Antibody Drug Conjugates: Future Directions

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Disclosures

- **Consulting or Advisory Role**
- Agenus
- AstraZeneca
- Bristol-Myers Squibb
- Clovis Oncology
- OncoMed
- Eisai
- GlaxoSmithKline/Tesaro
- GOG Partner
- Merck Sharp & Dohme
- Seattle Genetics
- Sutro Biopharma

- **DSMB**
- Genelux (GOG 3076/OnPrime)
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- GOG for Intuitive (GOG 3043/ROCC)

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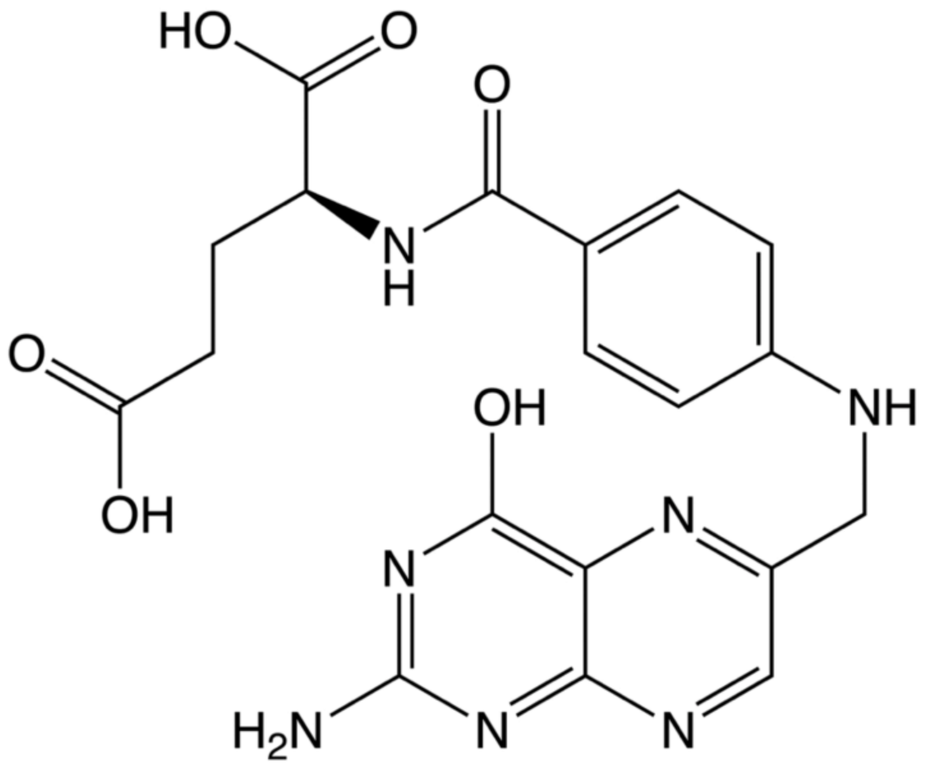
- Gynecologic Oncology Group
- Mersana
- GlaxoSmithKline/Tesaro

Targeting Drug Therapy

Folate

- **Transfers 1-carbon chemical units from donor to acceptor molecules**
- **Critical to synthesis of nucleotide precursors of DNA**

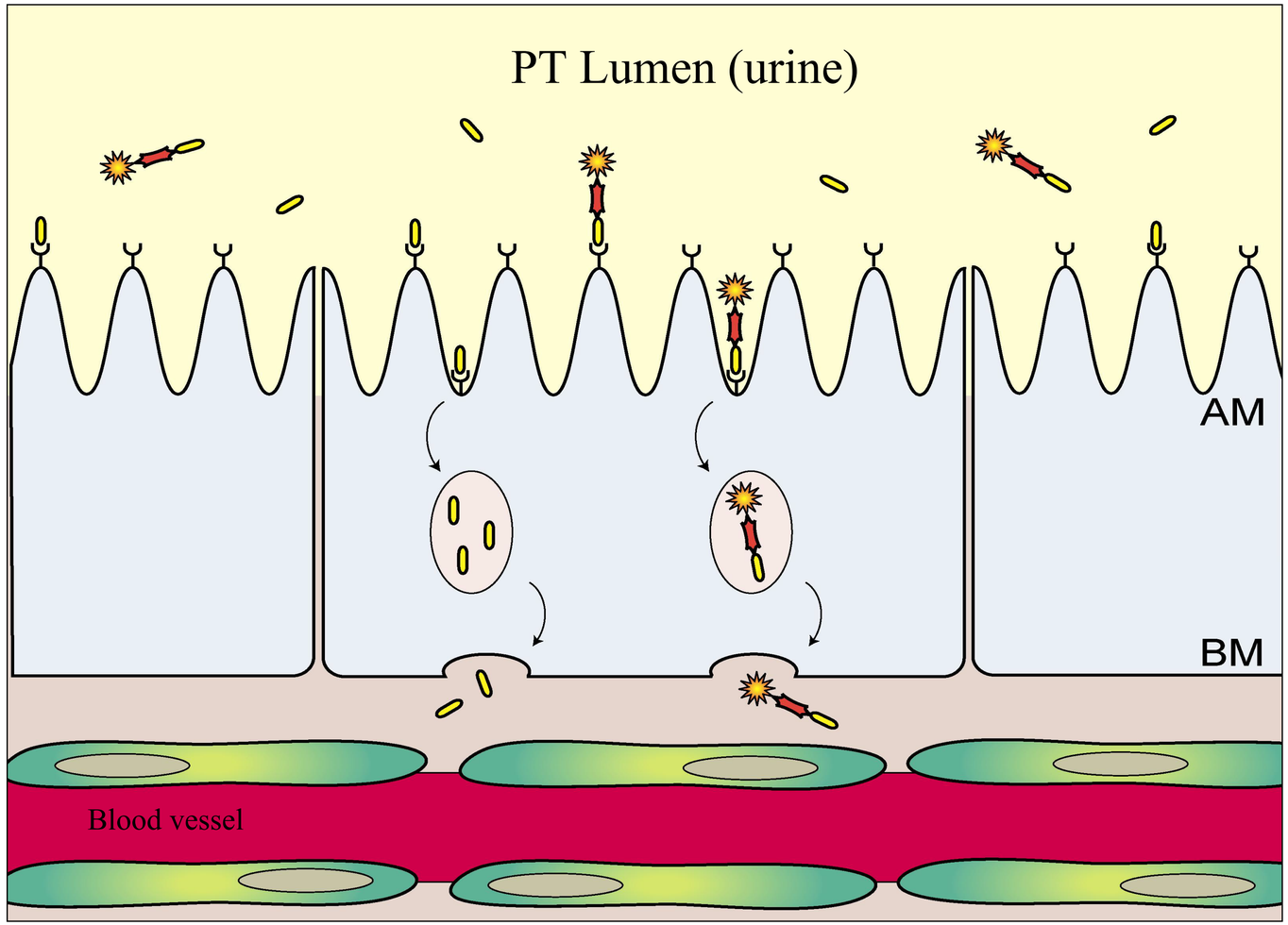


Folic Acid

The Folate Receptor (FR)

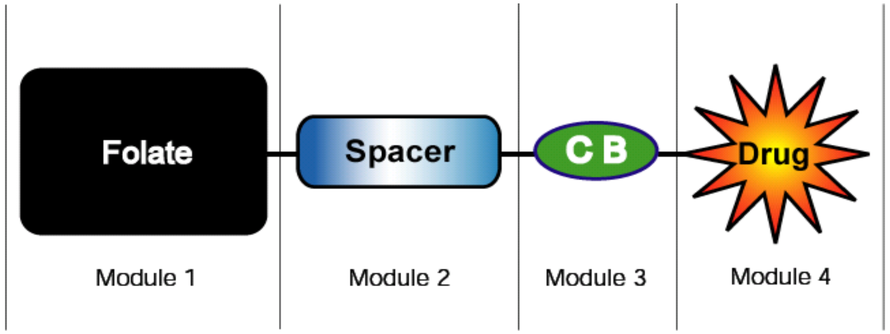
- **38 kDa membrane protein**
- **Different from normal folate entry pathway**
- **Binds folic acid and folate-drug conjugates with high affinity (K_d in low nM range)**
- **Enters cells via Endocytosis**
  - Non-destructive pathway
  - The FR is recycled, not destroyed
- **Recognized tumor-associated protein**
  - Predominant on epithelial cancers NOT on normal cells
  - Also found on CML, AML and lymphomas

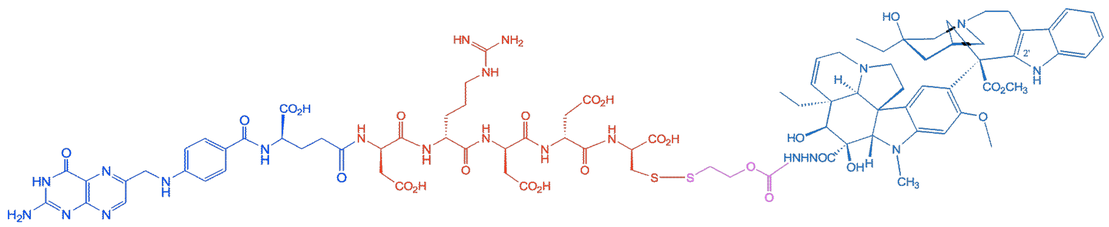
Folate Salvage Mechanism by Renal Proximal Tubule Cells

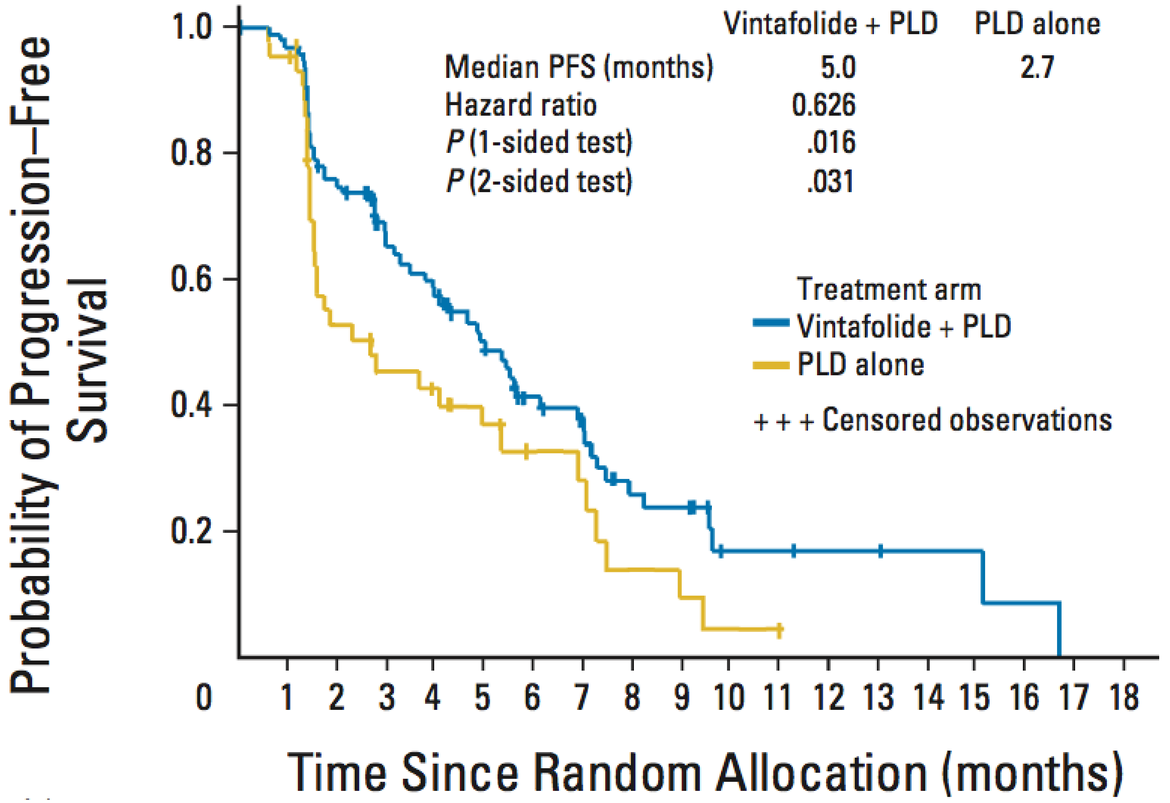


Vintafolide (EC145 or MK-8109)

A Folate-Vinca Conjugate







Naumann RW, J Clin Oncol 31(35):4400, 2013

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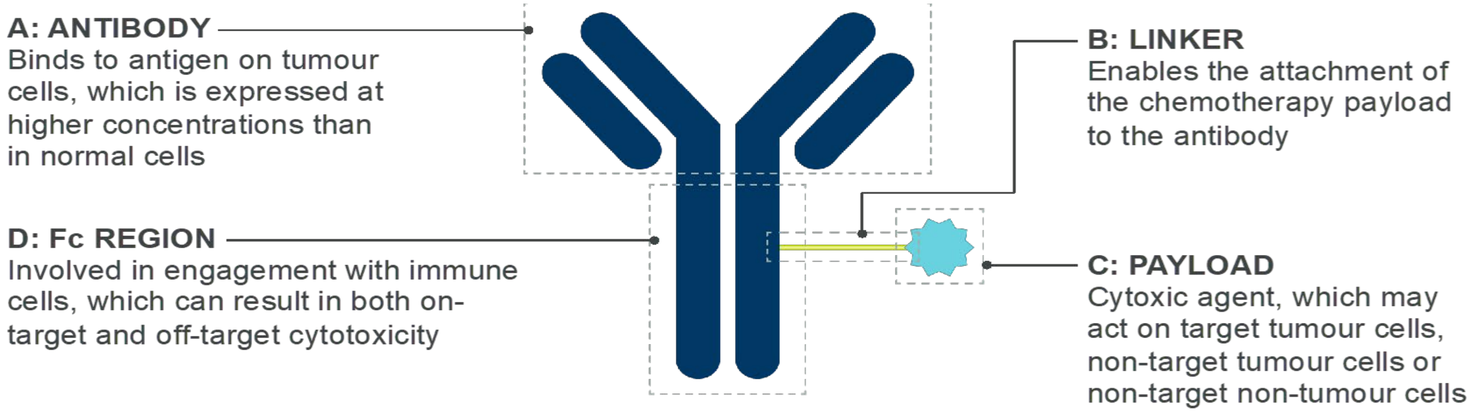
Where do we go from here?

Different components of the ADC are involved in different aspects of tumor targeting

Different targets?
-Cell surface targets
-I/O targets
-Custom?



*** ADC=antibody-drug conjugate**

<u>Non-specific conjugation</u>
-lysine
-cysteine
<u>Site Specific conjugation</u>
-Engineered cysteine
-Enzymatic conjugations
-Incorporations on UAA
-Hydrophilic polymers

<u>Noncleavable</u>
-Lysosomal degradation
<u>Cleavable</u>
-Lysosome protease
-Acid
-Redox

<u>Microtubule Agents</u>
-Auristatin
-Maytansinoids
-Tubulysisns
<u>DNA Targets</u>
-calicheamicins
-Duocarmycin
<u>I/O</u>
-Toll like receptors

Hoffmann RM, Oncoimmunology. 2018;7:e1395127
Zhao P, Acta Pharm Sincia B. https://doi.org/10.1016/j.apsb.2020.04.012

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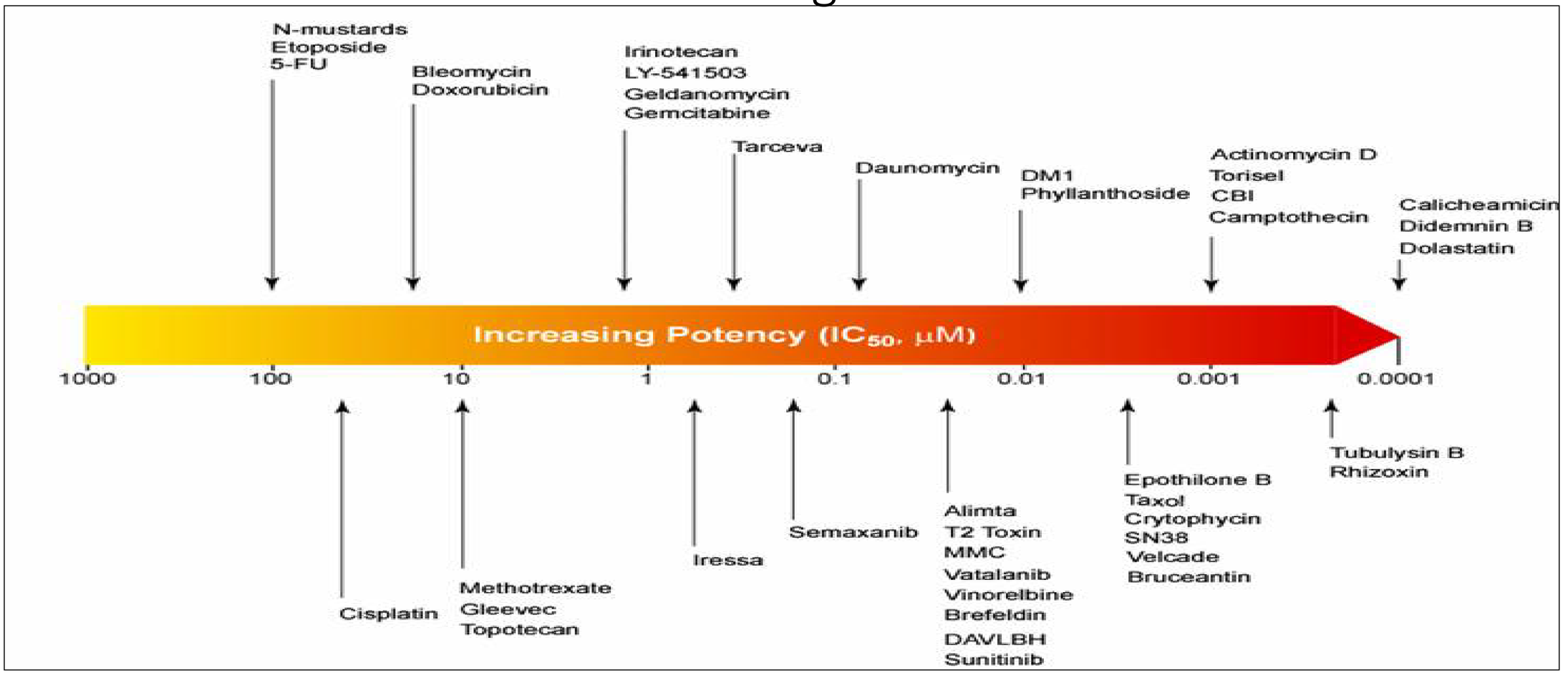
Drug Selection



Focus on targeting highly potent drugs

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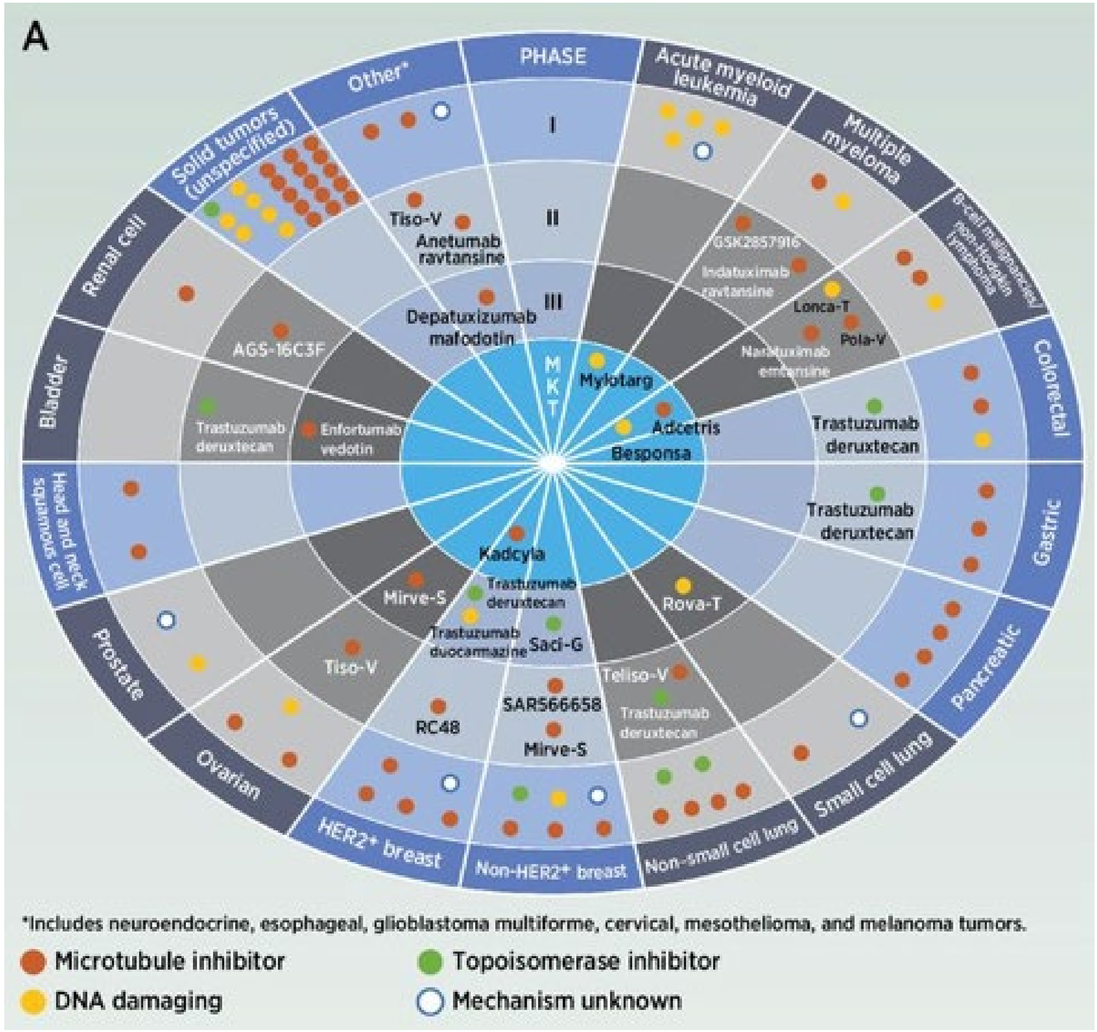
Chemotherapy Warheads

Family	Drug	MOA	Drug names
Auristatins (Dolstatin Direvatives)	MMAE - MMAF- more hydrophilic	Tubulin polymerase inhibitor	Vedotin Mafodotin
Maytansines	DM1 DM4 Hemiasterlin	Tubulin depolymerisation	Emtansne Soravtansine Tazevibulin
Calicheamicins		DNA cleavage	Ozogamicin
Duocarymycins		DNA minor groove alkylating agent	
Pyrrolobenzodiazepine dimer		DNA minor groove cross-linker	Pamozirine
alpha-Amanitin		RNA polymerase II inhibitor	

Current ADC development

- **406 trials currently listed on clinicaltrials.gov with ADCs**
- **Approximately 100 drugs in development**
  - 55 have been terminated
- **13 currently approved for use (Q3 2022)**
- **Ovarian Cancer**
  - 1 approval
  - 37 in development
- **Endometrial Cancer**
  - 13 in development
- **Cervical Cancer**
  - 1 approval



ADCs in Development as of 2019

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Review of Other Ongoing FR-α ADCs

Table 1. Main clinical trials of ADCs in ovarian cancer

Target	ADC	Trial	Phase	Setting	Treatment	Primary endpoint	Results
FRα	Mirvetuximab soravtansine	FORWARD I [47] (NCT02631876)	III	Platinum-resistant FRα positive	Mirvetuximab *vs.* chemotherapy of investigator's choice	PFS	ORR: 24 *vs.* 10% ($P = 0.014$) PFS: 4.1 *vs.* 4.4 months (HR 0.98)
		FORWARD II [48–51] (NCT02606305)	Ib/II	Platinum-sensitive FRα positive	Mirvetuximab soravtansine + carboplatin	Safety (phase Ib) ORR (phase II)	ORR: 71% PFS: 15 months
				Platinum-resistant FRα positive	Mirvetuximab soravtansine + pembrolizumab	Safety (phase Ib) ORR (phase II)	ORR: 43% PFS: 5.2 months
				Platinum-resistant FRα positive	Mirvetuximab soravtansine + bevacizumab	Safety (phase Ib) ORR (phase II)	ORR: 39% PFS: 6.9 months
				Platinum-resistant and sensitive FRα positive	Mirvetuximab soravtansine + bevacizumab	Safety (phase Ib) ORR (phase II)	ORR: 50% PFS: 8.3 months
	MORAb-202	NCT03386942 [52]	I	Platinum-resistant FRα positive	Farletuzumab conjugated with eribuline	DLTs	ORR: 37.5%
	STRO-002 Luveltamab	NCT03748186		Platinum-resistant FRα positive	Luveltumab Trazvebulin	RR	ORR 37.5%

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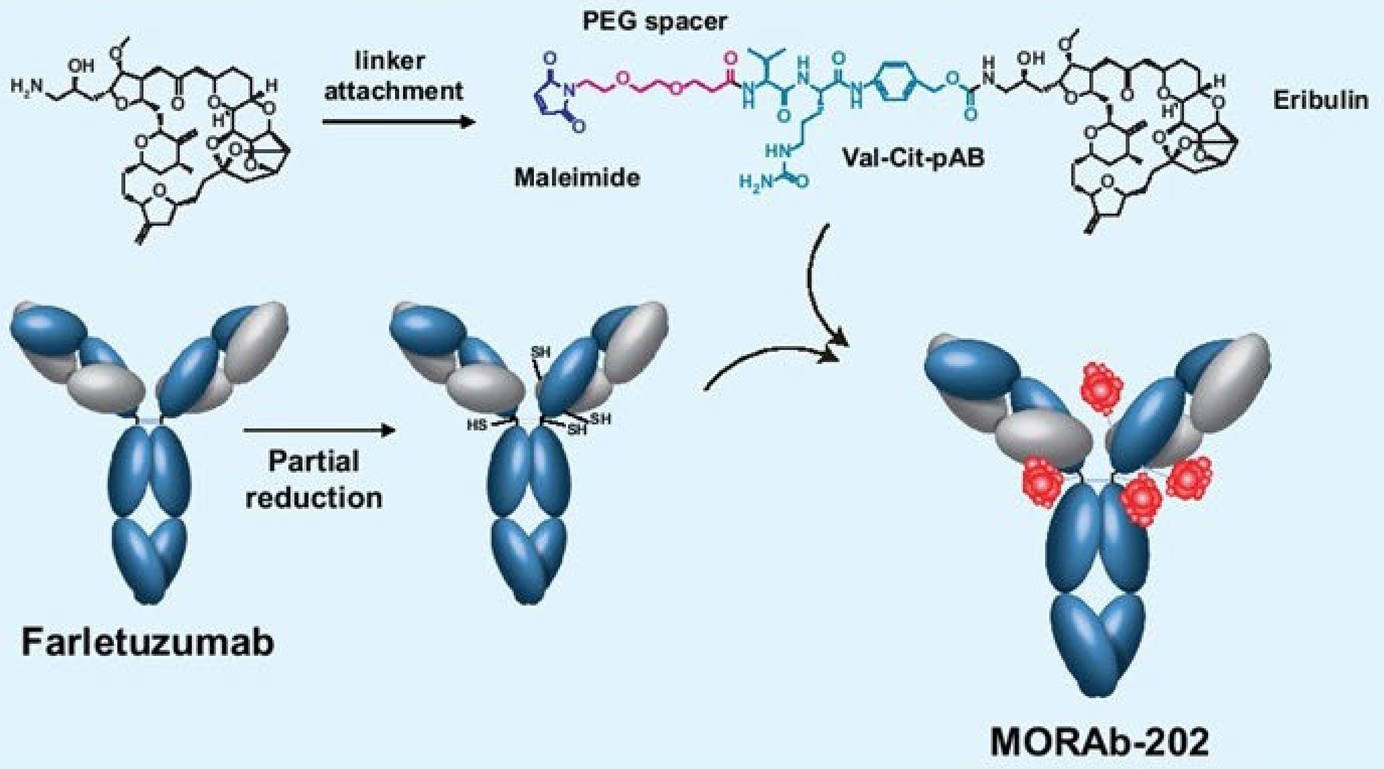
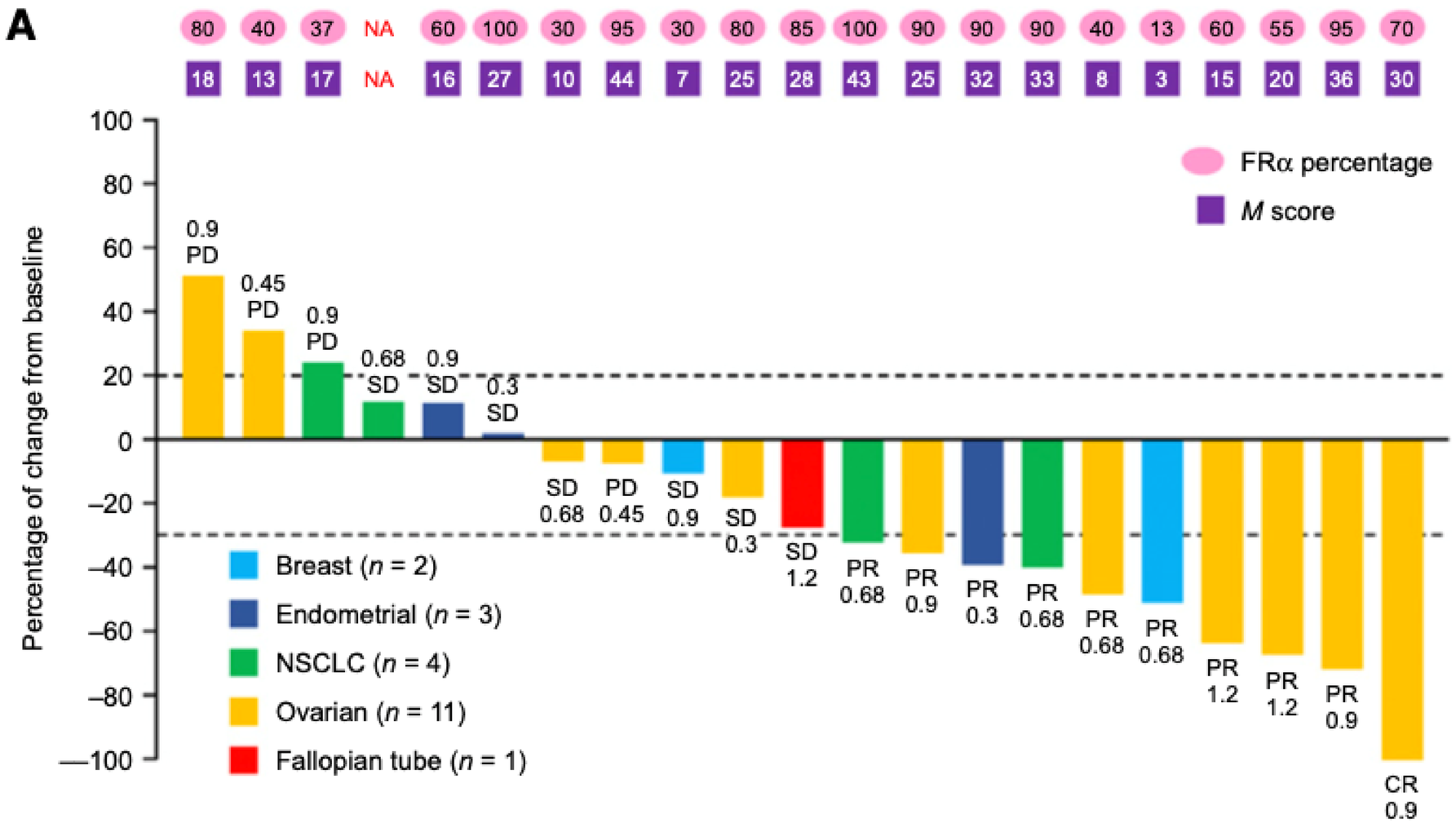
MORAb-202 Farletuzumab Eribulin

Figure 1. Structure of Cysteine-based Conjugation of Farletuzumab and Enzyme-cleavable Eribulin to Create MORAb-202



Shimizu T, ASCO Poster #5544, 2019

MORAb-202 in Patients with FR-a-Positive Solid Tumors



Shimizu T, Clin Cancer Res; 27(14) July 15, 2021

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Luveltamab Tazevibulin (STRO-002) Phase 1 Dose-Expansion Study

Naumann RW, Sutro Investor's Meeting, 1/9/23

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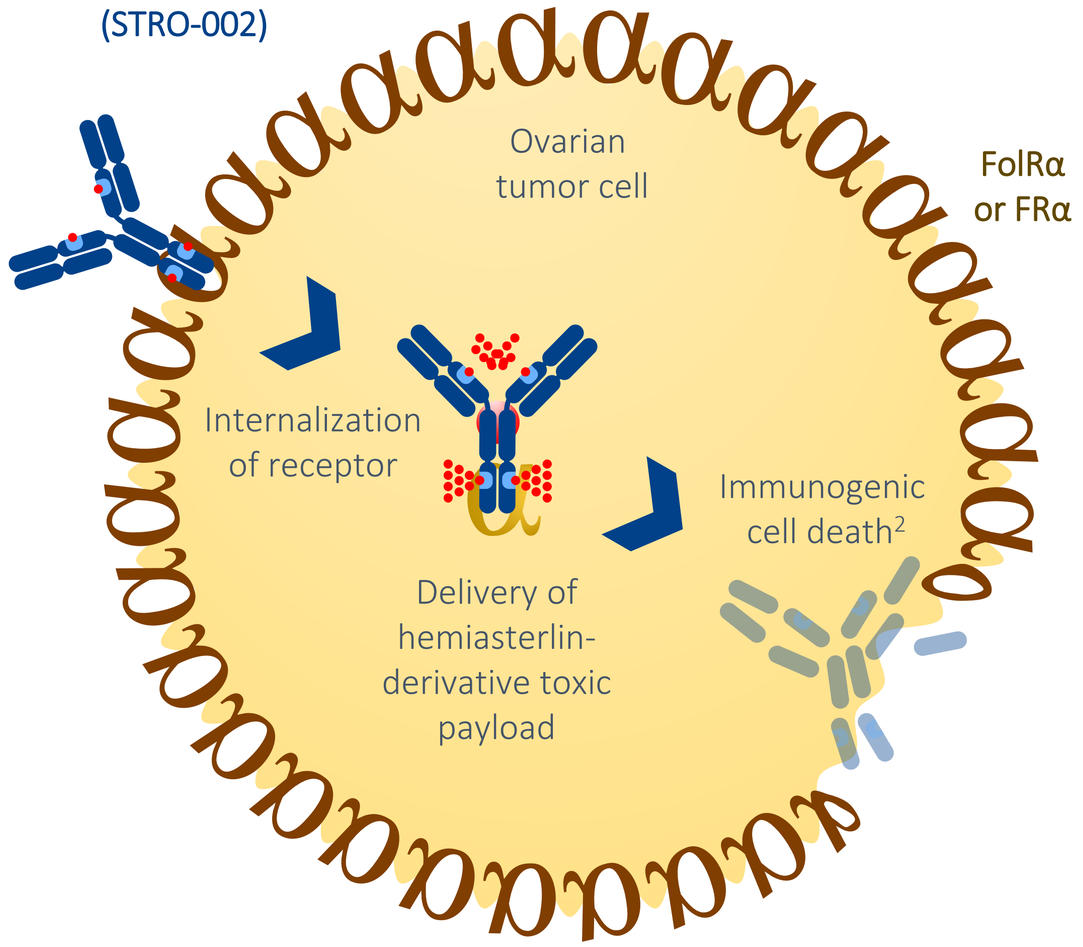
Luveltamab Tazevibulin (Luvelta, STRO-002)

Next generation ADC designed to have efficacy across a broad range of FolRα-expression levels

- Luveltamab (STRO-002), is a homogeneous ADC targeting FolRα
  - **DAR of exactly 4**
  - Precisely positioned **non-natural amino acids,** P-azidomethyl-L-phenylalanine (pAMF), at positions Y180 and F404 on the heavy chain
- **Stable protease-cleavable linkers**
  - Allows for rapid clearance of toxic catabolite after release and cell killing
- Warhead is hemiasterlin-derivative[1] with potentially **dual mechanism** against the tumor
  - **Tubulin-inhibitor cytotoxin,** which is less sensitive to P-gp transport and induces **immunogenic response upon cell death**[2]
  - Short half life and is cleared quickly in circulation once it leaves the tumor microenvironment



Naumann RW, Sutro Investor's Meeting, 1/9/23

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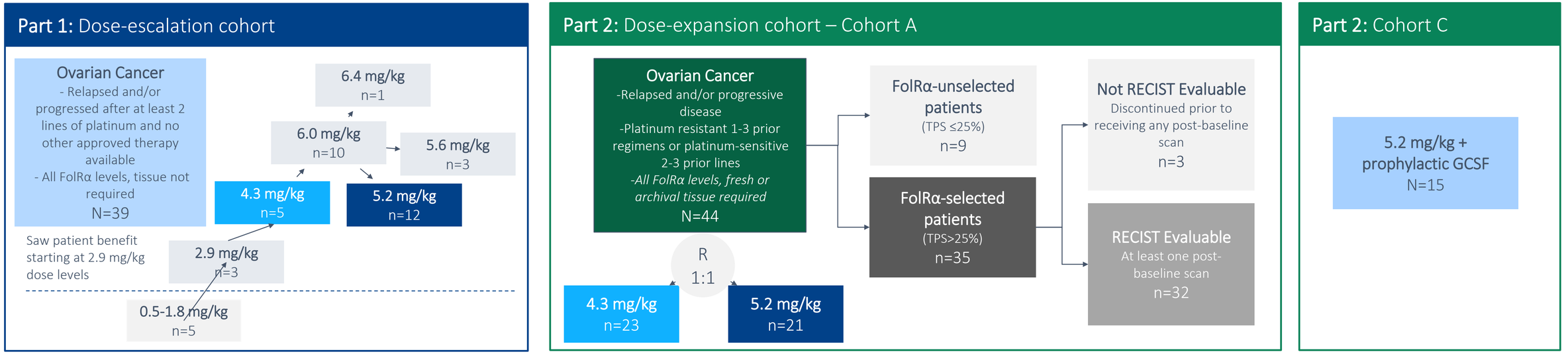
Two-Part Phase 1 Study for Patients with Advanced Ovarian Cancer



Patient Baseline Demographics – Part 2: Dose-Expansion – Cohort A	All Patients Enrolled (N=44)			FolRα-Selected Patients (N=35)		
	4.3 mg/kg n=23	5.2 mg/kg n=21	Total N=44	4.3 mg/kg n=19	5.2 mg/kg n=16	Total N=35
Median age (range), years	63 (39–91)	56 (40–72)	60 (39–91)	63 (39–91)	55.5 (45–72)	60 (39–91)
Median time since diagnosis (range), years	2.8 (0.8–9.3)	3.0 (0.7–7.8)	2.9 (0.7–9.3)	2.8 (0.9–9.3)	3.5 (1.0–7.8)	3.0 (0.9–9.3)
Mean number of prior lines of therapy	2.5	2.3	2.4	2.6	2.3	2.5
Prior Therapies						
Prior Bevacizumab, n (%)	13 (57)	16 (76)	29 (66)	12 (63)	12 (75)	24 (69)
Prior PARP inhibitor, n (%)	18 (78)	18 (86)	36 (82)	14 (74)	15 (94)	29 (83)

Naumann RW, Sutro Investor's Meeting, 1/9/23 NCT03748186

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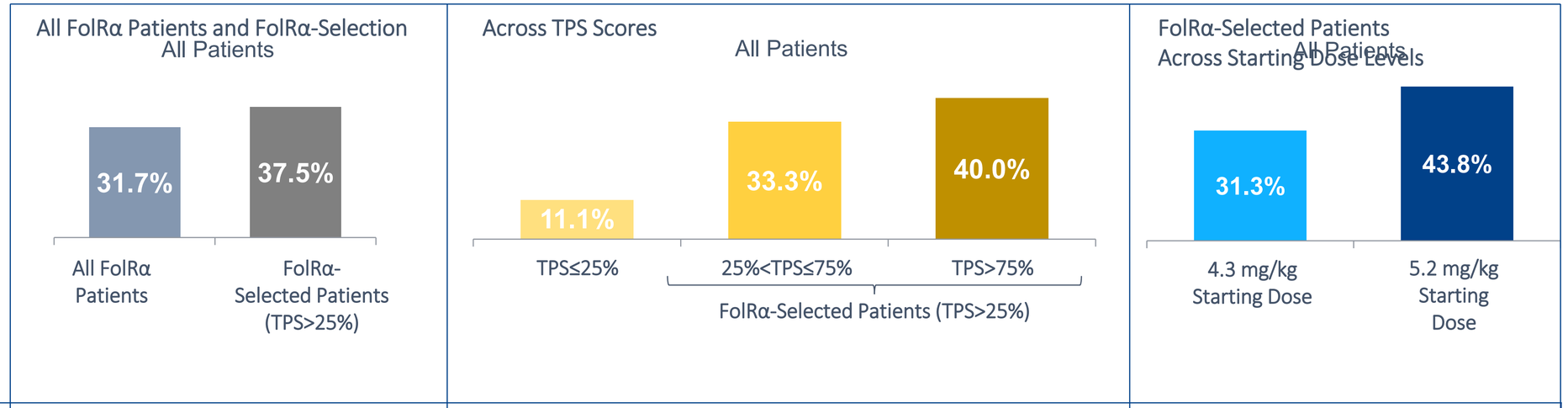
Data Establishes Appropriate FolRα-Selection Criteria

Dose-expansion efficacy data establishes TPS>25% as appropriate enrichment cutoff

Patients who started at 5.2 mg/kg experienced 43.8% ORR, 5.4 months DOR, and 6.6 months PFS

RECIST-Evaluable ORR (%), DOR (%), and PFS



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% (10.0%, 65.1%)**	**40.0% (19.1%, 63.9%)**	31.3% (11.0%, 58.7%)	43.8 (19.8%, 70.1%)
DOR (95% CI), mo	5.4 (2.9, 11.0)	5.5 (2.5, 11.0)	2.9	5.6 (2.5, NE)	5.5 (2.4, NE)	13 (4.5, NE)	5.4 (2.4, 6.1)
Patients for PFS	n=44	n=35	n=9	n=12	n=23	n=19	n=16
PFS (95% CI), mo	4.3 (4.0, 6.3)	6.1 (4.1, 7.0)	3.8 (1.3, 4.2)	6.4 (1.4, 10.4)	5.8 (4.0, 6.6)	6.1 (4.0, 8.3)	6.6 (2.9, 7.6)

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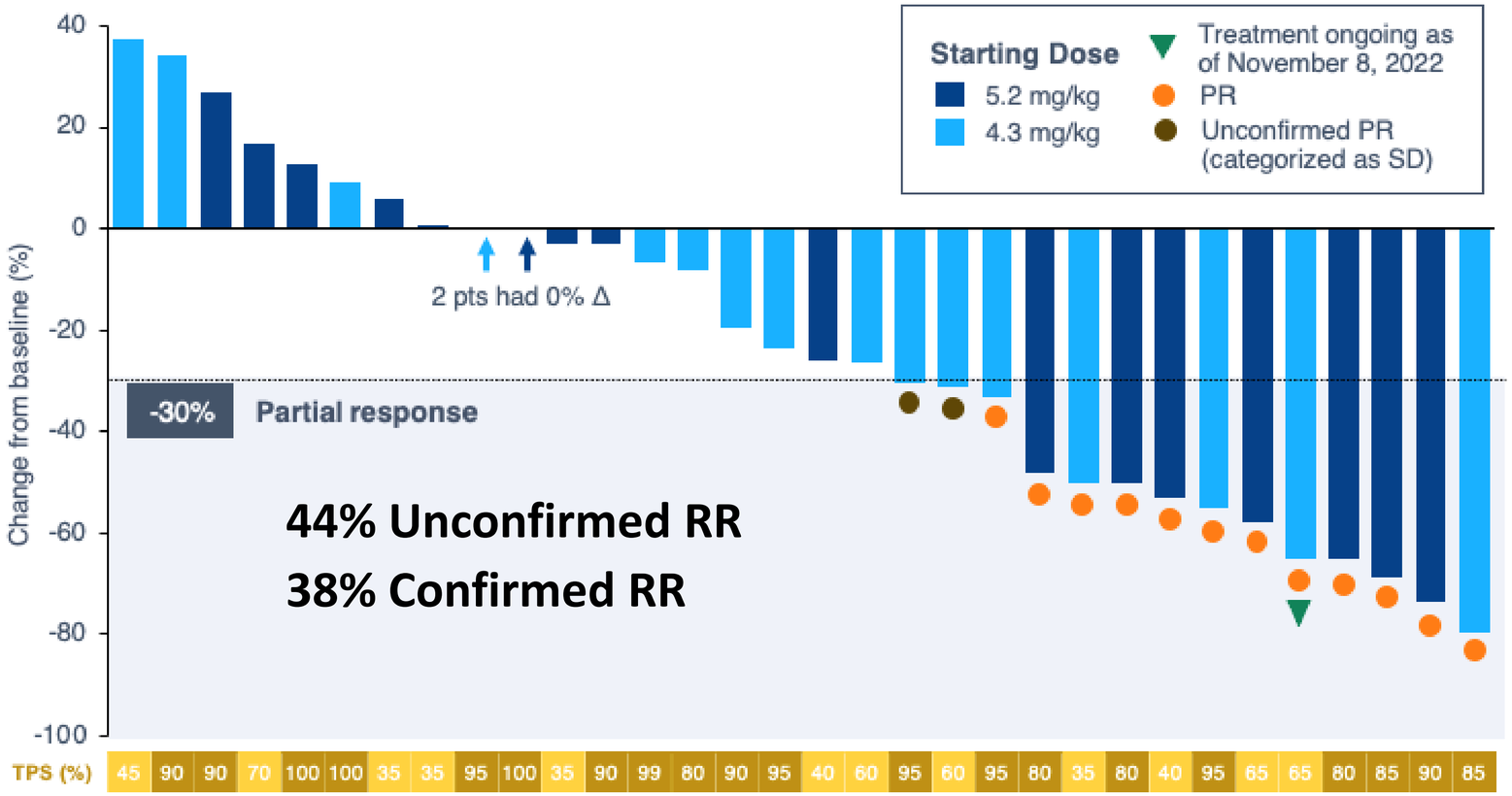
Majority of FolRα-Selected Patients Experienced Disease Control

BOR: Maximum Reduction in Tumor Target Lesions in FolRα-Selected Patients (N=32)



BOR in FolRα-Selected Patients

	Both Doses N=32	5.2 mg/kg n=16	4.3 mg/kg n=16
PR	12	7	5
ORR %	*37.5*	*43.8*	*31.3*
SD	14 (43.8)	6 (37.5)	8 (50.0)
DCR[a] %	*81.3%*	*81.3%*	*81.3%*
PD	6 (18.8)	3 (18.8)	3 (18.8)

FolRα Stratification

Number of patients, (%)	5.2 mg/kg n=16	4.3 mg/kg n=16
25%<TPS≤75%	7, (43.8%)	5, (31.3%)
TPS>75%,	9, (56.3%)	11, (68.8%)
TPS>25%	16, 100%	16, 100%

Naumann RW, Sutro Investor's Meeting, 1/9/23 NCT03748186

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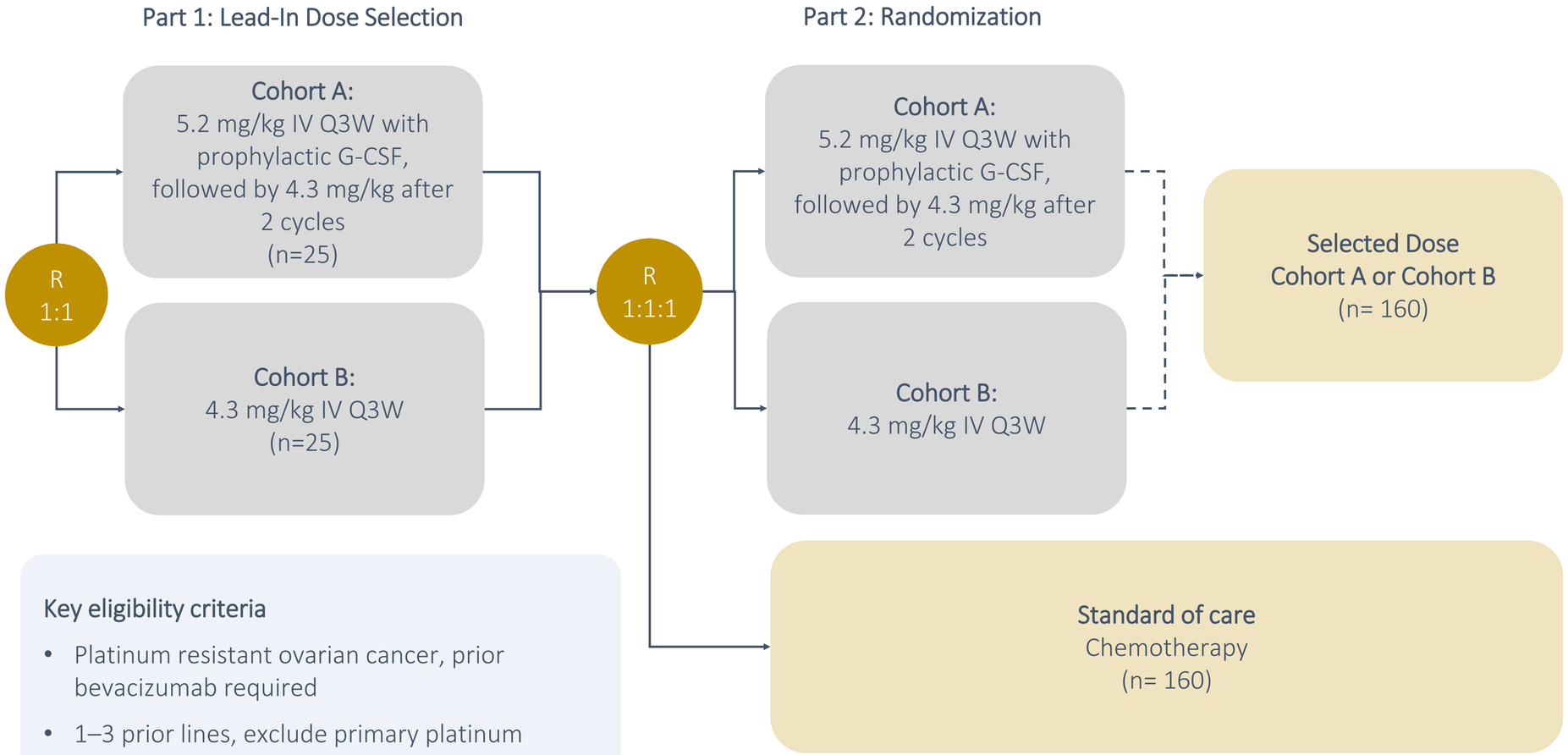
Luveltamab Integrated Strategy for Phase 2/3 Study, REFRaME (GOG 3086)

Potential to support Accelerated and Full Approvals in platinum-resistant ovarian cancer



Key eligibility criteria

- Platinum resistant ovarian cancer, prior bevacizumab required
- 1–3 prior lines, exclude primary platinum refractory
- FolRα-selected (TPS > 25%)

Interim analysis for Accelerated Approval

- Endpoint: ORR, DOR, safety
- Minimal hit to alpha,
- Interim analysis on n=110 patients in selected dose of luvelta

Final analysis for full approval

- Endpoints: PFS
- Full approval analysis at 160 patients, each in luvelta and standard of care
- Power 80%, HR, 0.72

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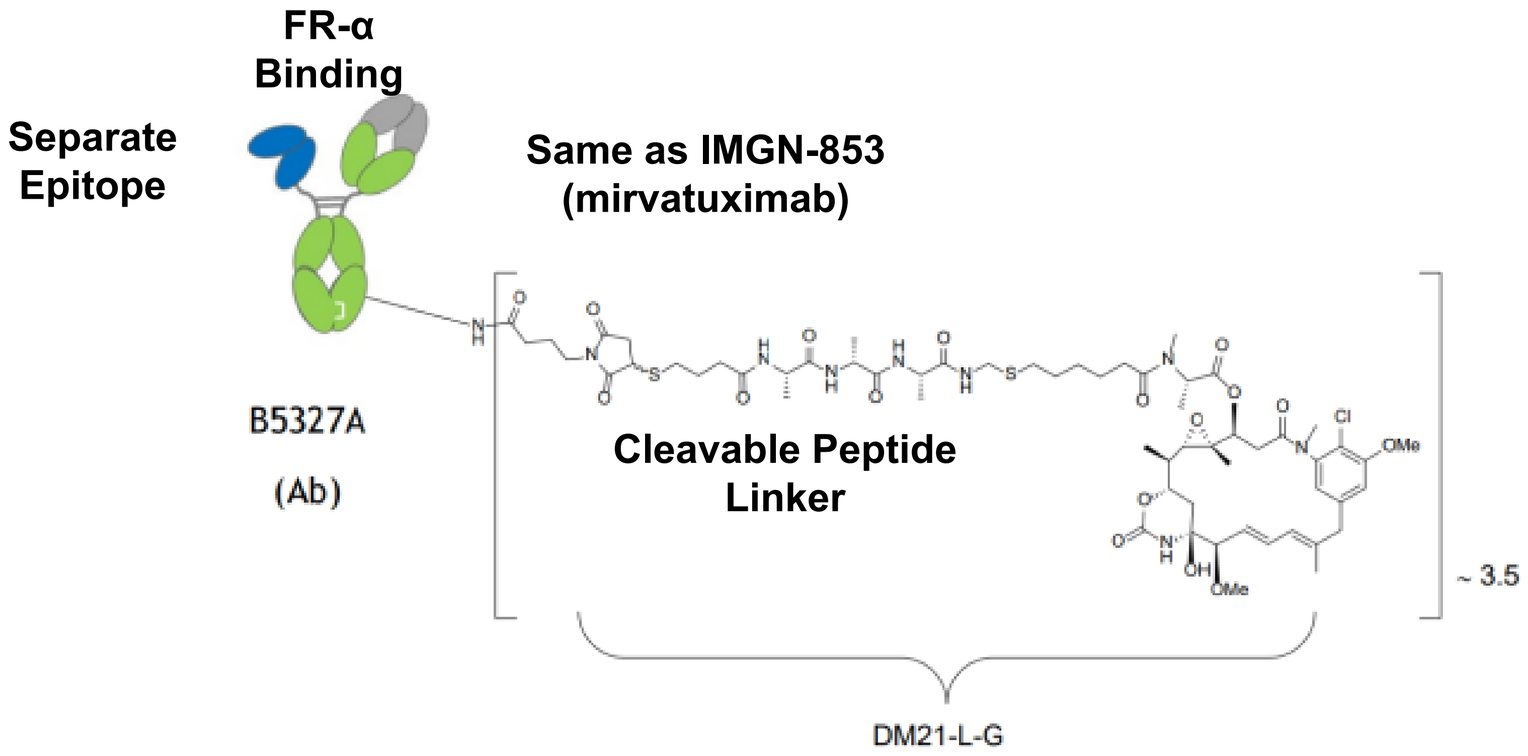
IMGN-151
Next generation FR-α ADC



- **Bivalent binding to FR-α**
- **Preclinical development**
  - Linker increased $t_{1/2}$ by 60 hours
  - Increased binding of medium expressing FR-α cell lines by 100% and internalization by 170%
  - 200x more active than than IMGN-853 against cell lines
  - Better bi-stander killing

Reported trials of ADCs in Ovarian Cancer

Target	ADC	Trial	Phase	Setting	Treatment		Primary endpoint
Mesothelin	Anetumab ravtansine	NCT01439152 [53]	I	Platinum-resistant and partially platinum sensitive	Anetumab ravtansine	DLTs	ORR: 9%
	DMOT4039A (RG7600)	NCT01469793 [54]	I	Platinum-resistant	DMOT4039A	DLTs/RP2D	ORR: 30%
	BMS-986148	CA008-008 [55] (NCT02341625)	I/IIa	Platinum unselected	BMS-986148	Safety	ORR: 10%
TF	Tisotumab vedotin	InnovaTV 201 [56] (NCT02001623)	I/II	Advanced solid tumors including ovarian cancer platinum unselected	Tisotumab vedotin	Safety	ORR: 13.9%
MUC16	DMUC4064A	NCT02146313 [57]	I	Platinum-resistant	DMUC4064A	Safety	ORR: 25%
NaPi2B	Lifastuzumab vedotin	NCT01363947 [58]	I	Platinum-resistant	Lifastuzumab vedotin	Safety	ORR: 36.7%
		NCT01991210 [59]	II	Platinum-resistant	Lifastuzumab vedotin *vs.* PLD	PFS	ORR: 34 *vs.* 15% PFS: 5.3 *vs.* 3.1 months (HR 0.78)
	XMT-1536 Upifitamab			Platinum-resistant	Upifitamab Rilsodotin	RR	ORR 37.5% DOR 5.0 months

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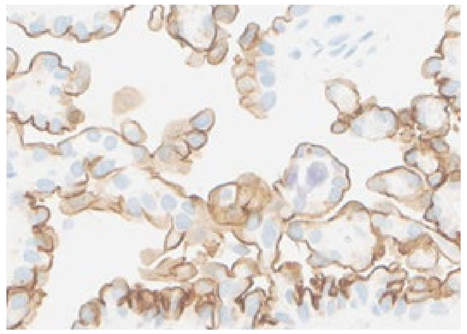
NaPi2b is an Ideal Antibody-Drug Conjugate (ADC) Target Assay Developed to Measure Antigen Expression

- ADC internalizing sodium phosphate transporter; not an oncogene
- Broadly expressed in ovarian cancer and NSCLC adenocarcinoma
- Limited expression in normal tissues
- IHC assay calibrated to distinguish wide range of expression

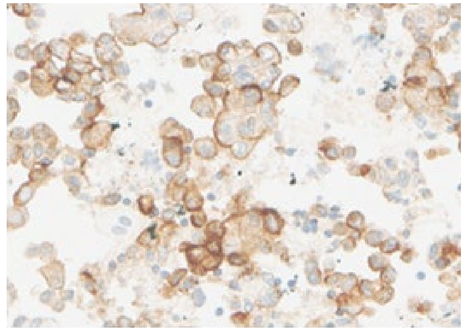
Epithelial ovarian cancer

H score = 293



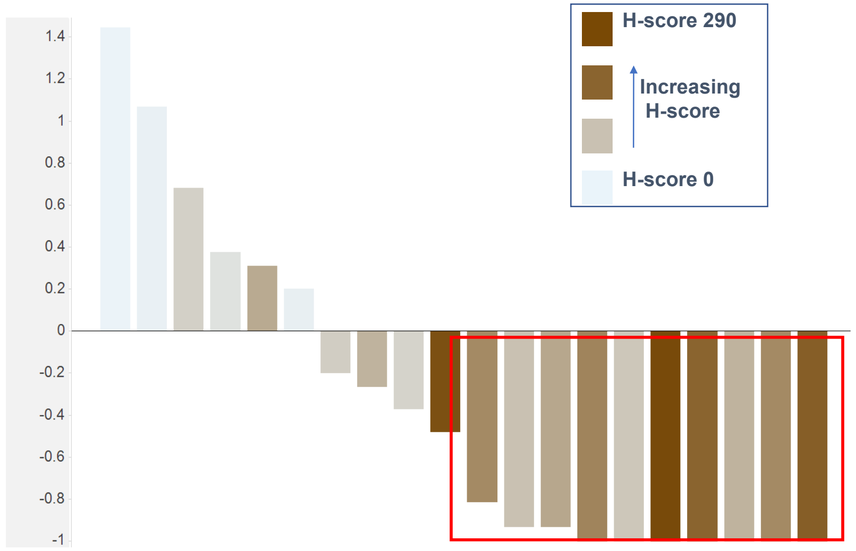
Lung adenocarcinoma

H score = 265



Ovarian Cancer Patient-Derived Xenograft Models

Response correlated with NaPi2b Expression



H-score measures the percentage of cells staining multiplied by their intensity (0, 1+, 2+, 3+) for a range of 0 - 300

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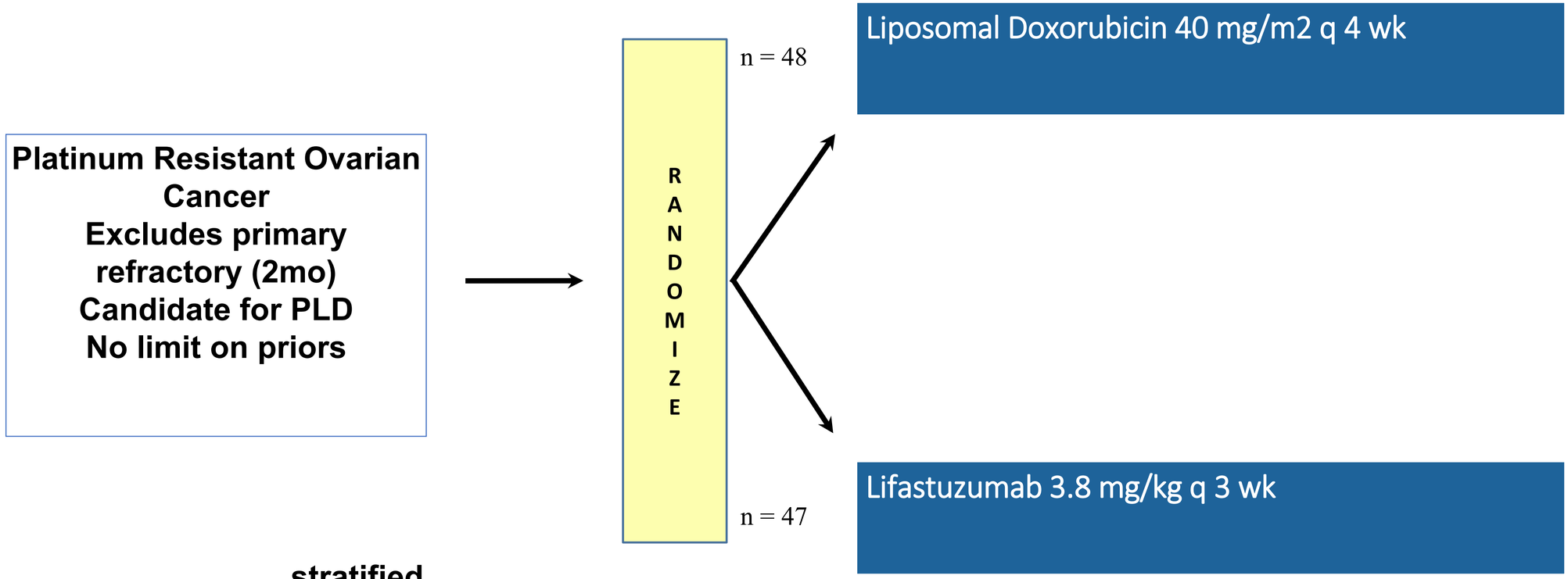
Anti-NaPi2b antibody–drug conjugate lifastuzumab vedotin (DNIB0600A) compared with pegylatedliposomal doxorubicin in patients with platinum-resistant ovarian cancer in a randomized, open-label, phase II study

median f/u = 17.4 mo



stratified
Platinum-free interval (<3 months versus 3–6 months)
Number of prior platinum-containing regimens (<2 versus 2)
Numberof regimens for PROC (0 versus 1–2)

Banerjee S, Anal Oncol 29(4):917-923 NCT01991210

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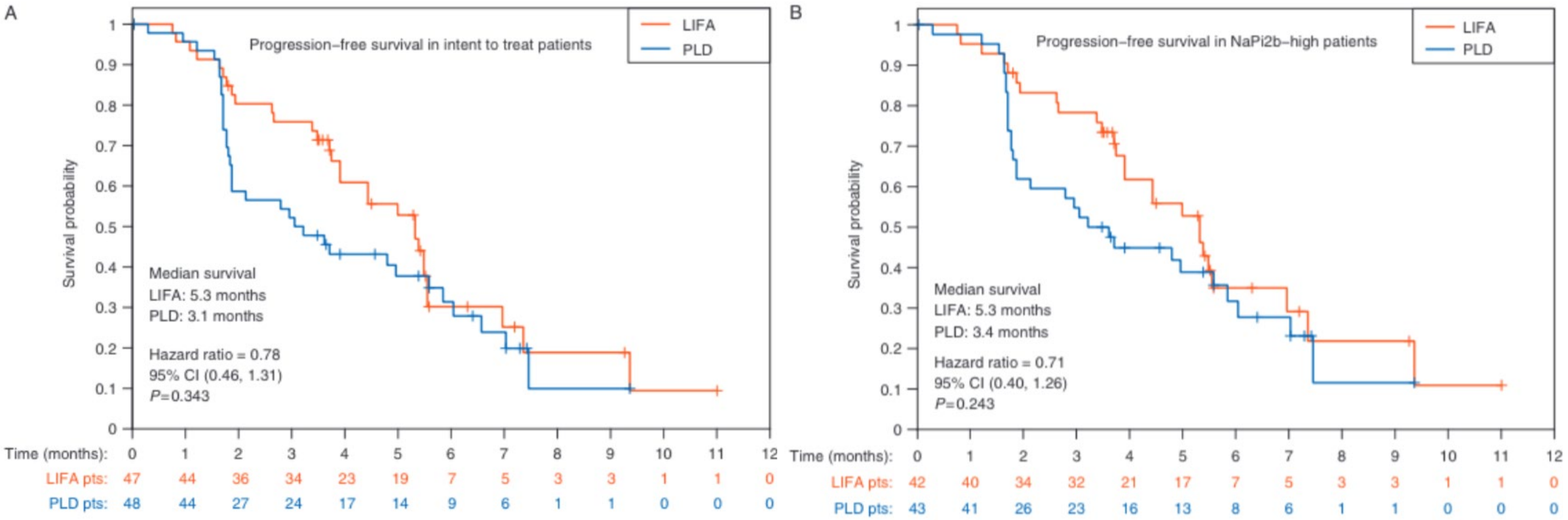
Anti-NaPi2b antibody–drug conjugate lifastuzumab vedotin (DNIB0600A) compared with pegylatedliposomal doxorubicin in patients with platinum-resistant ovarian cancer in a randomized, open-label, phase II study



Banerjee S, Anal Oncol 29(4):917-923 NCT01991210

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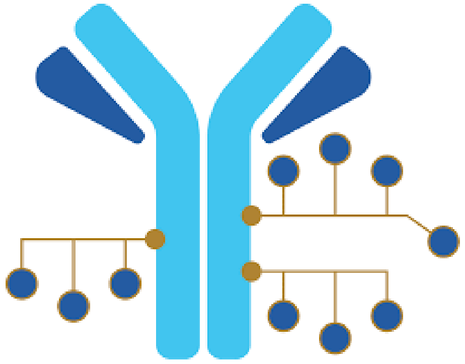
Upifitamab Rilsodotin (UpRi) – First-in-Class ADC Targeting NaPi2b



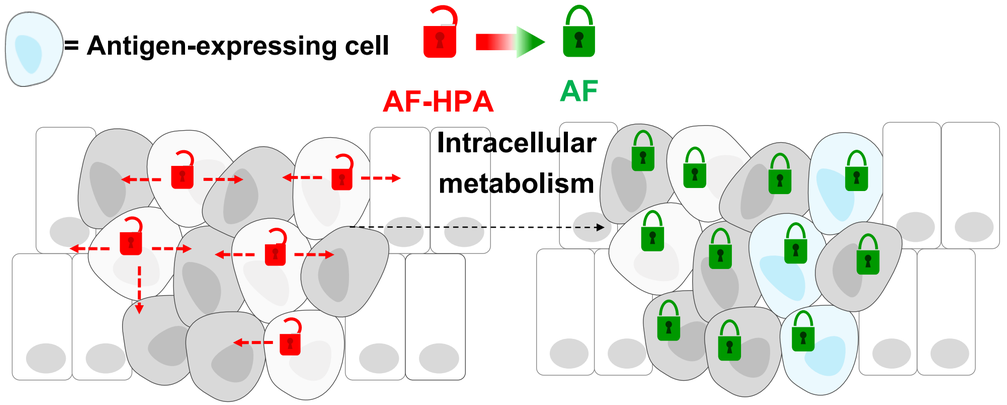
UpRi

Antibody: Humanized monoclonal anti-NaPi2b[1]

Linker: Polymer scaffold; cleavable ester linker[2]

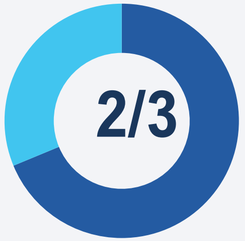
Payload: AF-HPA (DolaLock-controlled bystander effect)[1]

Drug-to-Antibody Ratio: ~10

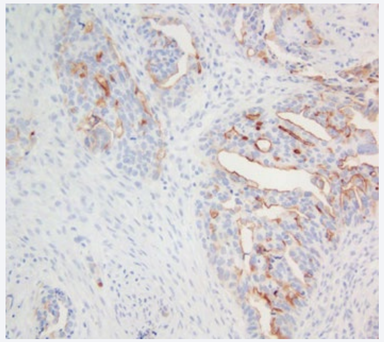


Upon ADC internalization into tumor cells and efficient release of payload, AF-HPA payload is metabolized to AF that remains highly potent but loses the ability to cross the cell membrane, locking it in the tumor, controlling the bystander effect, and consequently limiting impact on adjacent healthy cells[2,3]

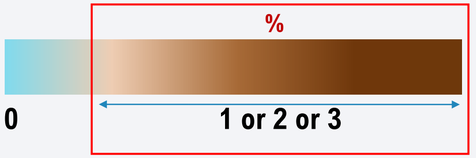
NaPi2b is a Sodium-Dependent Phosphate Transporter Broadly Expressed in Ovarian Cancer With Limited Expression in Healthy Tissues[4]



- NaPi2b expressed by tumor cells in two-thirds of patients with high-grade serous ovarian cancer[2]
- NaPi2b is a lineage antigen (not an oncogene)[1]



NaPi2b IHC assay in development – an optimal diagnostic assay would be robust, predictive, reproducible, easily able to distinguish a wide range of expression using TPS scoring method[2]



ADC, antibody drug conjugate; AF, auristatin F; AF-HPA, auristatin F-hydroxypropylamide; IHC, immunohistochemistry; NaPi2b, sodium-dependent phosphate transport protein 2B; TPS, tumor proportion score; UpRi, upifitamab rilsodotin.

1. Bodyak ND et al. Mol Cancer Ther. 2021;20(5):885–895. 2. Mersana. Data on File. 2022. 3. Tolcher AW et al. ASCO Annual Meeting 2019; Abstract 3010.
4. Lin K et al. Clin Cancer Res. 2015;21(22):5139–5150.

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Confirmed ORR by UpRi Dose Group and NaPi2b Level

44% ORR in Dose Group 36 for Patients with NaPi2b- High Ovarian Cancer

		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

Data cut: June 10, 2021. Analysis with 73 evaluable patients. Two patients excluded as post-baseline tumor measurement shows “Not Measurable”, yet “PD” was assigned by investigator in response dataset. 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.
CR, complete response; H, high; L, low; ND, not yet determined; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TPS, tumor proportion score; uPR, unconfirmed partial response; UpRi, upifitamab rilsodotin.

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UPLIFT

GOG 3048

Patient Population: HGSOC[a] progressing after standard treatments; measurable disease per RECIST v1.1; ECOG PS 0 or 1; enrolling regardless of NaPi2b expression

Global
US, Europe, Australia, Canada

Key Inclusion Criteria

- Platinum-resistant ovarian cancer (PROC)
- 1–4 prior lines of therapy
- Grade ≤2 peripheral neuropathy
- Archival or fresh tissue required for biomarker evaluation

Key Exclusion Criteria

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

UpRi 36 mg/m^2 up to max 80 mg; IV Q4W

Primary Endpoint

- Confirmed ORR in NaPi2b-high (N = ~100)

Secondary Endpoint

- Confirmed ORR in overall population (N = up to ~180 including 100 NaPi2b-high)

Other Secondary Endpoints

- DoR
- Safety

Prospectively-defined retrospective analysis to validate NaPi2b biomarker cutoff

NCT03319628: Trial Currently Enrolling Patients

[a] HGSOC including fallopian tube and primary peritoneal cancer.
DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HGSOC, high-grade serous ovarian cancer; IV, intravenous; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate, PROC, platinum-resistant ovarian cancer; PS, performance score; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab rilsodotin.

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UP-NEXT

GOG 3049

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

a HGSOC including fallopian tube and primary peritoneal cancer.
DoR, duration of response; ECOG, Eastern Cooperative Oncology Group; HGSOC, high-grade serous ovarian cancer; IV, intravenous; NaPi2b, sodium-dependent phosphate transport protein 2B; ORR, overall response rate, PROC, platinum-resistant ovarian cancer; PS, performance score; Q4W, every 4 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; UpRi, upifitamab rilsodotin.

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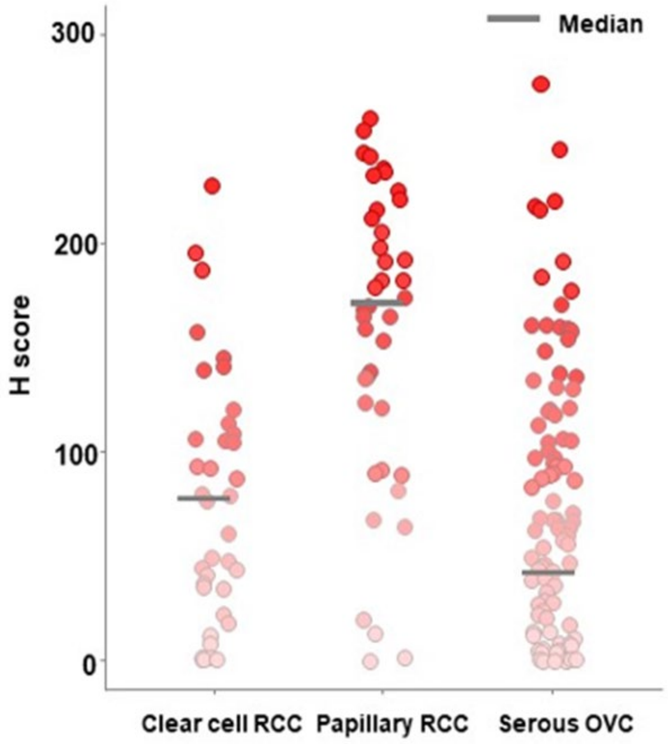
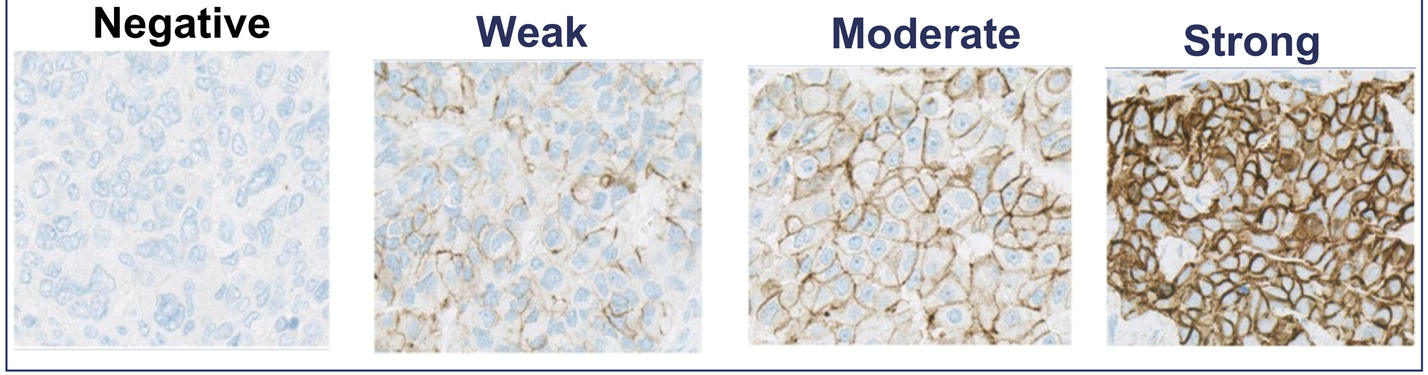
CDH6 Expression in RCC/Serous OVC

CDH6 Expression in RCC/Serous OVC



CD Expression in Human Tumor Tissue by IHC Assay



Tumor type	n	CDH6 H-score (n ,%)							
		0		1-100		101-200		201-300	
Clear cell RCC	39	0	0%	25	64%	13	33%	1	3%
Papillary RCC	41	1	2%	9	22%	18	44%	13	32%
Serous OVC	118	18	15%	71	60%	24	20%	5	4%

- CDH6 is part of the cadherin family, which is involved with cell-cell adhesion, organ development, and epithelial-mesenchymal transition
- The function of CDH6 has yet to be fully elucidated
- CDH6 is overexpressed in various cancers, particularly OVC and RCC

CDH6, cadherin 6; OVC, ovarian cancer; RCC, renal cell carcinoma.

Hirokazu S, et al. ESMO 2021. Abstract 10P.

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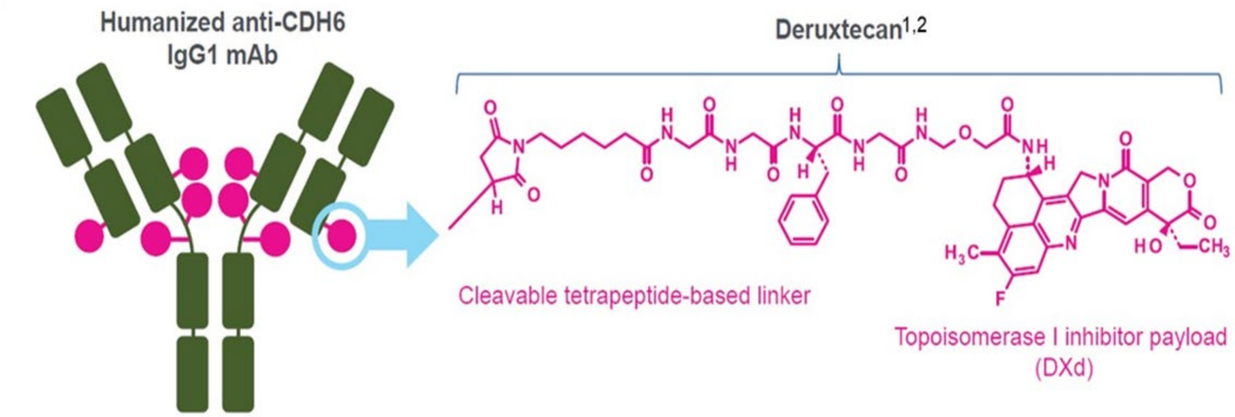
DS-6000 Design and Key Attributes

DS-6000 is a CDH6-directed ADC composed of 3 compnents[1,2]

- A humanized anti-CDH6 IgG1 monoclonal antibody covalently linked to
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker



Key attributes[2,7]

- Payload mechanism of action: topoisomerase I inhibitor [a,1-5]
- High potency of payload [a,2-5]
- Optimized drug to antibody ratio [a,b1-4]
- Payload with short systemic half-life [a,b,2,3]
- Stable linker-payload [a,2,3,5]
- Tumor-selective cleavable linker [a,2-6]
- Bystander antitumor effect [a,2,7]

[a]The clinical relevance of these features is under investigation. b Based on animal data.

1. Okajima D, et al. *Mol Cancer Ther*. 2021;(12):2329-2340. **2.** Nakada T, et al. *Chem Pharm Bull (Tokyo)*. 2019;67(3):173-185. **3.** Ogitani Y, et al. *Clin Cancer Res*. 2016;22(20):5097-5108. **4.** Hashimoto Y, et al. *Clin Cancer Res*. 2019;25:7151-7161. **5.** Koganemaru S, et al. *Mol Cancer Ther*. 2019;18:2043-2050. **6.** Haratani K, et al. *J Clin Invest*. 2020;130(1):374-388. **7.** Ogitani Y, et al. *Cancer Sci*. 2016;107(7):1039-1046.

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Ongoing ADC Trials in Endometrial and Cervical Cancer

Table 1

Target	ADC	Trial	Phase	Setting	Endpoint
HER2	Trastuzumab duocarmzaine (SYD985)	NCT04205630	II	HER2 (+) Endometrial Ca	ORR
	T-DXd	NCT04482309	II	HER2 (+) Endometrial/Ovarian/Cx Ca	ORR
FR-α	Mirvetuximab soravtansine	NCT03832361	II	FR-α r/m Endometrial Ca	ORR
		NCT03835819	II	FR-α r/m UPSC	ORR/PFS
	Luveltamab Tazevibulin (Stro-002)		I/II	FR-α r/m Endometrial Ca	RR
Trop2	Sacituzumab govitecan	NCT04251416	II	Trop2 r/m Endometrial Ca	ORR
TF	Tisotumab vedotin	NCT04697628	III	r/m cervical cancer	OS

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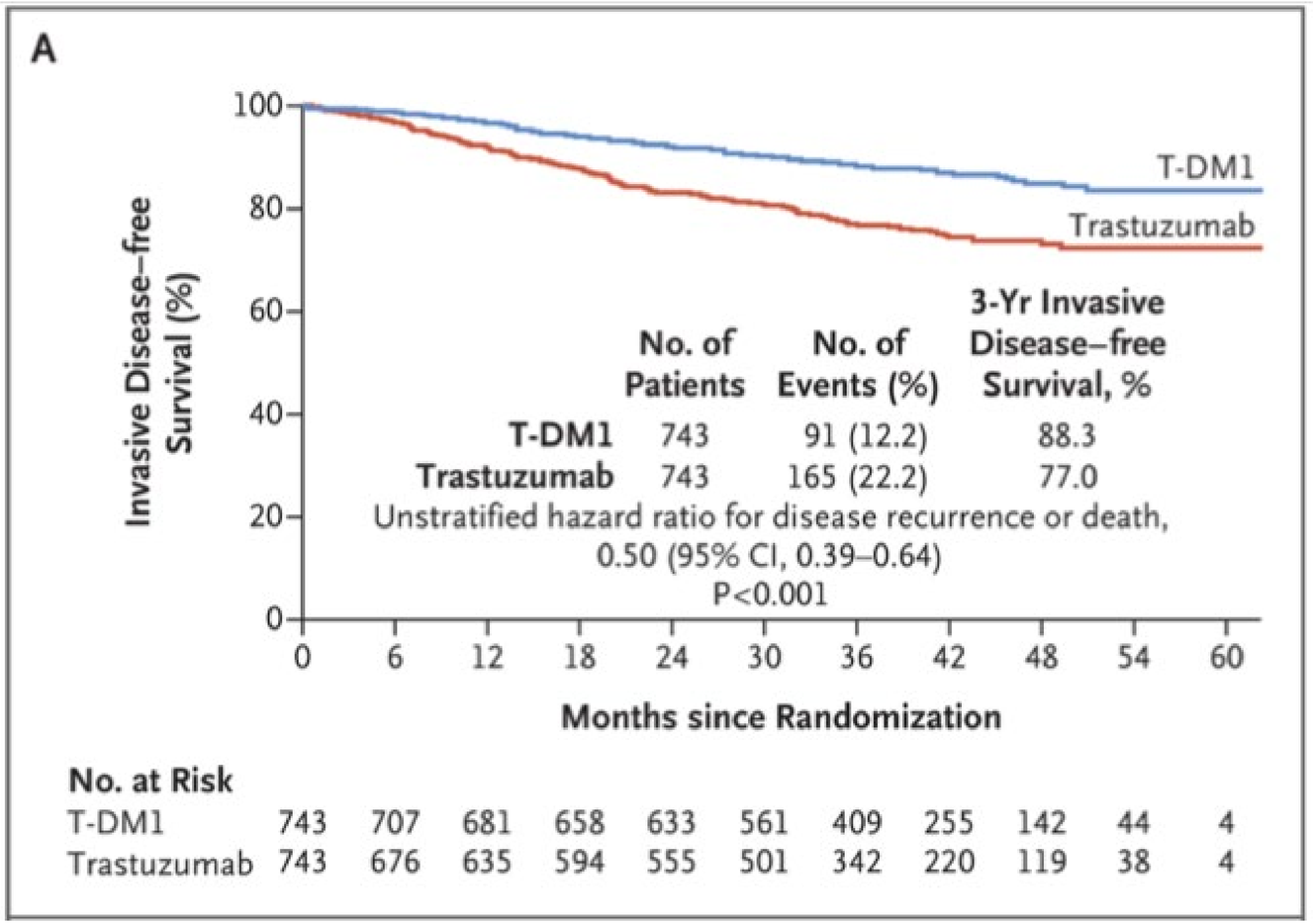
Trastuzumab vs T-DM1 in Breast Cancer (KATHERINE)



Von Minckwitz, G, *N Eng J Med* 380.7:617-628, 2019.

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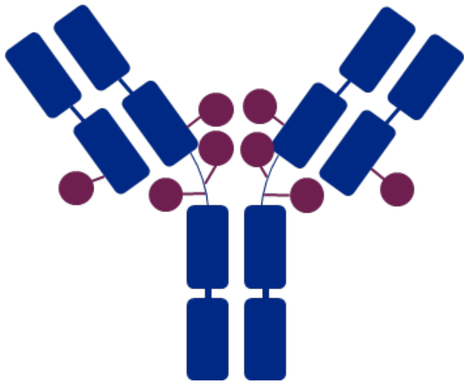
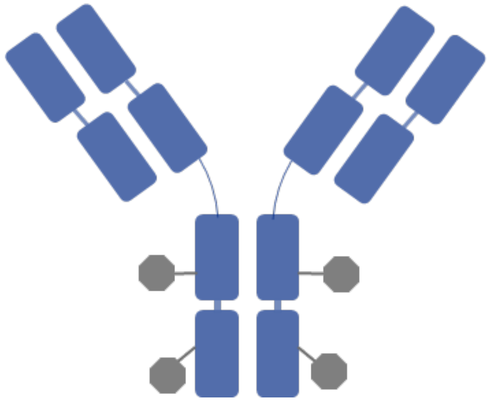
ADC Characteristic Differences Between T-DXd and T-DM1

Trastuzumab deruxtecan (T-DXd)[1]



T-DXd[1-4,a]	ADC Attributes	T-DM1[3-5]
Topoisomerase I inhibitor	**Payload MoA**	Anti-microtubule
~8:1	**Drug-to-antibody ratio**	~3.5:1
Yes	**Tumor-selective cleavable linker?**	No
Yes	**Evidence of bystander anti-tumor effect?**	No

Trastuzumab emtansine (T-DM1)[5]



Modi. NEJM. 2020;382:610

1. Nakada T et al. Chem Pharm Bull (Tokyo). 2019;67:173-85. 2. Ogitani Y et al. Clin Cancer Res. 2016;22:5097-108. 3. Trail PA et al. Pharmacol Ther. 2018;181:126-42.
4. Ogitani Y et al. Cancer Sci. 2016;107:1039-46. 5. LoRusso PM et al. Clin Cancer Res. 2011;17:6437-47.

DESTINY-Breast03: First Randomized Ph3 Study of T-DXd

An Open-Label, Multicenter Study (NCT03529110)

Patients
- Unresectable or metastatic HER2-positive[a] breast cancer
- Previously treated with trastuzumab and taxane in advanced/metastatic setting[b]
- Could have clinically stable, treated brain metastases

Stratification Factors
- Hormone receptor status
- Prior treatment with pertuzumab
- History of visceral disease

R 1:1

T-DXd
5.4 mg/kg Q3W
(n = 261)

T-DM1
3.6 mg/kg Q3W
(n = 263)

Primary Endpoint
- PFS (BICR)

Key Secondary Endpoint
- OS

Secondary Endpoints
- ORR (BICR and investigator)
- DOR (BICR)
- PFS (investigator)
- Safety

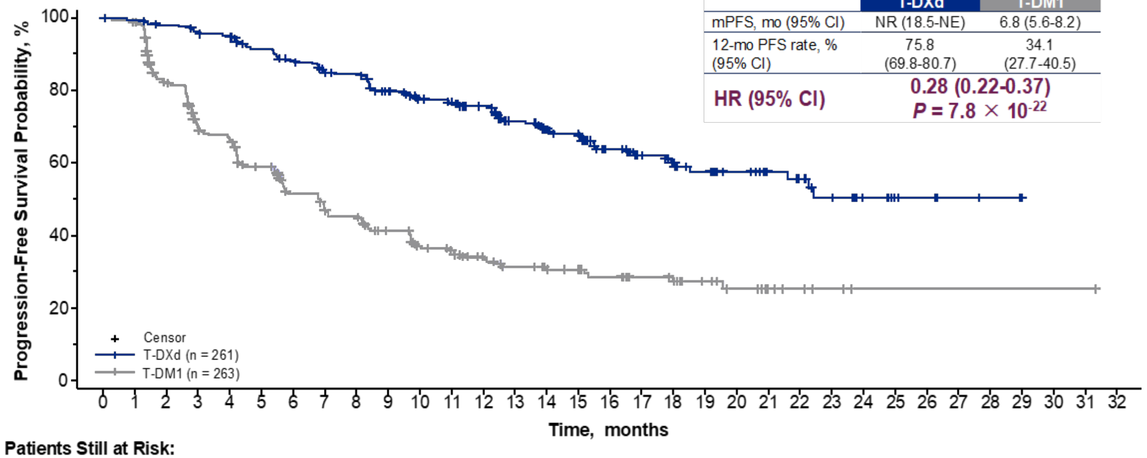
Interim analysis for PFS (data cutoff: May 21, 2021)
- Efficacy boundary for superiority: $P < 0.000204$ (based on 245 events)
- IDMC recommendation to unblind study (July 30, 2021)

Key secondary endpoint, OS: boundary for efficacy: $P < 0.000265$ (based on 86 events)

Details:
- HR+: 50%
- Brain mets: 24 vs 20%
- Prior pertuzumab: 61%
- One line of prior rx: 50 vs 47%

BICR: blinded independent central review; DOR: duration of response; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; Ph3: phase 3; Q3W: every 3 weeks.
[A] HER2 IHC3+ or IHC2+/ISH+ based on central confirmation. [b] Progression during or <6 months after completing adjuvant therapy involving trastuzumab and taxane.

Primary Endpoint: PFS by BICR

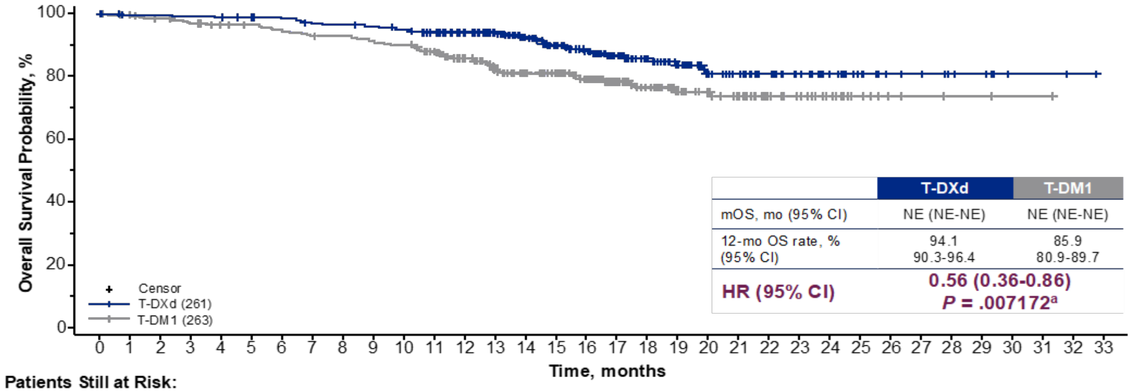


	T-DXd	T-DM1
mPFS, mo (95% CI)	NR (18.5-NE)	6.8 (5.6-8.2)
12-mo PFS rate, % (95% CI)	75.8 (69.8-80.7)	34.1 (27.7-40.5)
HR (95% CI)	0.28 (0.22-0.37) $P = 7.8 \times 10^{-22}$	

Patients Still at Risk:

T-DXd (261)	261	256	250	244	240	224	214	202	200	183	168	164	150	132	112	105	79	64	53	45	36	29	25	19	10	6	5	3	2	0
T-DM1 (263)	263	252	200	163	155	132	108	96	93	78	65	60	51	43	37	34	29	23	21	16	12	8	6	4	1	1	1	1	1	1	1	0

Key Secondary Endpoint: OS



	T-DXd	T-DM1
mOS, mo (95% CI)	NE (NE-NE)	NE (NE-NE)
12-mo OS rate, % (95% CI)	94.1 (90.3-96.4)	85.9 (80.9-89.7)
HR (95% CI)	0.56 (0.36-0.86) $P = .007172$[a]	

Patients Still at Risk:

T-DXd (261)	261	256	256	255	254	251	249	244	243	241	237	230	218	202	180	158	133	108	86	71	56	50	42	33	24	18	11	10	7	6	2	2	1	0
T-DM1 (263)	263	258	253	248	243	241	236	232	231	227	224	210	188	165	151	140	120	91	75	58	52	44	32	27	18	11	5	4	3	3	1	1	0	

Early OS data with relatively few events (33 in the T-DXd arm, 53 in the T-DM1 arm)
[a]$P = .007172$, but does not cross pre-specified boundary of $P < .000265$

PFS by Investigator Assessment

	T-DXd	T-DM1
mPFS, mo (95% CI)	25.1 (22.1-NE)	7.2 (6.8-8.3)
12-mo PFS rate, % (95% CI)	76.3 (70.4-81.2)	34.9 (28.8-41.2)
HR (95% CI)	**0.26 (0.20-0.35)** $P = 6.5 \times 10^{-24}$	

PFS in Key Subgroups

		Number of Events		Median PFS (mo, 95% CI)		HR (95% CI)
		T-DXd	T-DM1	T-DXd	T-DM1	
All patients		87/261	158/263	NE (18.5-NE)	6.8 (5.6-8.2)	0.2840 (0.2165-0.3727)
Hormone Receptor Status	Positive (n = 272)	46/133	84/139	22.4 (17.7-NE)	6.9 (4.2-9.8)	0.3191 (0.2217-0.4594)
	Negative (n = 248)	41/126	73/122	NE (18.0-NE)	6.8 (5.4-8.3)	0.2965 (0.2008-0.4378)
Prior Pertuzumab Treatment	Yes (n = 320)	57/162	98/158	NE (18.5-NE)	6.8 (5.4-8.3)	0.3050 (0.2185-0.4257)
	No (n = 204)	30/99	60/105	NE (16.5-NE)	7.0 (4.2-9.7)	0.2999 (0.1924-0.4675)
Visceral Disease	Yes (n = 384)	72/195	123/189	22.2 (16.5-NE)	5.7 (4.2-7.0)	0.2806 (0.2083-0.3779)
	No (n = 140)	15/66	35/74	NE (NE-NE)	11.3 (6.8-NE)	0.3157 (0.1718-0.5804)
Prior Lines of Therapy[a]	0-1 (n = 258)	46/132	75/126	22.4 (17.9-NE)	8.0 (5.7-9.7)	0.3302 (0.2275-0.4794)
	≥2 (n = 266)	41/129	83/137	NE (16.8-NE)	5.6 (4.2-7.1)	0.2828 (0.1933-0.4136)
Brain Metastases	Yes (n = 114)	31/62	31/52	15.0 (12.6-22.2)	5.7 (2.9-7.1)	0.3796 (0.2267-0.6357)
	No (n = 410)	56/199	127/211	NE (22.4-NE)	7.0 (5.5-9.7)	0.2665 (0.1939-0.3665)

Cortes et al, ESMO 2021

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Select HER2 ADCs Clinical Trials in GYN Cancers

Phase 2 study evaluating T-DM1 in HER2-amplified or HER2-mutant solid tumors including n=20 patients with endometrial cancer (NCT02675829)

- ORR in the endometrial cancer cohort was 25% (95% CI, 9-49)
- mDOR was not reached (95% CI, 2-25+ months)
- mPFS: 3 months (95% CI, 2-9)

STATICE, phase 2 study evaluating T-DXd in HER2-positive uterine carcinosarcoma (N=32)

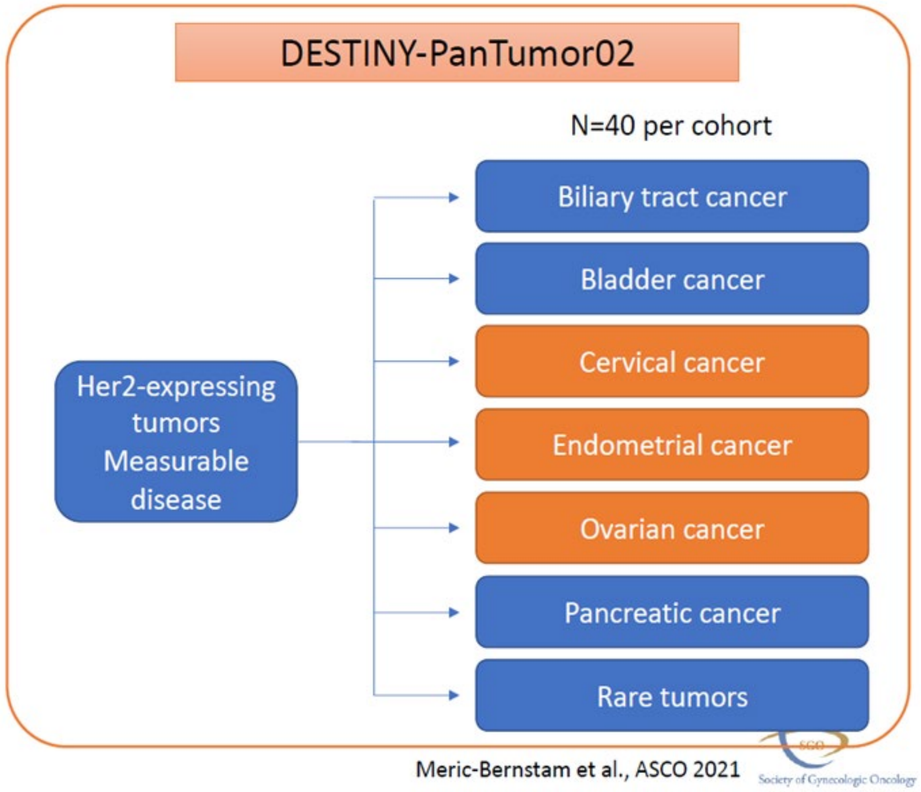
- ORR: 54.5% (95% CI, 32.2-75.6) in the HER2-high population and 70% in HER2-low
- CBR was 100% in both patient populations (no progressive disease at data cutoff)
- mPFS: 6.7 months (95% CI, 5.4-8.8); mOS: 15.8 months (95% CI, 10.5-NR)

DESTINY-PanTumor02, Phase 2, T-DXd in select advanced HER2-expressing tumors (including GYN tumors)

Phase 1/2 PETRA study, AZD5305 (PARPi) combinations (including T-DXd and Dato-DXd) in several solid tumors (including GYN tumors; NCT04644068)

Phase 1/2 trial, A166 in patients with HER-2 positive solid tumors, including patients with cervical and endometrial cancers (NCT03602079)

- Among 27 patients evaluable for efficacy 36% ORR was observed
- Promising preliminary results in endometrial cancer with response rates greater than 50%



Hasegawa K et al. *Annals of Oncology.* 2021; Li BT et al *JCO* 2018; Liu y et al *JCO* 2020

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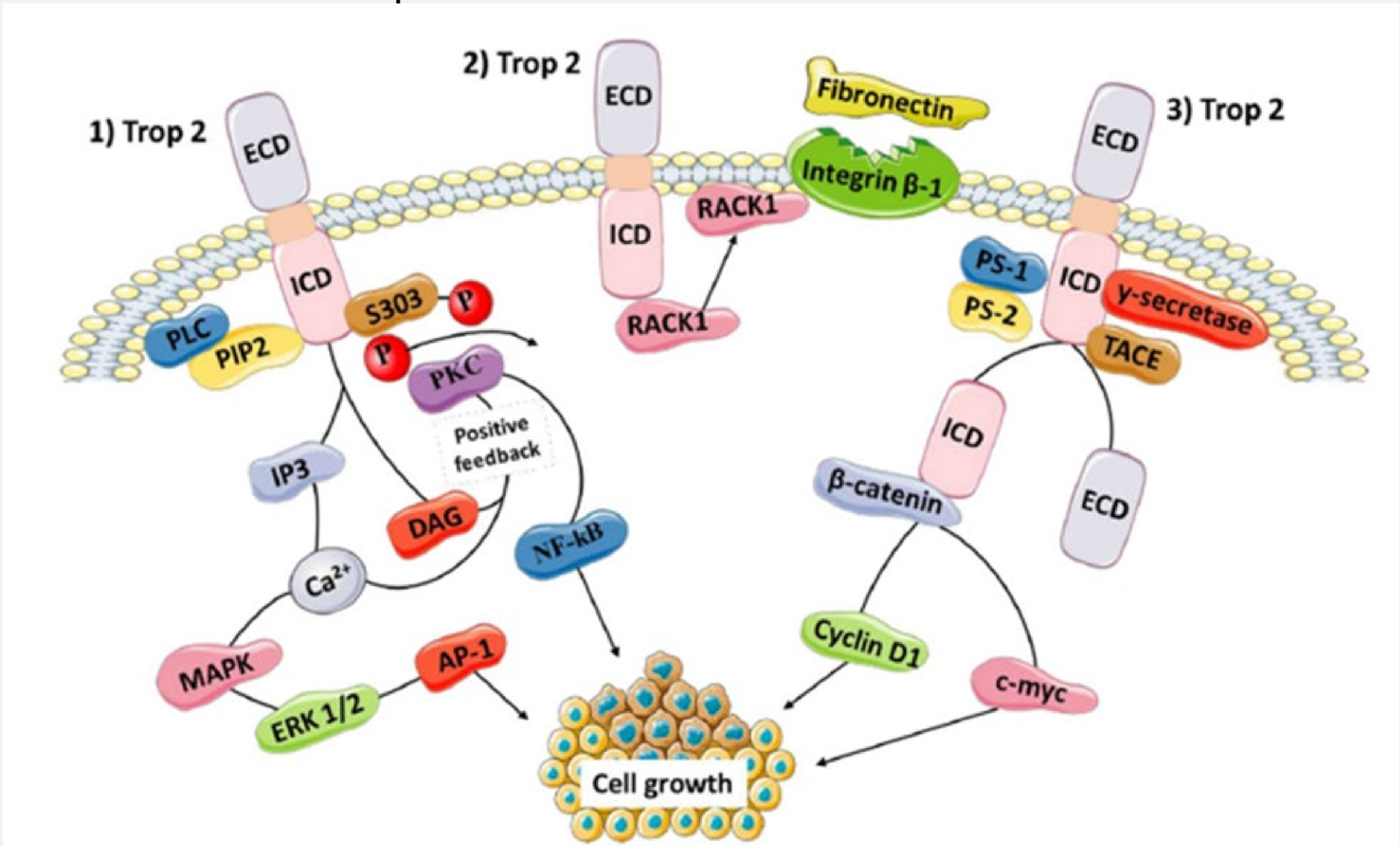
TROP-2: Tumor-Associated Calcium Transducer 2

TROP-2 promotes tumor invasion and metastasis



Liao S, Drug Development Research 2021

TROP-2 in GYN Cancers
Overview and Select ADC Clinical Trials

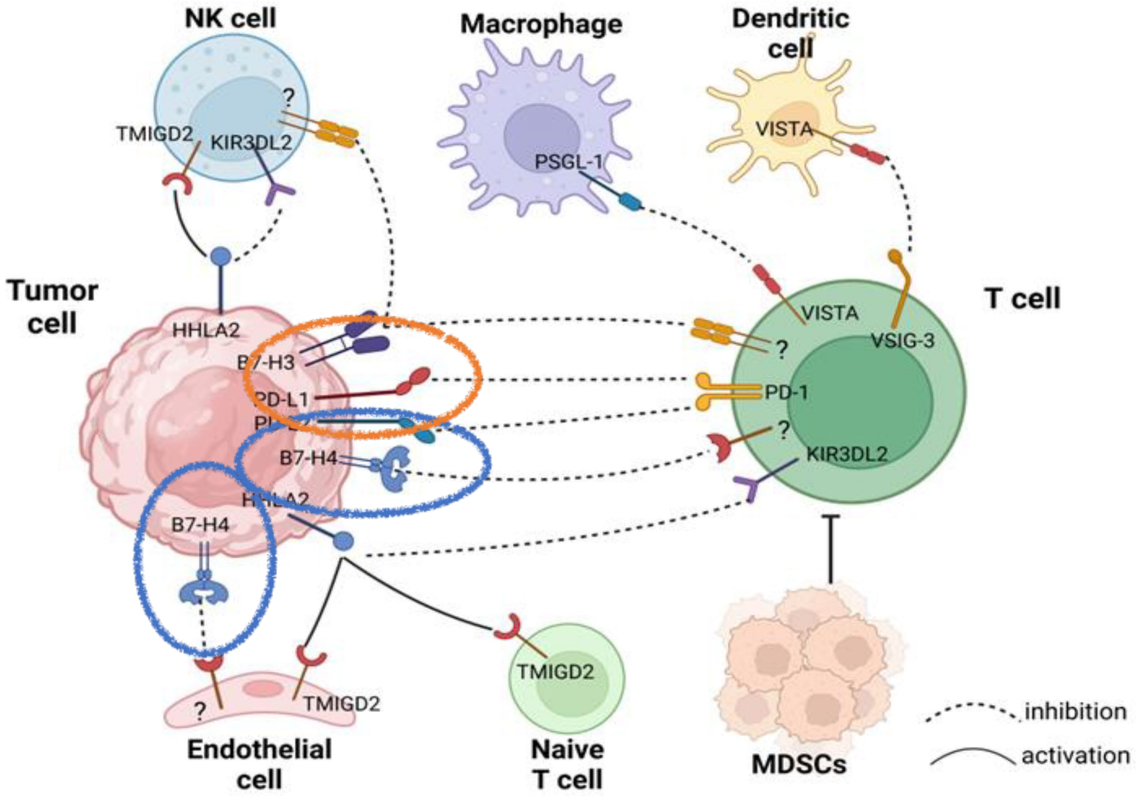
- **TROP-2 overexpression among uterine cancers**
  - 96% in endometrioid endometrial cancers (regardless of MMR status)
  - 65% in uterine serous carcinoma
  - 90% in cervical cancer
- **IMMU-132-01** basket study evaluating sacituzumab govitecan (SG) in epithelial cancers demonstrated activity in the endometrial cancer cohort with 22.2% (4/18) ORR
- **Sacituzumab govitecan phase II (NCT04251416), is currently exploring efficacy of TROP-2 ADCs in patients with persistent or recurrent endometrial cancers**
- **TROP-2 ADC clinical data in cervical and ovarian cancers is very limited, however a number of ph1 and 2 studies basket studies including these tumor types are ongoing**

Bignotti E et al J Gynecol Cancer 2011
Varughese J et al Cancer 2011
Lopez S et al Oncotarget 2020; Bardia, et al, Annals of Oncology, 2021

SGN-B7H4V and SGN-PDL1V
Targeting Immune Checkpoint Inhibitors

SGN-B7H4V

- **Aby to B7-H4 ligand expressed on breast, ovarian and endometrial cancer cells**
  - Inhibitory modulator of T-cell function
  - Receptor is unknown
- **MMAE Warhead**
- **Cleavable peptide linker**
- **Currently in phase I development (NCT05194072)**



GEN-1047

- **Bispecific Aby to B7H4 and CD3**
- **Phase I**

SGN-PDL1V

- **Aby to PD-L1**
- **MMAE Warhead**
- **Cleavable peptide linker**
- **Preclinical**

Gray E, J Immune Therp Ca 2021;9:doi: 10.1136/jitc-2021-SITC2021.854

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Emerging ADC Treatment Landscape in OVC

▲ Primary completion date (Based on CT.gov unless noted)
▲ Study completion date (Based on CT.gov unless noted)
★ PDUFA date

Trials	2021	2022	2023	2024	2025	2026+	Primary Endpoint	Study Locations by Region[a]
innovaTV 208 (Ph2, N=98, Seagen) Tisotumab vedotin with safety run-in		Feb 2022					DLTs, ORR	
SORAYA (Ph3, N=106, ImmunoGen) Single arm: Mirvetuximab soravtansine	Nov 2021	Nov 28, 2022 Dec 2022					ORR	
DESTINY-PT02 (Ph2, N=268, DSI/AZ) Trastuzumab deruxtecan			Jun 2023				ORR	
UPLIFT (Ph1b/2, N=444, Mersana) Upifitamab rilsodotin DES, EXP			Q3 2022[b]	Dec 2023			DES, EXP, ORR	
STRO-002-GM2 (Ph1, N=58, Sutro) STRO-002 + bevacizumab DES, EXP				Dec 2023 Jan 2024			DES, EXP	
QUARTZ-101 (Ph1, N=298, Exelixis) XL102 vs XL102 + fulvestrant vs XL102 + abiraterone/prednisone DES, EXP					Jun 2024 Oct 2024		MTT, ORR	
MORAb-202 (Ph1/2, N=58, Eisai) Farletuzumab ecteribulin DES, EXP					Mar 2025		DES, ORR, DLT, AE/AESI	
STRO-002-GM3 (Ph2/3, N=320, Sutro) Luveltamab					DEC 2024		PFS	

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Thank You!

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THANK YOU

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