Antibody-Drug Conjugates (ADCs) and Ongoing Clinical Trials

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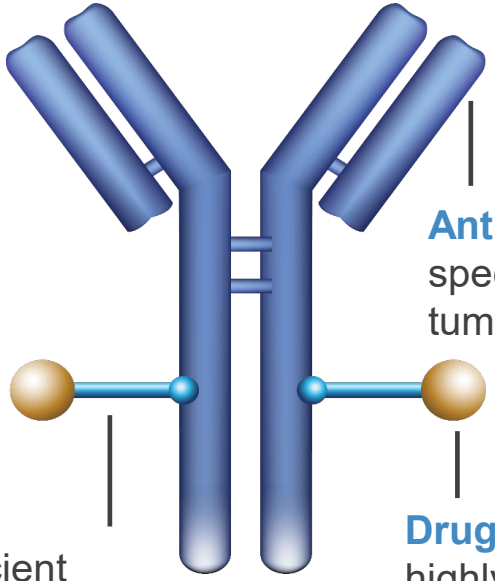
Anatomy of an antibody-drug conjugate (ADC)



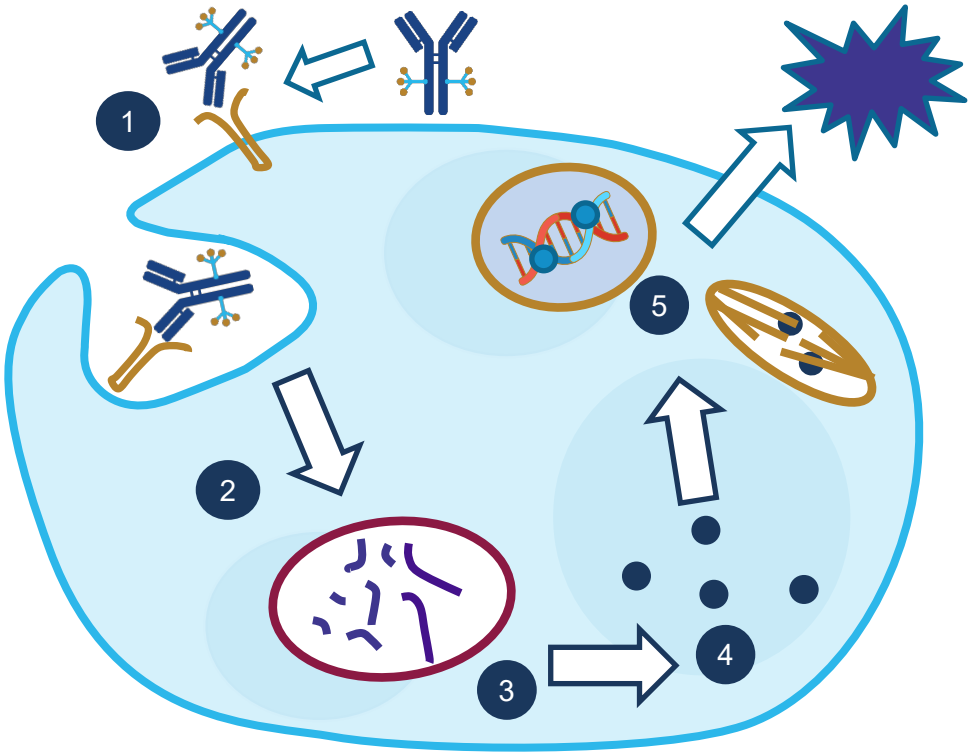
Antibody: specific to a tumor antigen

Drug payload: highly potent antitumor agent

Linker: efficient release of payload at tumor site; stable in circulation

Panowski S et al. *MAbs*. 2014;6(1):34–45.

Mechanism of action of ADCs[1,2]



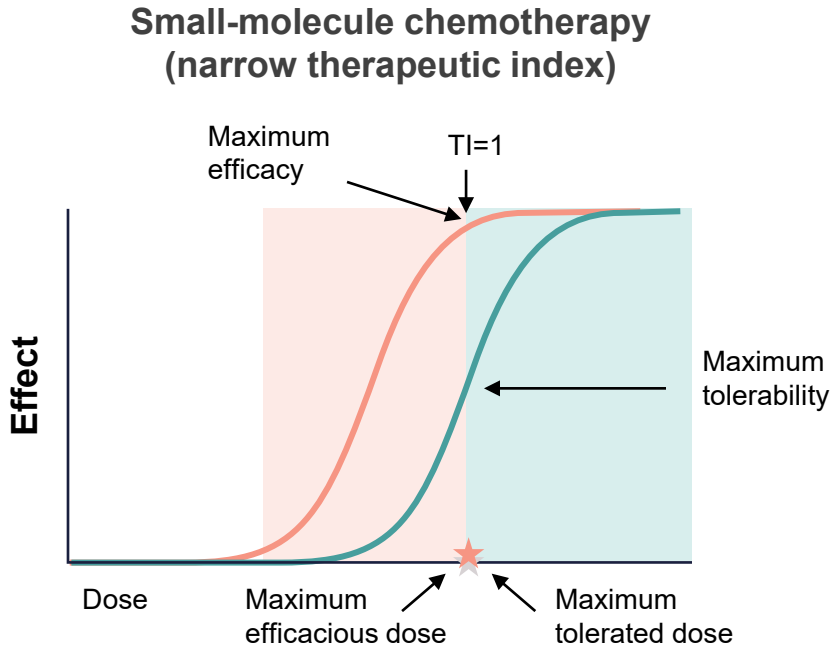
Mechanism of action

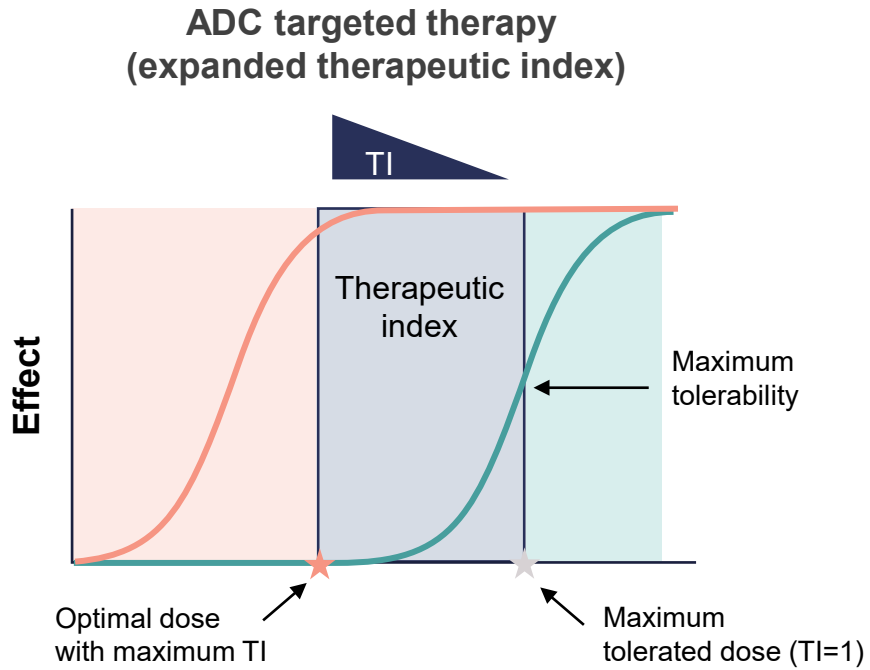
1. Antibody binds to the target antigen at the surface of the cancer cell
2. ADC–antigen complex is internalized and trafficked through the endolysosomal compartment
3. Payload is released in the lysosome
4. Drug payload enters the cytoplasm
5. Drug payload acts on microtubules or DNA, resulting in cell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

The goal: optimizing therapeutic index[a] through targeting and design[1,2]



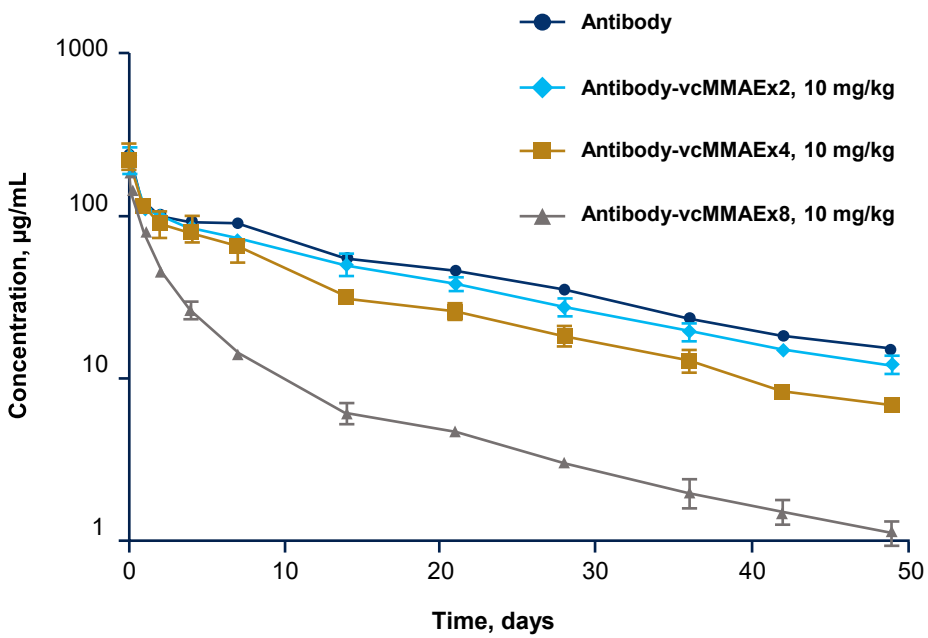


[a] Therapeutic index is the ratio between the toxic dose and the dose at which the drug becomes effective.[2]

ADC, antibody-drug conjugate; TI, therapeutic index.

1. Adapted from Tarcsa E et al. *Drug Discov Today Technol*. 2020;37:13–22. 2. Coats S et al. *Clin Cancer Res*. 2019;25(18):5441–5448.

Drug-to-antibody ratio (DAR)



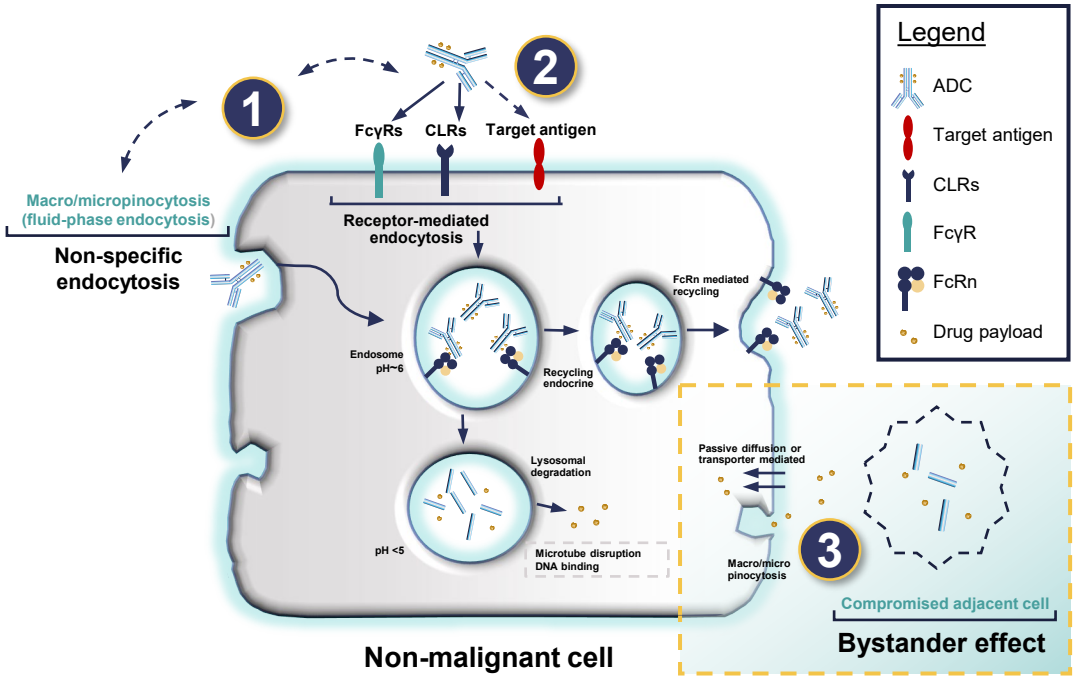
- DAR is **the average number of drugs conjugated to the antibody**[1]
- The DAR affects the efficacy of the drug: low drug loading reduces the potency while high drug loading can negatively affect pharmacokinetics and toxicity[1,2]
- Most ADC platforms are **limited to a DAR of 3–4** in order to maintain suitable drug-like properties[3]

Traditional ADCs with a DAR >3–4 see a decline in the drug's physiochemical properties[4]

ADC, antibody-drug conjugate; vcMMAE, valine-citrulline monomethyl auristatin E.

1. Wakankar A et al. *MAbs*. 2011;3(2):161–172. 2. Perez HL et al. *Drug Discov Today*. 2014;19(7):869–881. 3. Yurkovetskiy AV et al. *Mol Cancer Ther*. 2021;20(5):885–895. 4. Hamblett KJ et al. *Clin Cancer Res*. 2004;10(20):7063–7070.

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

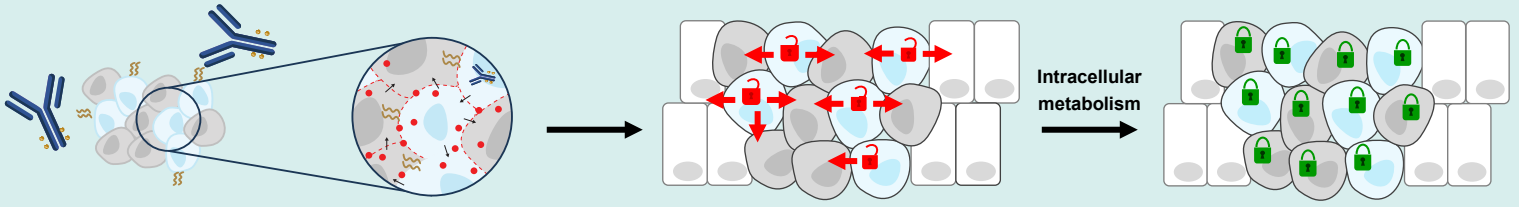
ADC, antibody-drug conjugate; CLR, C-type leptin receptor; DM1, maytansinoid DM1; DM4, maytansinoid DM4; FcRn, neonatal FC receptor; FcγR, Fc gamma receptor; MMAE, monomethyl auristatin E; MMAF, monomethyl auristatin F.

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

Opportunities for innovation through ADC design

- Improvements in ADC design are aimed at enhancing its activity in cancer cells and limiting toxicity to healthy cells[1]
- Heterogeneity and/or low target expression throughout the tumor can be addressed by **increasing the DAR**[1,2]
- Off-target toxicity can be mediated by **controlling the bystander effect**[2]

The bystander effect can be controlled by utilizing intratumoral metabolism to limit diffusion to adjacent cells[3]



ADC binds to tumor antigen, is internalized, and releases payload

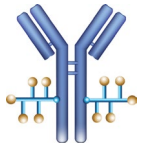
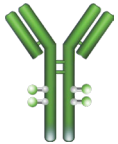
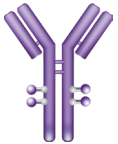
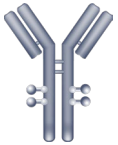
Initially released payload is capable of crossing cell membranes

Once metabolized within the tumor, the payload is incapable of crossing cell membranes

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio.

1. Yurkovetskiy AV et al. *Mol Cancer Ther*. 2021;20(5):885–895. 2. Drago JZ et al. *Nat Rev Clin Oncol*. 2021;18(6):327–344.

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 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: safety and antitumor activity of mirvetuximab soravtansine in patients with FRα-high PROC

TRAE, n (%)	All grades	Grade 3	Grade 4
Patients with any event	91 (86)	30 (29)	1 (1)
Blurred vision	43 (41)	**6 (6)**	0
Keratopathy	31 (29)	**8 (8)**	1 (1)
Nausea	31 (29)	0	0
Dry eye	26 (25)	2 (2)	0
Fatigue	25 (24)	1 (1)	0
Diarrhea	23 (22)	**2 (2)**	0
Neutropenia	14 (13)	**2 (2)**	0
Peripheral neuropathy	14 (13)	0	0

- **9% discontinuation due to TRAEs**
- **Blurred vision (6%), keratopathy (8%), neutropenia (2%), and diarrhea (2%) were the most common Grade 3 AEs**

Endpoint	Investigator-assessed (n=105)	BICR-assessed (n=96)
Response rates[a]		
ORR, n (%)[b]	34 (32.4)	29 (30.2)
95% CI[c]	[23.6, 42.2]	[21.3, 40.4]
Best overall response, n (%)		
Complete response	5 (4.8)	6 (6.3)
Partial response	29 (27.6)	23 (24.0)
Stable disease[d]	48 (45.7)	54 (56.3)
Progressive disease	20 (19.0)	9 (9.4)
Not evaluable	3 (2.9)	4 (4.2)
Duration of response[a]		
mDOR,[e] months	6.9	NR
95% CI	[5.6, 9.7]	[5.0, NR]
mPFS, months	4.3[f]	5.5[g]
95% CI	[3.7, 5.2]	[3.8, 6.9]

Data cutoff: April 29, 2022.

[a] Based on RECIST v1.1. [b] ORR is defined as proportion of patients with confirmed CR or PR. Patients without at least 1 postbaseline RECIST assessment were treated as not evaluable. [c] Clopper-Pearson exact CI. [d] Minimum duration of 35 days from date of first dose of mirvetuximab soravtansine. [e] Kaplan-Meier estimate. DOR was defined as time from date of first response (CR or PR) to date of PD or death from any cause, whichever occurred first. DOR was only defined for patients with a confirmed best overall response (BOR) of CR or PR only. [f] Investigator efficacy evaluable population. [g] BICR efficacy evaluable population.

AE, adverse event; BICR, blinded independent central review; CI, confidence interval; CR, complete response; DOR, duration of response; FRα, folate receptor alpha; mDOR, median duration of response; mPFS, median progression-free survival; NR, not reached; ORR, overall response rate; PD, progressive disease; PR, partial response; PROC, platinum-resistant ovarian cancer; RECIST, Response Evaluation Criteria in Solid Tumors; TRAE, treatment-related adverse event.

Matulonis UA et al. ASCO Annual Meeting 2022; Abstract 5512.

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

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

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

MIRASOL

Key inclusion criteria:

- Platinum-resistant ovarian cancer[b]
- 1-3 prior lines of therapy
- Prior bevacizumab and PARPi allowed
- Patients with *BRCA* mutations allowed
- FRα-high by PS2+ scoring (≥75% PS2+)[c]
- At least 1 lesion measurable disease by RECIST v1.1

N=430
R 1:1

Stratified by:

- Investigator's choice chemotherapy
- Prior therapy (1 vs 2 vs 3)

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

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

Secondary
- ORR, OS, PRO (ERORTC-OCV28)

[a] High-grade epithelial ovarian, primary peritoneal, or fallopian tube cancers. [b] Patients with platinum-resistant ovarian cancer were defined as patients with platinum-free interval ≤ 6 months; patients with first platinum-refractory disease (platinum-free interval < 3 months) were excluded. [c] Tumor (archival or biopsy) must be positive for FRα expression as defined by the Ventana FOLR1 (FOLR-2.1) CDx assay.

BRCA, breast and ovarian cancer susceptibility gene; FRα, folate receptor alpha; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PRO, patient reported outcomes; PS2+, sum of staining of 2+ and 3+ intensity; q3w, every 3 weeks; q4w, every 4 weeks; R, randomized.

1. Moore KN, et al. SGO Annual Meeting on Women's Cancer 2022; Abstract 296. 2. Immunogen, Inc. Press Release. ImmunoGen Submits Biologics License Application to the US Food and Drug Administration for Mirvetuximab Soravtansine in Ovarian Cancer. March 29, 2022. 3. ClinicalTrials.gov. NCT04209855. Accessed September 27, 2022.

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

GLORIOSA: phase 3 mirvetuximab soravtansine + bevacizumab maintenance in 2L platinum-sensitive ovarian cancer

GLORIOSA

Key inclusion criteria

- Platinum-sensitive HGSOC
- 2 prior lines of therapy
  - Patients must be appropriate for, currently be on, or have completed platinum-based triplet therapy in 2L
- Bevacizumab in most recent platinum-based regimen required
- Best response to last line of treatment: CR, PR, or SD
- FRα-high by Ventana FOLR1 assay (PS2+)
- Prior PARPi required if *BRCA*m
- ECOG PS 0–1

CR
PR
SD

N=418
R 1:1

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

Bevacizumab 15 mg/kg q3w

Bevacizumab 15 mg/kg q3w

Endpoints

Primary
- PFS by investigator

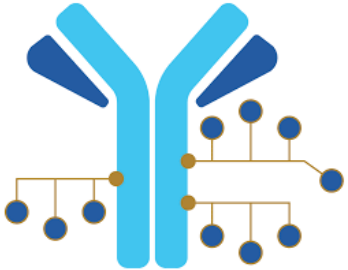
Secondary
- OS, ORR, DOR, CA-125 response
- Safety and tolerability

2L, second line; BRCA, breast and ovarian cancer susceptibility protein; CR, complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FOLR1, folate receptor 1; FRα, folate receptor alpha; HGSOC, high-grade serous ovarian cancer; ORR, objective response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PFS, progression-free survival; PLD, pegylated liposomal doxorubicin; PR, partial response; PS2+, sum of staining of 2+ and 3+ intensity; q3w, every 3 weeks; R, randomized; SD, stable disease.

ClinicalTrials.gov. NCT05445778. Accessed Sep 27, 2022.

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

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

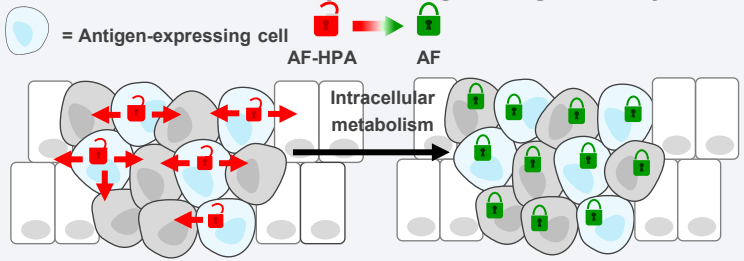
Payload[1]: AF-HPA (*DolaLock-controlled bystander effect*); selectively toxic to rapidly dividing cells

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.

UpRi Phase 1b study: ovarian cancer expansion cohort study design

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

Key inclusion criteria:

- 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 endpoints

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

Secondary endpoints

- 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 antineoplastic activity (DOR)

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

[a] HGSOC, including fallopian tube and primary peritoneal cancer.

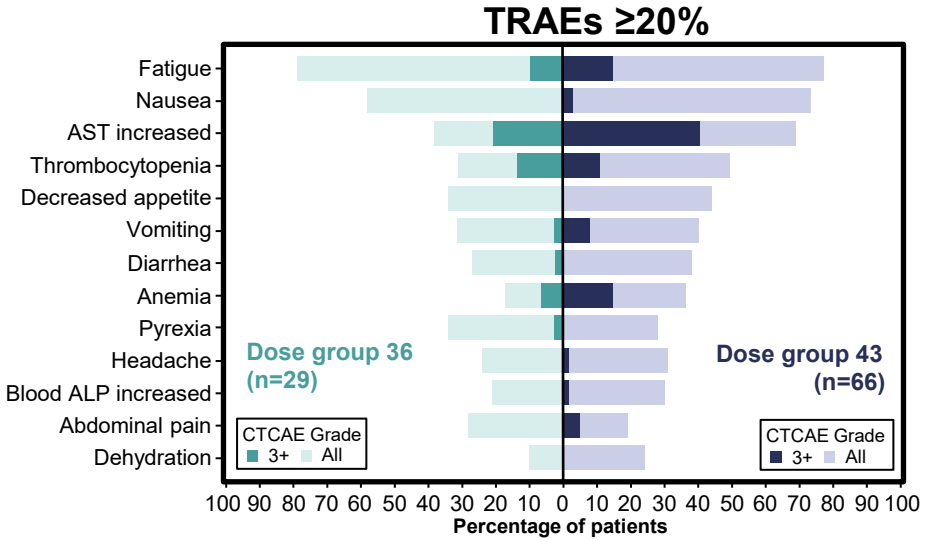
CT, computed tomography; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HGSOC, high-grade serous ovarian cancer; IHC, immunohistochemistry; IV, intravenous; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase 2 dose; UpRi, upifitamab rilsodotin.

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.

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.

UPLIFT (ENGOT-ov67/GOG-3048): phase 2 UpRi single-arm registrational trial in platinum-resistant ovarian cancer[1,2]

UPLIFT

Key inclusion criteria:

- Platinum-resistant[a] HGSOC[b]
- 1–4 prior lines of therapy
- Prior bevacizumab required if patient received only 1–2 prior lines of therapy
- ECOG PS 0–1
- Available archived or fresh tissue for retrospective NaPi2b evaluation
- Grade ≤2 peripheral neuropathy
- Measurable disease per RECIST v1.1

Key exclusion criteria:

- 1–2 prior lines AND bevacizumab-naive
- Primary platinum-refractory disease

UpRi 36 mg/m^2 up to max 80 mg; IV q4w

36 mg/m^2 dose selected based on favorable safety profile and similar efficacy as Dose Group 43 seen in the Phase 1b study

Primary endpoint

- Investigator-assessed confirmed ORR in NaPi2b-positive

Secondary endpoints

- Investigator-assessed confirmed ORR in overall population
- DOR
- Safety

Prospectively defined retrospective analysis to validate NaPi2b biomarker cutoff

[a] Platinum-resistant is defined as disease that has progressed within 6 months of the last dose of platinum. [b] HGSOC, including fallopian tube and primary peritoneal cancer.

DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; HGSOC, high-grade serous ovarian cancer; IV, intravenous; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate; q4w, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab rilsodotin.

1. Richardson DL et al. SGO Annual Meeting on Women's Cancer 2022; Abstract 76. 2. ClinicalTrials.gov. NCT03319628. Accessed Sep 27, 2022.

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

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UP-NEXT (GOG-3049/ENGOT-ov71-NSGO-CTU): phase 3 study of UpRi monotherapy maintenance in recurrent PSOC[1,2]

UP-NEXT

Key enrollment criteria

- Platinum-sensitive recurrent HGSOC[a]
- 2–4 prior platinum-containing chemotherapy regimens[b]
- Best response to last line of treatment: NED, CR, PR, or SD[c]
- ECOG PS 0–1
- NaPi2b-positive (TPS ≥75%) tumor (archival or fresh biopsy)
- Prior PARPi required for patients with known deleterious *BRCA* mutations
- Patients who received bevacizumab in combination with their last platinum-containing regimen are excluded

NED
CR
PR
SD

N=350
R 2:1

Study open to enrollment

UpRi 30 mg/m² (capped at BSA 2.2 m²) IV q4w

All patients continue until PD or unacceptable AE, or up to 18 months

Placebo q4w

Endpoints

Primary
- PFS by BICR

Secondary
- PFS by investigator, ORR, OS

[a] Carboplatin or cisplatin ± paclitaxel, docetaxel, pegylated liposomal doxorubicin, or gemcitabine. [b] HGSOC, including fallopian tube and primary peritoneal cancer. [c] For SD, no increase in disease confirmed by central review of imaging and absence of CA-125 rise >15% in 7 days prior to first dose.

AE, adverse event; BICR, blinded independent central review; *BRCA*, BRCA DNA repair associated gene; BSA, body surface area; CA-125, cancer antigen 125; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HGSOC, high-grade serous ovarian cancer; IV, intravenous; NaPi2b, sodium-dependent phosphate transport protein 2B; NED, no evidence of disease; ORR, overall response rate; OS, overall survival; PARPi, poly (ADP-ribose) polymerase inhibitor; PD, progressive disease; PFS, progression-free survival; PR, partial response; PSOC, platinum-sensitive ovarian cancer; q4w, every 4 weeks; R, randomized; SD, stable disease; TPS, tumor proportion score; UpRi, upifitamab rilsodotin.

1. Richardson DL et al. IGCS Annual Global Meeting 2022; Abstract 453. 2. ClinicalTrials.gov. NCT05329545. Accessed September 27, 2022.

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Summary

- ADCs consist of three components: (1) the antibody, (2) the drug payload, and (3) the linker to join the two[1,2]
- ADCs are designed to ideally enhance antitumor activity and minimize off-target side effects by selectively delivering a high drug payload to tumor cells[3]
- Innovative ADC design incorporates features such as the controlled bystander effect which limits diffusion and reduces off-target toxicity by locking the payload in tumor cells[4]
- Antibody polymer scaffolds allow for high DAR resulting in each ADC molecule delivering more payload to the cancer cell, which may lead to improved activity without compromising physiochemical properties[3]
- Upifitamab rilsodotin and mirvetuximab soravtansine have shown robust clinical activity in initial and ongoing clinical trials in platinum-resistant ovarian cancer[5,6]
- ADCs are a promising strategy for patients who progress on PARP inhibitors, and these agents are under investigation in platinum-sensitive ovarian cancer[7,8]

ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio, PARP, poly (ADP-ribose) polymerase.

1. Beck A et al. *Nat Rev Drug Discov*. 2017;16(5):315–337. 2. Lambert JM et al. *Adv Ther*. 2017;34(5):1015–1035. 3. Yurkovetskiy AV et al. *Mol Cancer Ther*. 2021;20(5):885–895. 4. Lin K et al. *Clin Cancer Res*. 2015;21(22):5139–5150. 5. Richardson DL et al. SGO Annual Meeting on Women's Cancer 2022; Abstract 76. 6. Matulonis UA et al. ASCO Annual Meeting 2022; Abstract 5512. 7. ClinicalTrials.gov. NCT05329545. Accessed Sep 27, 2022. 8. ClinicalTrials.gov. NCT05445778. Accessed Sep 27, 2022

UpRi and mirvetuximab soravtansine are investigational drugs not currently approved for use by any health authority in any indication.