not reached first scan. Of 4 unevaluable patients in dose group 36, 2 were NaPi2b-positive; of 18 unevaluable patients in dose group 43, 10 were NaPi2b-positive.

AF-HPA, auristatin F-hydroxypropylamide; ALP, alkaline phosphatase; AST, aspartate aminotransferase; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; EXP, expansion; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; PR, partial response; PROC, platinum-resistant ovarian cancer; TPS, tumor proportion score; TRAE, treatment-related adverse event.

Richardson DL et al. SGO Annual Meeting on Women's Cancer 2022; Abstract 76.

UpRi is an investigational drug not currently approved for use by any health authority in any indication.

UpRi Ph Ib – Ovarian Cancer Expansion Cohort

Patient Population: HGSOC[a] progressing after standard treatments; measurable disease per RECIST v1.1; ECOG PS 0 or 1

Ovarian Cancer Cohort[1 – 3]

- 1–3 prior lines in platinum-resistant
- 4 prior lines regardless of platinum status
- High-grade serous histology
- Archived tumor and fresh biopsy (if medically feasible) for NaPi2b
- Exclusion: Primary platinum-refractory disease

UpRi IV Q4W until disease progression or unacceptable toxicity

36 mg/m^2 cohort initiated in August 2019

43 mg/m^2 to a max of ~80 mg cohort initiated in December 2019

Primary Objectives

- Evaluate safety and tolerability of MTD or RP2D
- Assess preliminary efficacy (ORR, DCR)

Secondary Objectives

- Association of tumor NaPi2b expression and objective tumor response using an IHC assay with a broad dynamic range to distinguish tumors with high and low NaPi2b expression
- Further assessment of preliminary anti-neoplastic activity (DoR)

Assessment: Tumor imaging (MRI or CT) at baseline and every 2nd cycle; response assessed per RECIST v1.1

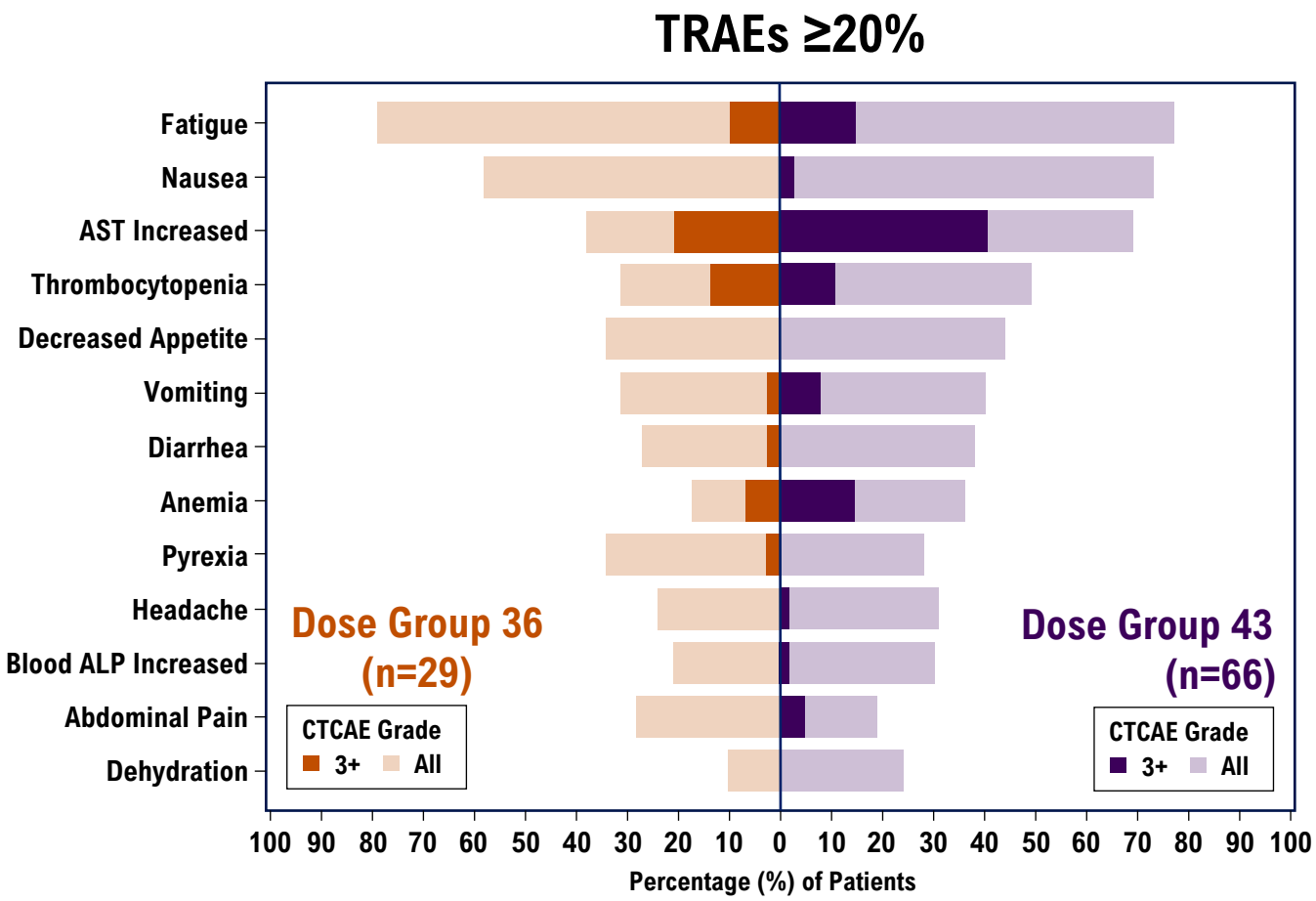
Patients in Dose Group 36 received an actual dose of 33 to 38 mg/m^2 and Dose Group 43 received an actual dose >38 mg/m^2

Best Response by UpRi Dose Group

		All Dose Levels	Dose Group 36	Dose Group 43
NaPi2b-High (TPS ≥75)	N	38	16	22
	ORR, n (%)	**13 (34)**	**7 (44)**	**6 (27)**
	CR, n (%)	2 (5)	2 (13)	0
	PR, n (%)	11 (29)	5 (31)	6 (27)
	DCR, n (%)	33 (87)	12 (75)	21 (95)
All NaPi2b Levels	N	75	25	48
	ORR, n (%)	**17 (23)**	**9 (36)**	**8 (17)**
	CR, n (%)	2 (3)	2 (8)	0
	PR, n (%)	15 (20)	7 (28)	8 (17)
	DCR, n (%)	54 (72)	18 (72)	35 (73)

- **Median DoR in patients (all dose levels) with NaPi2b-high ovarian cancer (n=13): 5 months**
- No obvious difference in median DoR observed between Dose Groups 36 and 43

Treatment-Related AEs by UpRi Dose Group



- No severe ocular toxicity, neutropenia, or peripheral neuropathy in either dose group
- 4 (14%) patients had treatment-related SAEs in Dose Group 36 vs 18 (27%) in Dose Group 43
- Lower frequencies and lower grade pneumonitis occurred in Dose Group 36 (with no Grade 3+) vs Dose Group 43[a]
- 10 (34%) patients had treatment-related dose modifications in Dose Group 36 vs 32 (48%) in Dose Group 43
- 2 (7%) patients in Dose Group 36 and 8 (12%) patients in Dose Group 43 discontinued treatment due to TRAEs

GOG-3049 / ENGOT-OV71-NSGO-CTU
PHASE 3 STUDY OF UPRI MONOTHERAPY MAINTENANCE VS PLACEBO IN RECURRENT PLATINUM-SENSITIVE OVARIAN CANCER

UP-NEXT

Key Enrollment Criteria

- CR, PR, or SD as best response following platinum in recurrent disease
- 2–4 prior lines of platinum (including the immediately preceding platinum)
- NaPi2b-high (TPS ≥75)
- Prior PARPi therapy only required for *BRCA*mut

Randomize 2:1 N=350

- **UpRi** IV Q4W
- **Placebo**

Primary Endpoint

- PFS by BICR

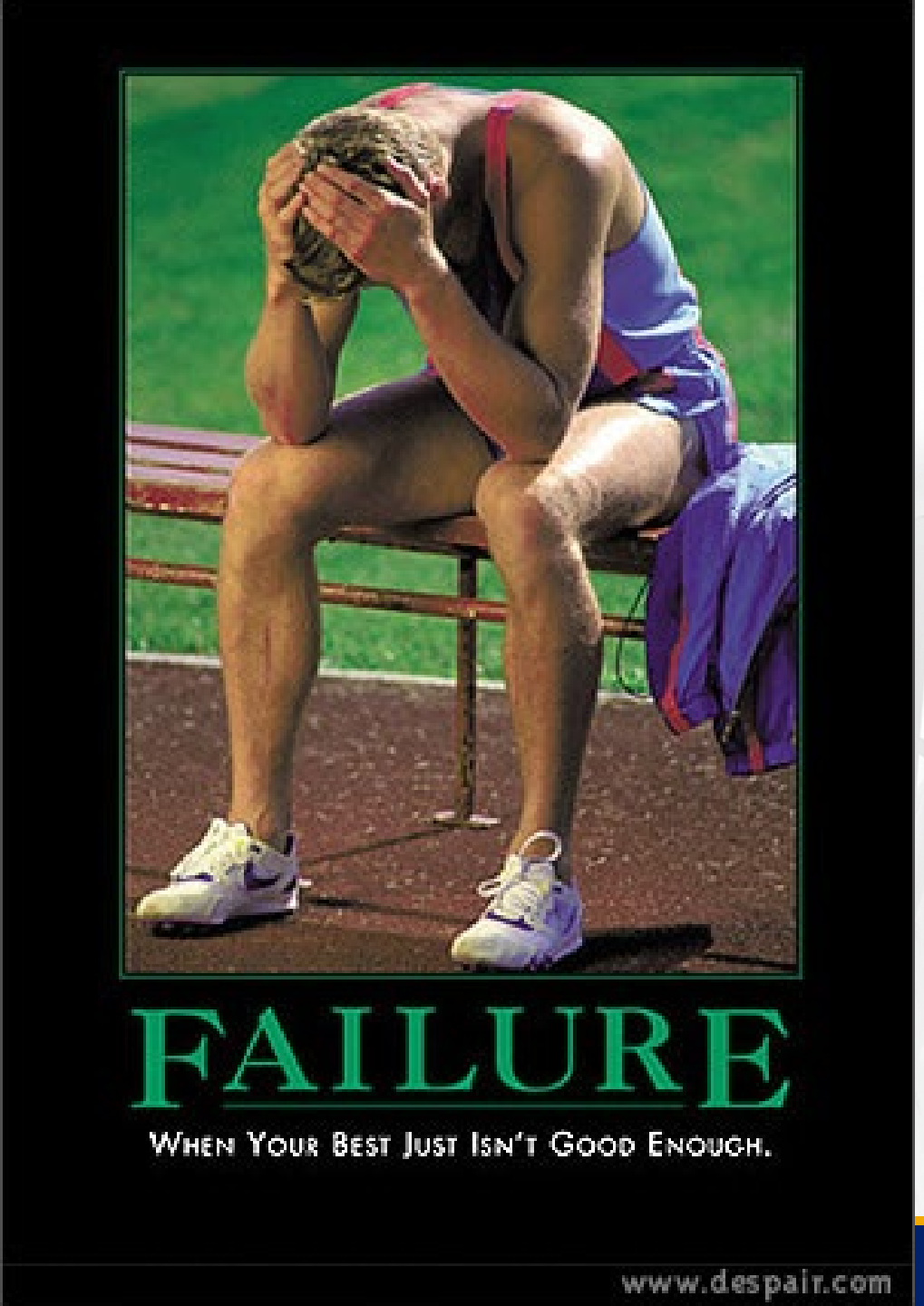
Secondary Endpoints

- PFS by Investigator
- ORR
- OS

On partial clinical hold as 6/15/23

ENGOT European Network of Gynaecological Oncological Trial groups

GOG FOUNDATION Transforming the standard of care

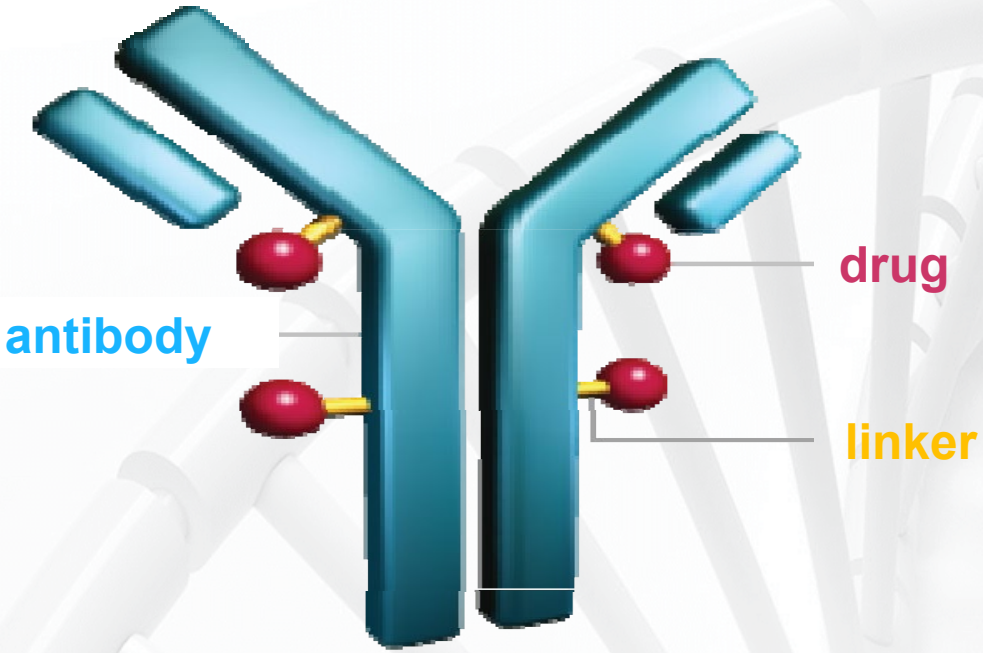


June 15, 2023

U.S. Food and Drug Administration (FDA) has issued a partial clinical hold pausing new patient enrollment in UP-NEXT and UPGRADE-A following a submission of a recent assessment of aggregate treatment-emergent hemorrhage safety data from all UpRi trials, comprised of approximately 560 patients dosed with UpRi to date. This assessment suggested a potential risk of serious bleeding. Although available data are limited, the incidence of bleeding appears to be higher than the general background rate in patients with ovarian cancer. While most bleeding cases in this aggregate safety analysis were low grade, five (<1%) Grade 5 (fatal) bleeding events were observed. The cause of these events remains under investigation.

QUESTIONS?

ADC'S HIGHLY ENGINEERED COMPONENTS



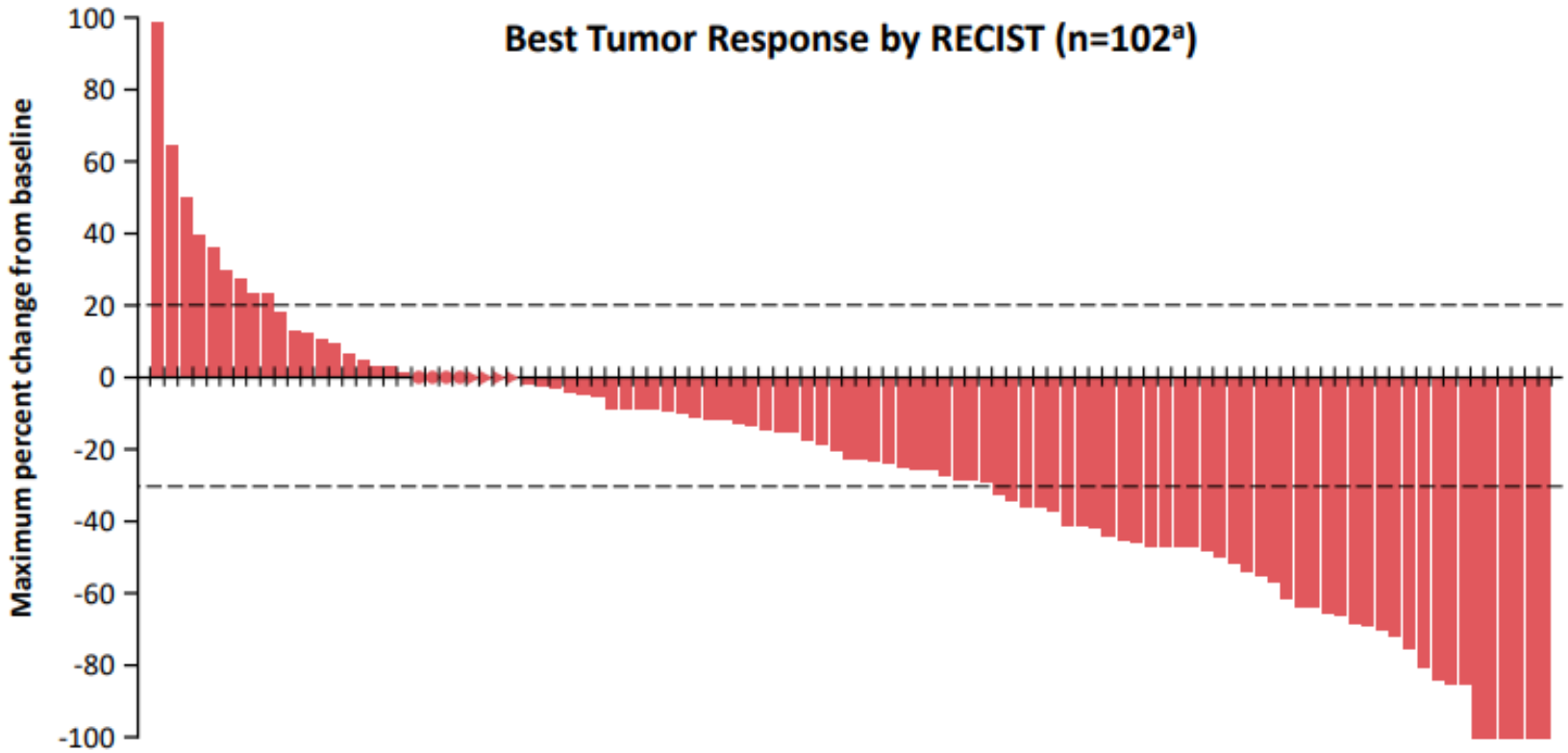
1. Antibody | 2. Linker | 3. Drug

1. A highly selective monoclonal antibody for a tumor-associated antigen with restricted expression on normal cells
2. A potent cytotoxic agent designed to induce target cell death when internalized in the cell and released

3. A linker that is stable in circulation, but releases the cytotoxic agent in target cells (controlled by altering stability & degree of hindrance around disulfide bond)

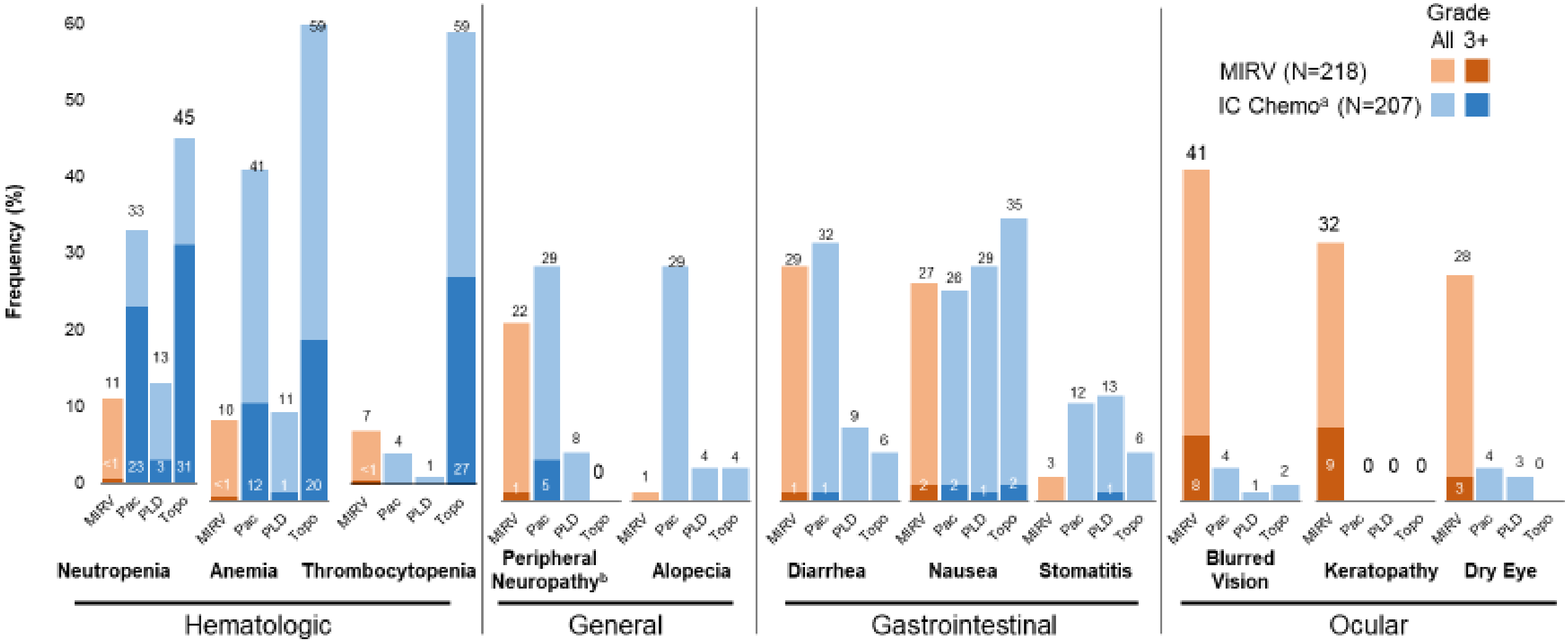
Best Tumor Response

- 71% of patients experienced tumor reduction
- 51% of patients had disease control (defined as CR, PR, or SD for ≥12 weeks)



Data cutoff: April 29, 2022
CR, complete response; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.
[a]Three patients had no postbaseline tumor assessment.

Differentiated Safety Profile: Treatment-Emergent Adverse Events



Data cutoff: March 6, 2023

MIRV, mirvetuximab soravtansine; IC Chemo: investigator's choice chemotherapy; Pac, paclitaxel; PLD, pegylated liposomal doxorubicin; Topo, topotecan.

[a]Pac n=82 (39%), PLD n=76 (37%), Topo n=49 (24%). [b]Grade 2+ peripheral neuropathy events were observed in 12% and 16% of patients that received MIRV or paclitaxel, respectively.

PRESENTED BY: Kathleen Moore, Associate Director of Clinical Research, Stephenson Cancer Center University of Oklahoma College of Medicine

PICCOLO

SINGLE-ARM TRIAL FOR MIRVETUXIMAB IN HIGH FRα PATIENTS WITH PLATINUM-SENSITIVE OVARIAN CANCER

Enrollment completed

Global Trial Top Line Results 2024

PRIMARY ENDPOINT

ORR by Investigator

SECONDARY ENDPOINT

DOR by Investigator

ENROLLMENT AND KEY ELIGIBILITY

75 patients
Platinum-sensitive ovarian cancer
2+ prior systemic treatments
At least 2 prior platinum-containing regimens
Prior PARPi required if BRCA+
Appropriate for single-agent therapy

ORR: overall response rate; DOR: duration of response; BRCA: BReast CAncer gene

GLORIOSA

RANDOMIZED PHASE 3 TRIAL FOR MIRVETUXIMAB + BEVACIZUMAB MAINTENANCE IN FRα-HIGH PSOC PATIENTS

TARGET TIMELINES

- Open for Accrual
- Global trial
- POTENTIAL APPROVAL 2026

PRIMARY ENDPOINT

PFS

SECONDARY ENDPOINT

OS by BICR

ENROLLMENT AND KEY ELIGIBILITY

438 patients
Platinum-sensitive ovarian cancer
1 prior systemic treatment
Prior PARPi required if BRCA+
CR, PR, or SD after treatment with platinum-based doublet + bevacizumab required

PRIOR MIRV EXPERIENCE

Strong MIRV/BEV treatment efficacy and tolerability in > 120 patients
FRα high rPSOC, MIRV/BEV has an ORR of 69% and mPFS of 13.3 months

PFS (progression-free survival); BICR (blinded independent central review); OS (overall survival); CR (complete response); PR (partial response); SD (stable disease); BRCA (BReast CAncer gene); MIRV (mirvetuximab soravtansine); ORR (objective response rate); mPFS (median PFS); ORR (overall response rate

Safety

Most Common TEAEs (>25%)

n (%)	4.3 mg/kg (n=23)		5.2 mg/kg (n=21)		Total (N=44)	
	Any Grade	G3+	Any Grade	G3+	Any Grade	G3+
Patients reporting ≥1 event	23 (100)	18 (78.3)	21 (100)	20 (95.2)	44 (100)	38 (86.4)
Hematological						
Neutropenia*	17 (73.9)	15 (65.2)	18 (85.7)	16 (76.2)	35 (79.5)	31 (70.5)
Febrile neutropenia	1 (4.3)	1 (4.3)	1 (4.8)	1 (4.8)	2 (4.5)	2 (4.5)
Platelet count decreased	11 (47.8)	1 (4.3)	10 (47.6)	2 (9.5)	21 (47.7)	3 (6.8)
Anemia	8 (34.8)	1 (4.3)	12 (57.1)	5 (23.8)	20 (45.5)	6 (13.6)
WBC count decreased	11 (47.8)	6 (26.1)	4 (19)	4 (19)	15 (34.1)	10 (22.7)
Non-hematological						
Nausea	17 (73.9)	0	16 (76.2)	0	33 (75)	0
Fatigue	16 (69.6)	3 (13)	11 (52.4)	1 (4.8)	27 (61.4)	4 (9.1)
Arthralgia	14 (60.9)	6 (26.1)	12 (57.1)	2 (9.5)	26 (59.1)	8 (18.2)
Constipation	9 (39.1)	0	13 (61.9)	1 (4.8)	22 (50)	1 (2.3)
Neuropathy†	11 (47.8)	1 (4.3)	8 (38.1)	0	19 (43.2)	1 (2.3)
Abdominal pain	8 (34.8)	0	10 (47.6)	0	18 (40.9)	0
Decreased appetite	8 (34.8)	0	10 (47.6)	0	18 (40.9)	0
Diarrhea	8 (34.8)	2 (8.7)	7 (33.3)	1 (4.8)	15 (34.1)	3 (6.8)
Vomiting	7 (30.4)	0	8 (38.1)	2 (9.5)	15 (34.1)	2 (4.5)
Pyrexia	8 (34.8)	0	7 (33.3)	1 (4.8)	15 (34.1)	1 (2.3)
AST increased	8 (34.8)	0	7 (33.3)	0	15 (34.1)	0
ALT increased	8 (34.8)	0	6 (28.6)	0	14 (31.8)	0
Myalgia	6 (26.1)	0	7 (33.3)	0	13 (29.5)	0
Headache	9 (39.1)	0	3 (14.3)	0	12 (27.3)	0

Best Response by UpRi Dose Group