ADCs in Ovarian Cancer

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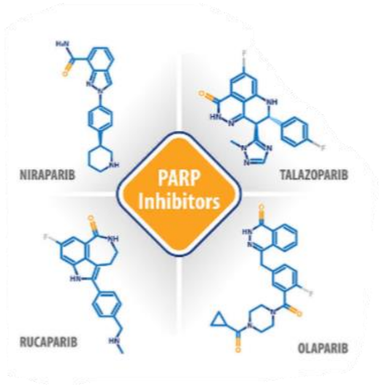
Antibody Drug Conjugates: Continuing the Paradigm Shift Towards Individualized Therapy

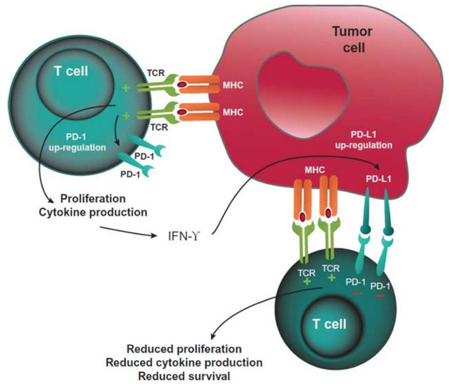
Treatment for Gynecologic Malignancies is becoming more individualized

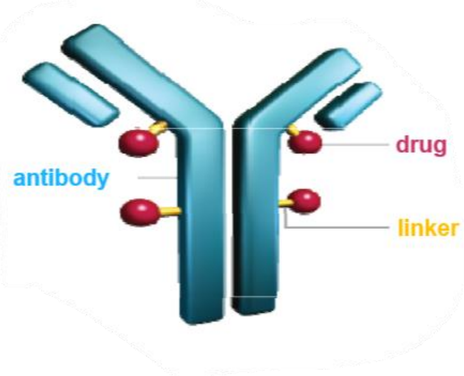
- PARP inhibition for BRCA and HRD
- Immune checkpoint inhibition for MSI-Hi/MMRd

Antibody Drug Conjugates are the next frontier in personalized therapy, allowing us to

- Target specific tumor associated antigens
- Deliver highly potent chemotherapy directly to the tumor
- Offer patients a differentiated safety profile
- Offer combination therapies in the near future which may replace standard, systemic chemotherapy







Buchbinder et al. Am J Clin Oncol. 2016

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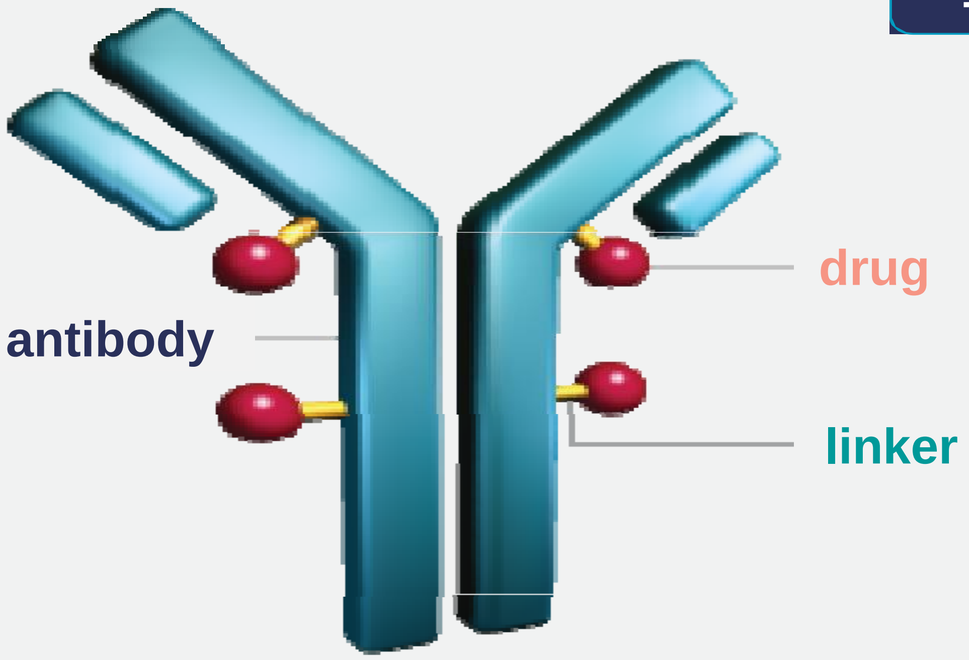
ADC’s Highly Engineered Components



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)

ADCs are already changing the landscape in oncology

Generic Name	Conjugate	Indication	Target	Year approved
Gemtuzumab ozogamicin	Calcheamicin	Hematological	CD33	2010/2017
Brentuximab vedotin	Monomethyl Auristatin E (MMAE)	Hematological	CD30	2011
Inotuzumab ozogamicin	Calcheamicin	Hematological	CD22	2017
Polatuzumab vedotin	MMAE	Hematological	CD79b	2019
Trastuzumab emtansne	Maytansinoid (DM1)	Solid tumor	HER2	2013
Trastuzumab deruxtecan	Deruxtecan (Dxd)	Solid tumor	HER2	2019
Enfortumab vedotin	MMAE	Solid tumor	Nectin-4	2019
Sacituzumab govtecan	Govitecan SN-38	Solid tumor	Trop-2	2020
Belantamab mafodotin	MMAF	Myeloma	BCMA	2020
Loncastuximab tesrine-lpyl	SG3199	B-cell lymphoma	CD19	2021
Tisotumab vedotin	MMAE	Solid tumor (cervix)	Tissue Factor	2021
Mirvatuximab Soravtansine	DM4	Ovarian	FRα	2022

Pettinato. Antibodies 2021, 10, 42; https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-tisotumab-vedotin-tftv-recurrent-or-metastatic-cervical-cancer - accessed January 19, 2022

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ADCs in Gynecologic Cancers

Generic Name	Conjugate	Indication	Target	Phase	NCT
Mirvetuximab soravtansine	Maytansinoid (DM4)	Ovary	Folate Receptor α	3: Gloriosa 3: MIRASOL 2: SORAYA 2: PICCOLO	NCT05445778 NCT04209855 NCT04296890 NCT05041257
STRO-002 Luveltamab Tazevibulin	SC209 (tubulin targeting)	Ovary	Folate Receptor α	2/3	NCT03748186 NCT05200364
MORAb-202	Eribulin	Ovary	Folate Receptor α	2	NCT05613088
Upifitamab Rilsodotin	AF-HPA (DolaLOck-controlled bystander effect)	Ovary	NaPi2b	2 UPLIFT 3: UP-NEXT	NCT03319628 NCT05329545
Sacituzumab Govitecan (IMMU-132)	SN-38 (metabolite of topo 1 inhibitor)	Solid tumor (endo)	TROP2	2	NCT04251416
KL 264 01/SKB264	Belotecan (novel camptothecin derivative)	Solid tumors	TROP2	1	NCT04152499
BDC-1001	TLR 7/8 dual agonist	Solid tumor	HER2	1	NCT04278144
DB1303	Topoisomerase 1 inhibitor (P1003)	Solid tumor (endo)	HER2	1	NCT05150691
Ado-trastuzumab emtansine	DM1	Solid tumor (endo & ovary)	HER2	2	NCT04439110
Trastuzumab Deruxtecan	Deruxtecan	Solid tumor (endo, ovary, cervix)	HER2	2	NCT04482309
Trastuzumab duocarmycin	Duocarmycin	Solid tumor (endo)	HER2	2	NCT04205630
DS6000a	deruxtecan	Solid tumor	CDH6	1	NCT04707248
XB002	auristatin	Solid tumor	TF	1	NCT04925284
Tisotumab vedotin	MMAE	Cervix	TF	3	NCT04697628

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

PD-1/PD-L1
IL-2 Cytokine
ADC
AXL decoy protein
TTFields
GRA

Trials	2021	2022	2023	2024	2025	2026+	Primary Endpoint	Study Locations by Region
innovaTV 204 (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	

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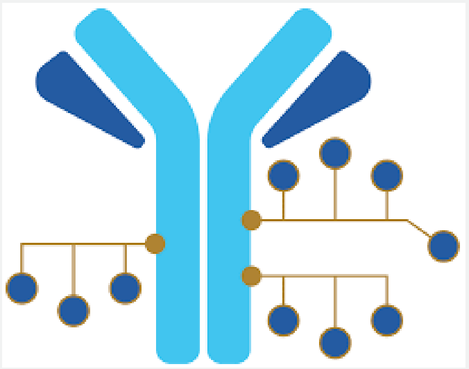
Upifitamab Rilsodotin (UpRi) – First-in-Class ADC Targeting NaPi2b



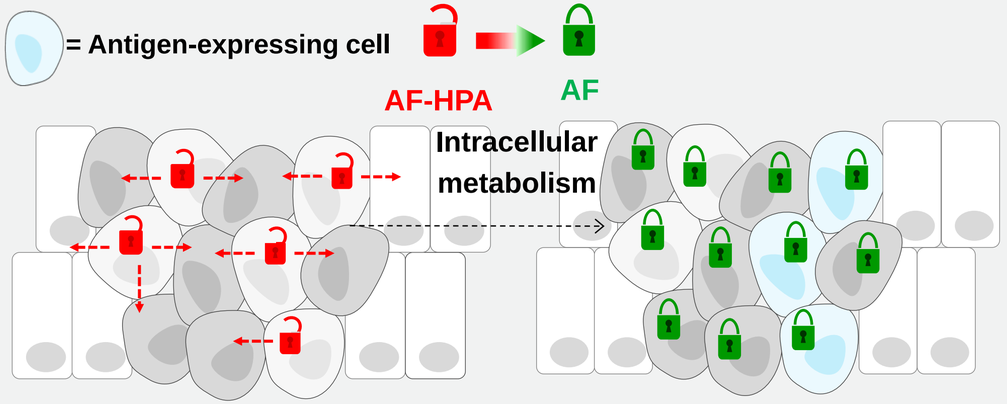
UpRi

Antibody: Humanized monoclonal anti-NaPi2b[1]

Linker: Polymer scaffold; cleavable ester linker[2]

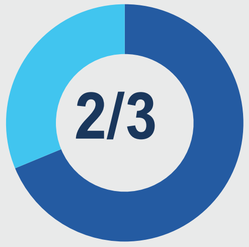
Payload: AF-HPA (DolaLock-controlled bystander effect)[1]

Drug-to-Antibody Ratio: ~10

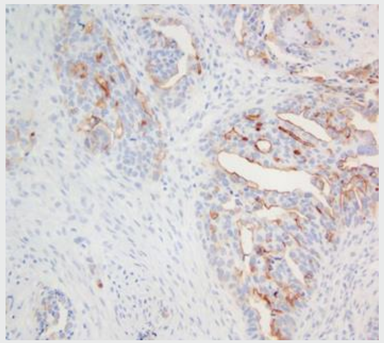


Upon ADC internalization into tumor cells and efficient release of payload, AF-HPA payload is metabolized to AF that remains highly potent but loses the ability to cross the cell membrane, locking it in the tumor, controlling the bystander effect, and consequently limiting impact on adjacent healthy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

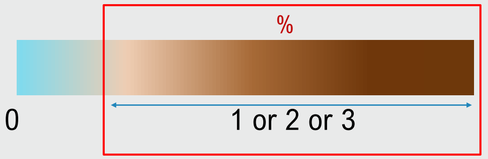
NaPi2b Is a Sodium-Dependent Phosphate Transporter Broadly Expressed in Ovarian Cancer With Limited Expression in Healthy Tissues[4]



- 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]



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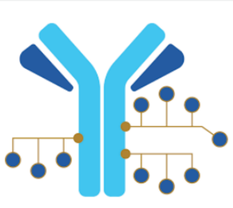
Antibody Drug Conjugates (ADCs) Are Emerging as Highly Active Therapeutics in Gynecologic Cancers: Upifitamab Rilsdotin

Upifitamab Rilsdotin



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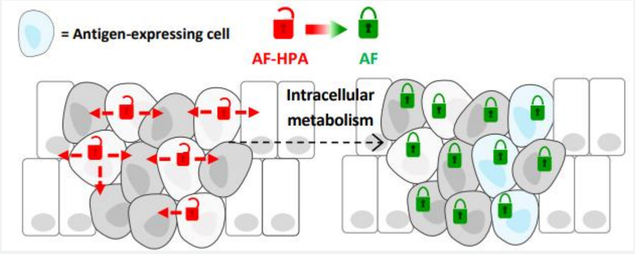
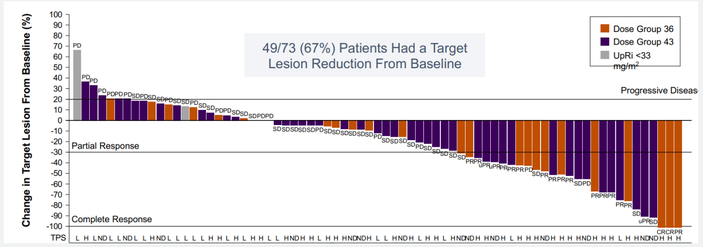


ADC targeting the sodium gated phosphate channel conjugated with AF-HPA (Dola-Lock controlled bystander effect)

Efficacy

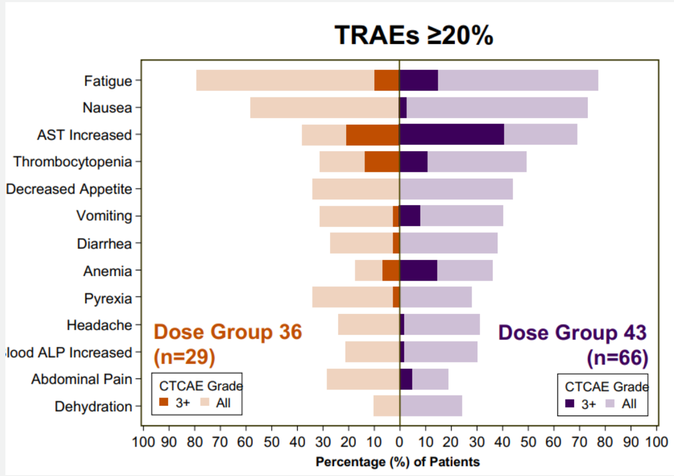


		All Dose Levels	Dose Group 36	Dose Group 43
NaPi2b-High (TPS ≥75)	N	38	16	22
	ORR, n (%)	**13 (34)**	**7 (44)**	**6 (27)**
	CR, n (%)	2 (5)	2 (13)	0
	PR, n (%)	11 (29)	5 (31)	6 (27)
	DCR, n (%)	33 (87)	12 (75)	21 (95)
All NaPi2b Levels	N	75	25	48
	ORR, n (%)	**17 (23)**	**9 (36)**	**8 (17)**
	CR, n (%)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

Richardson et al. SGO 2022

Key TRAEs



Pneumonitis:
43mg/m²: G1-2 (5); G3+ (4)
36mg/m²: G1-2 (2); G3+ (0)

On partial clinical hold as of 6/15/23

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ENGOT-ov67 / GOG-3048

UpRi Single-Arm Registrational Trial in Platinum-Resistant Ovarian Cancer

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

[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.

NCT03319628;
(FPD April 2021)

GOG-3049 / ENGOT-OV71-NSGO-CTU

Phase 3 Study of UpRi Monotherapy Maintenance vs Placebo in Recurrent Platinum-Sensitive Ovarian Cancer

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

Informed by FDA Feedback and CHMP Scientific Advice; Partial Clinical Hold

Phase 1 UpRi Combination Studies

UPGRADE

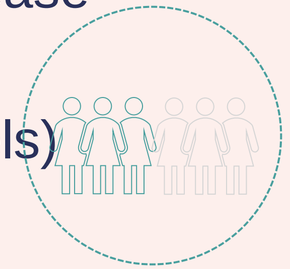
On Partial Clinical Hold as of 6/15/23

UPGRADE-A (UpRi/Carbo)

- Regimen: UpRi/carbo Q4W up to 6 cycles → UpRi maintenance
- Key eligibility
  - PSOC, 1 – 2 prior LOT
- Primary endpoints/sample size
  - DES = MTD (n=18)
  - EXP = Feasibility (n=30)

(UpRi/Bev)

- Regimen: UpRi/bev
- Key eligibility
  - Inclusion:
    - PROC, PSOC
    - Up to 1 prior bev containing regimen; no contraindications to bev
  - Exclusion
    - Primary platinum-refractory disease
- Primary endpoints/sample size
  - DES = MTD (n=6 x # of dose levels)
  - EXP = Feasibility (n=30)

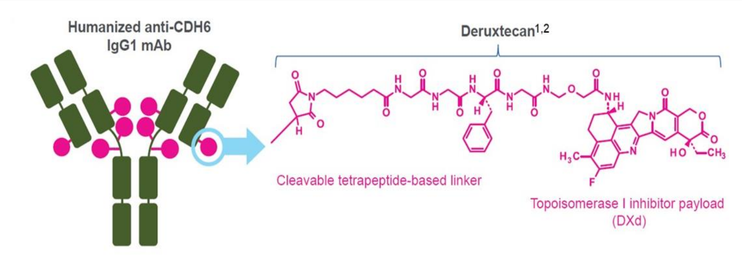


bev, bevacizumab; carbo, carboplatin; DES, dose escalation study; EXP, dose expansion; LOT, lines of therapy; MTD, maximum tolerated dose; PROC, platinum-resistant ovarian cancer; Q4W, every 4 weeks, PSOC, platinum-sensitive ovarian cancer; UpRi, upifitamab rilsodotin.

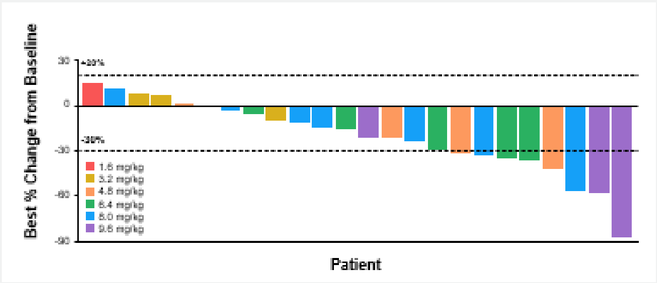
NCT04907968; trial currently enrolling patients (FPD July 2021)
Additional combination cohorts will be added

Antibody Drug Conjugates (ADCs) Are Emerging as Highly Active Therapeutics in Gynecologic Cancers: Claudin 6 and TROP2 Targets

DS-6000 in Ovarian



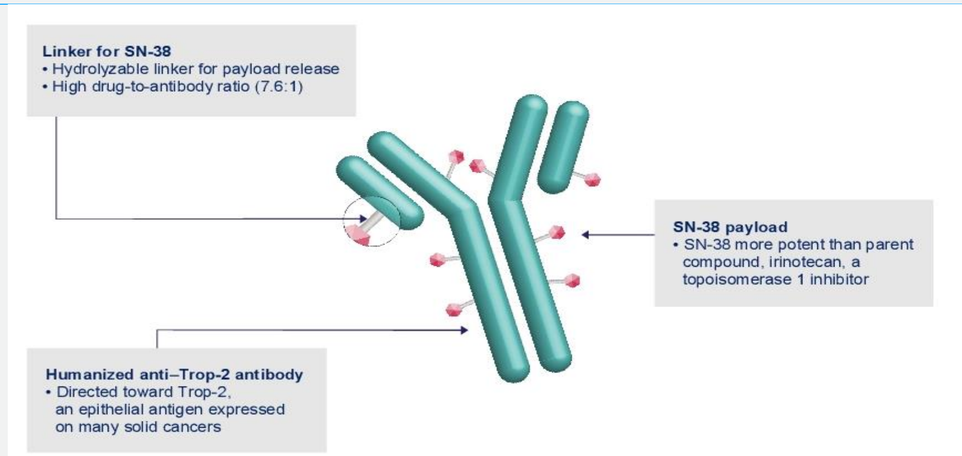
- A humanized anti-CDH6 IgG1 monoclonal antibody covalently linked to
- A topoisomerase I inhibitor payload, an exatecan derivative, via
- A tetrapeptide-based cleavable linker

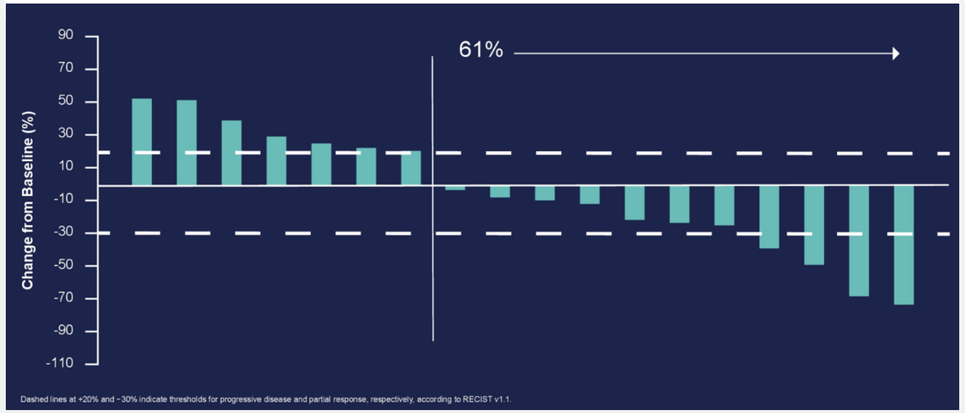


TRAEs:
G3 neutrophils
G2 pneumonits (both appear dose related)

Hamilton et al. ASCO 2022

Sacituzumab Govitecan in Endometrial





Santin AD et la. ASCO 2020; Bardia et al. Ann Oncol. 2021 32(6): 746

TRAE All G/G ≥ 3
Nausea 83%/3.6%
Diarrhea 67%/7.9%
Neutropenia 56%/27.5%
FN 5.3%

Reduction in tumor size from baseline observed in 61% (11/18)
DOR NR (9.1- 26.6 mos)
ORR 22% (95% CI 6.4, 47.6)

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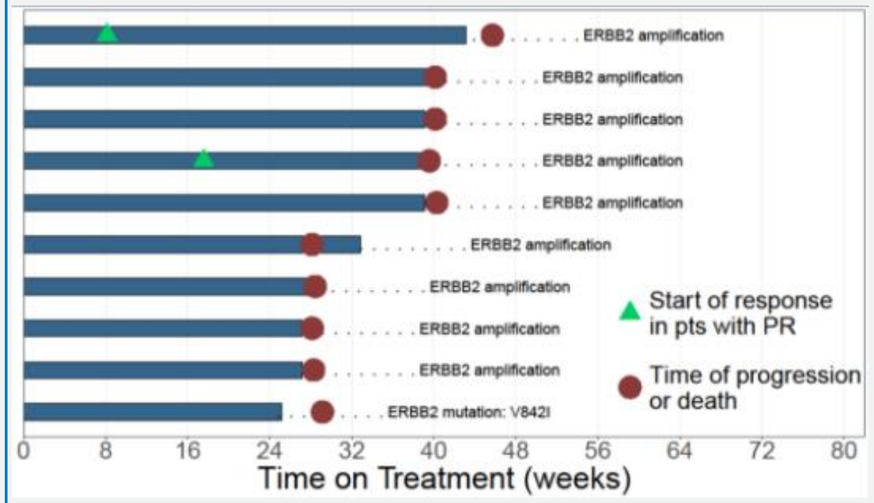
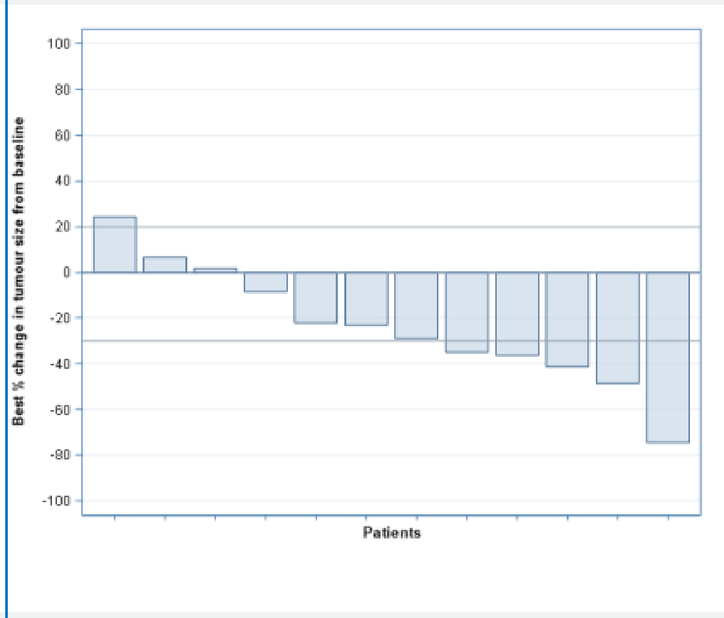
Antibody Drug Conjugates (ADCs) Are Emerging as Highly Active Therapeutics in Gynecologic Cancers: Targeting HER2

Trastuzumab and Pertuzumab HER2 +(amp, mut, over-expression) ORR 7%



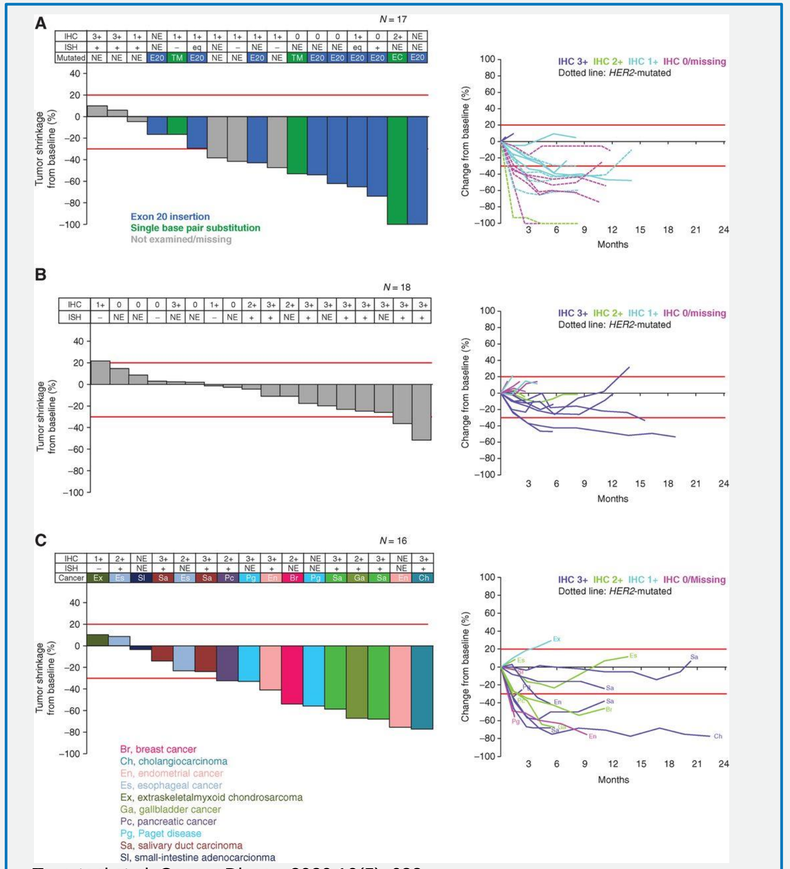
Ali-Ahmad et al. ASCO abs 5508 2021

Trastuzumab duocarmazine N=14 (12 eval) ORR 50%



Banerji et al. Lancet Oncol 2019

Trastuzumab deruxtecan

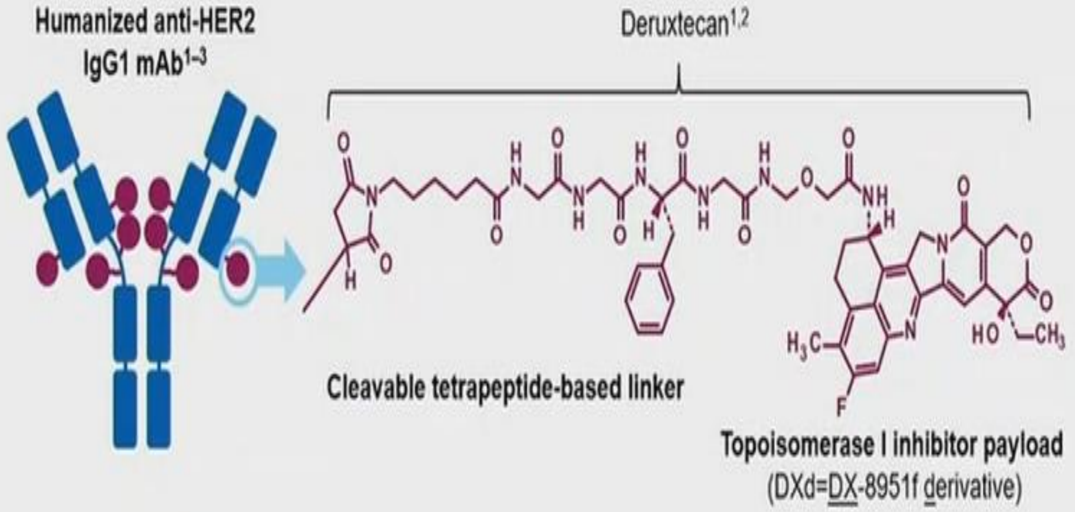


Tsurutani et al. Cancer Discov. 2020 10(5): 688

Efficacy and safety of trastuzumab deruxtecan in patients with HER2 expressing solid tumors: DESTINY PanTumor 02 interim results

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



An open-label, multicenter study (NCT04482309)

- 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

Meric-Bernstam et al. ASCO 2023 LBA 3000

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Efficacy endpoints: ORR, DCR and DOR

		Cervical (n=40)	Endometrial (n=40)	Ovarian (n=40)	BTC (n=41)	Pancreatic (n=25)	Bladder (n=41)	Other (n=40)	All patients (N=267)
Investigator assessment									
ORR, n (%)		**20 (50.0)**	**23 (57.5)**	**18 (45.0)**	**9 (22.0)**	**1 (4.0)**	**16 (39.0)**	**12 (30.0)**	**99 (37.1)**
Best overall response, n (%)	Complete response	2 (5.0)	7 (17.5)	4 (10.0)	1 (2.4)	0	1 (2.4)	0	15 (5.6)
	Partial response	18 (45.0)	16 (40.0)	14 (35.0)	8 (19.5)	1 (4.0)	15 (36.6)	12 (30.0)	84 (31.5)
	Stable disease	12 (30.0)	13 (32.5)	14 (35.0)	25 (61.0)	17 (68.0)	18 (43.9)	24 (60.0)	123 (46.1)
	PD	7 (17.5)	4 (10.0)	7 (17.5)	7 (17.1)	7 (28.0)	7 (17.1)	3 (7.5)	42 (15.7)
	Not evaluable	1 (2.5)	0	1 (2.5)	0	0	0	1 (2.5)	3 (1.1)
DCR[a] at 12 weeks, n (%)		27 (67.5)	32 (80.0)	28 (70.0)	27 (65.9)	9 (36.0)	29 (70.7)	30 (75.0)	182 (68.2)
Median DOR, months (95% CI)		9.8 (4.2–NE)	NR (9.9–NE)	11.3 (4.1–NE)	8.6 (2.1–NE)	NR	8.7 (4.3–11.8)	NR (4.1–NE)	11.8 (9.8–NE)
Independent central review: ORR, n (%)		16 (40.0)	21 (52.5)	17 (42.5)	11 (26.8)	3 (12.0)	17 (41.5)	13 (32.5)	98 (36.7)

Analysis of response and DCR was performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of DOR was performed in patients with objective response who received ≥1 dose of T-DXd (n=99).
[a]Confirmed complete response, confirmed partial response or stable disease.
BTC, biliary tract cancer; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not estimable; NR, not reached; ORR, objective response rate; PD, progressive disease.

Meric-Bernstam et al. ASCO 2023 LBA 3000

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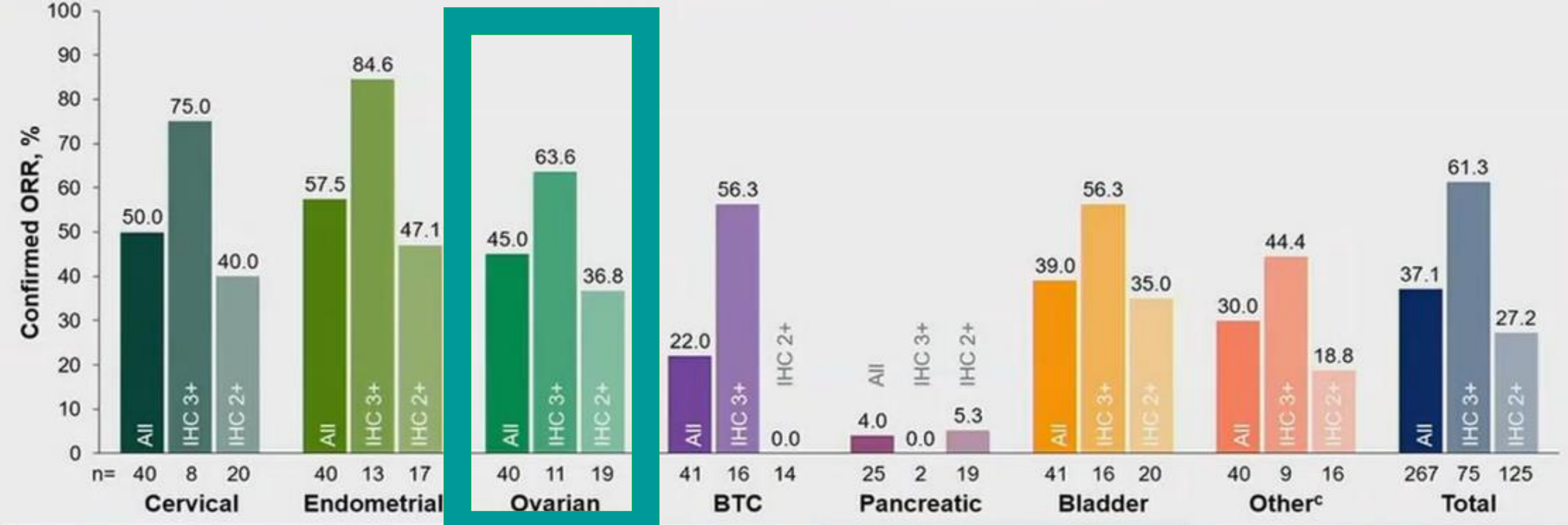
Objective Response Rate by HER2 status



	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.

Meric-Bernstam et al. ASCO 2023 LBA 3000

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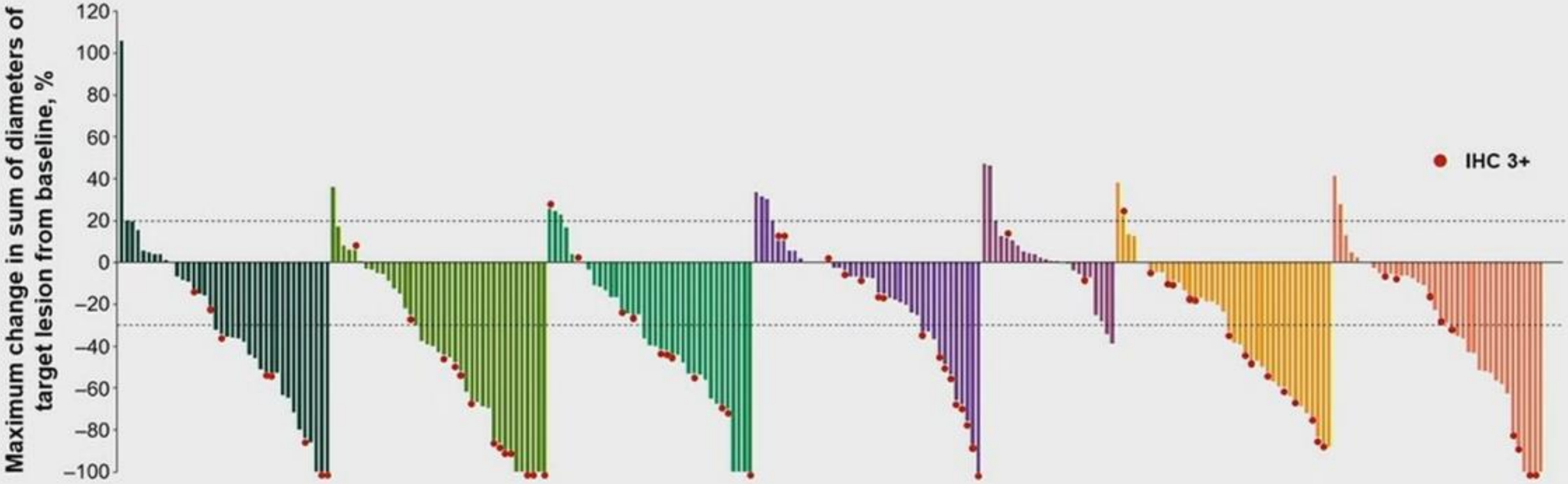
Best Percentage Change in Target Lesion From Baseline



ORR in IHC 3+ n (%)	Cervical (n=8)	Endometrial (n=13)	Ovarian (n=11)	BTC (n=16)	Pancreatic (n=2)	Bladder (n=16)	Other[a] (n=9)
	6 (75.0)	11 (84.6)	7 (63.6)	9 (56.3)	0	9 (56.3)	4 (44.4)

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). Analysis of ORR in IHC 3+ was performed in patients with centrally confirmed HER2 status (n=75).
[a]Responses in extramammary Paget's disease, head and neck cancer, oropharyngeal neoplasm, and salivary gland cancer.
BTC, biliary tract cancer; IHC, immunohistochemistry; ORR, objective response rate.

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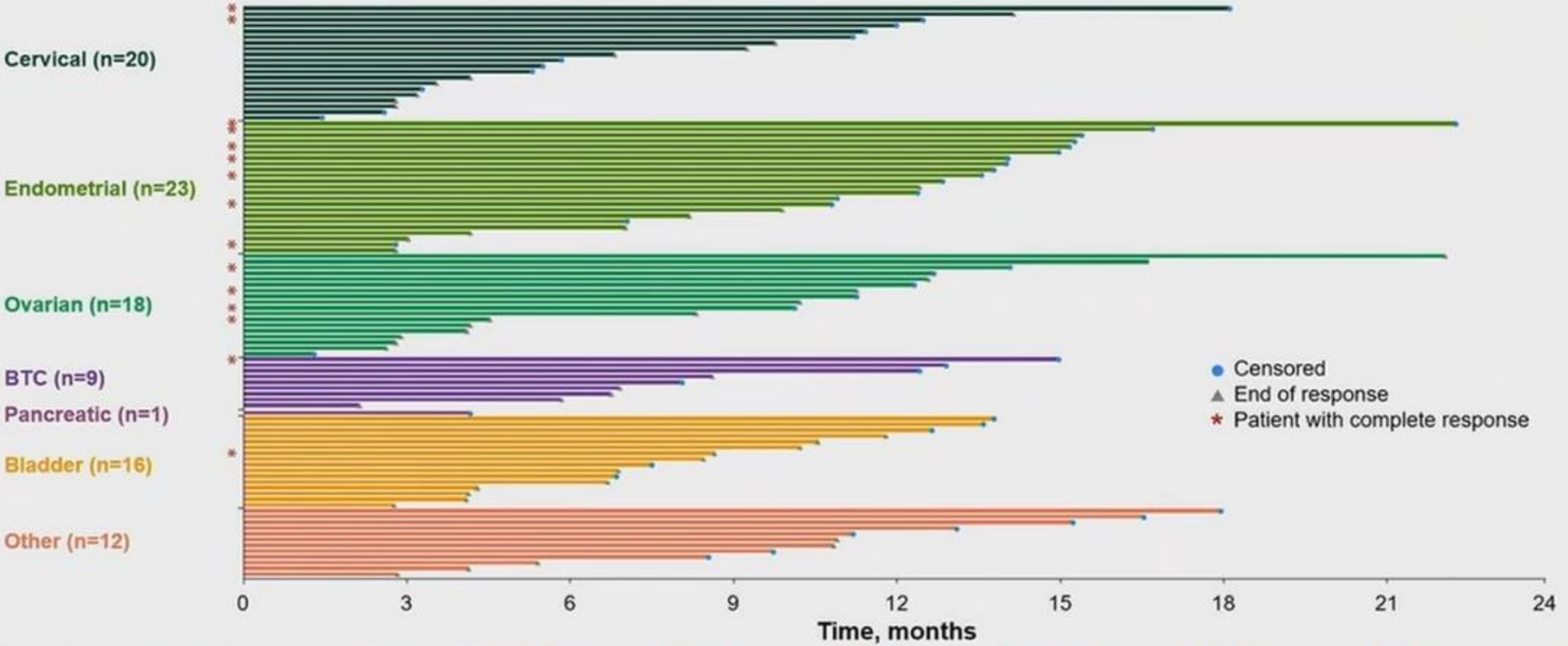
Duration of Objective Response



Kaplan-Meier estimate of response at 12 months (%)	Cervical	Endometrial	Ovarian	BTC	Pancreatic	Bladder	Other	All
	47.6	72.3	45.8	41.7	0	23.2	53.6	49.6

Analyses were performed in patients with objective response who received ≥1 dose of T-DXd (n=99). At data cut-off, 44 patients (16.5%) are still ongoing treatment, and 128 patients (47.9%) remain in the study. BTC, biliary tract cancer.

Meric-Bernstam et al. ASCO 2023 LBA 3000

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Adverse Events of Special Interest

ILD/pneumonitis adjudicated as T-DXd–related

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N=267)	6 (2.2)	12 (4.5)	1 (0.4)	0	1 (0.4)	20 (7.5)

Left ventricular dysfunction[a]

n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
Ejection fraction decreased						
All patients (N=267)	1 (0.4)	4 (1.5)	1 (0.4)	0	0	7 (2.6)[b]
Cardiac failure						
All patients (N=267)	0	0	1 (0.4)	0	0	1 (0.4)

Analyses were performed in patients who received ≥1 dose of T-DXd (n=267).
[a]Left ventricular dysfunction was reported in a total of 12 (4.5%) patients, of which 8 (3.0%) were considered possibly T-DXd–related. [b]One patient had unknown grade of ejection fraction decrease.
ILD, interstitial lung disease; T-DXd, trastuzumab deruxtecan.

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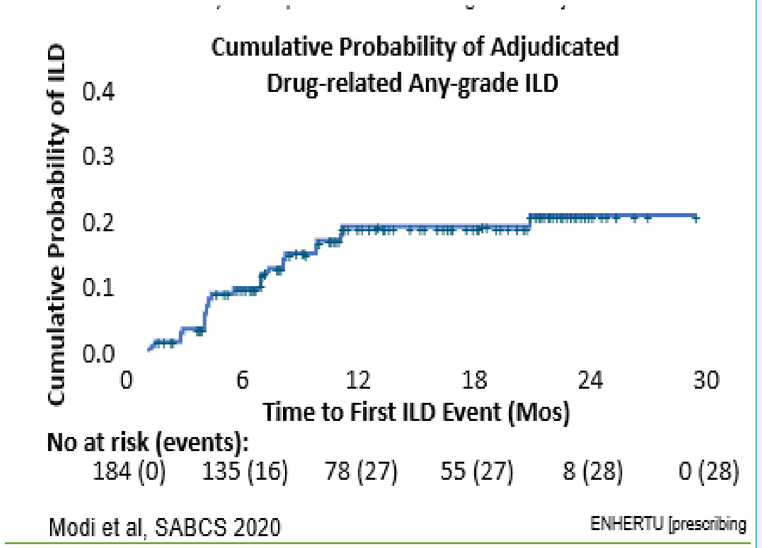
Antibody Drug Conjugates (ADCs)
Mitigation of Treatment Related Adverse Events: Pneumonitis

Incidence over time



Mitigation

Interrupt trastuzumab deruxtecan and initiate corticosteroid treatment if ILD/pneumonitis is suspected

Promptly Investigate Evidence of ILD

- Evaluate patients with suspected ILD by radiographic imaging
- Consider consultation with a pulmonologist

For Asymptomatic ILD (Grade 1)

- Consider corticosteroid treatment (eg, ≥ 0.5 mg/kg prednisone or equivalent)
- Withhold trastuzumab deruxtecan until recovery to Grade 0
  - If resolved in ≤ 28 days from date of onset, maintain dose
  - If resolved in > 28 days from date of onset, reduce dose one level

For Symptomatic ILD (Grade ≥ 2)

- Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg prednisone or equivalent)
- Permanently discontinue trastuzumab deruxtecan

Results of Mitigation

Updated toxicity management guidelines implemented (December 2019)

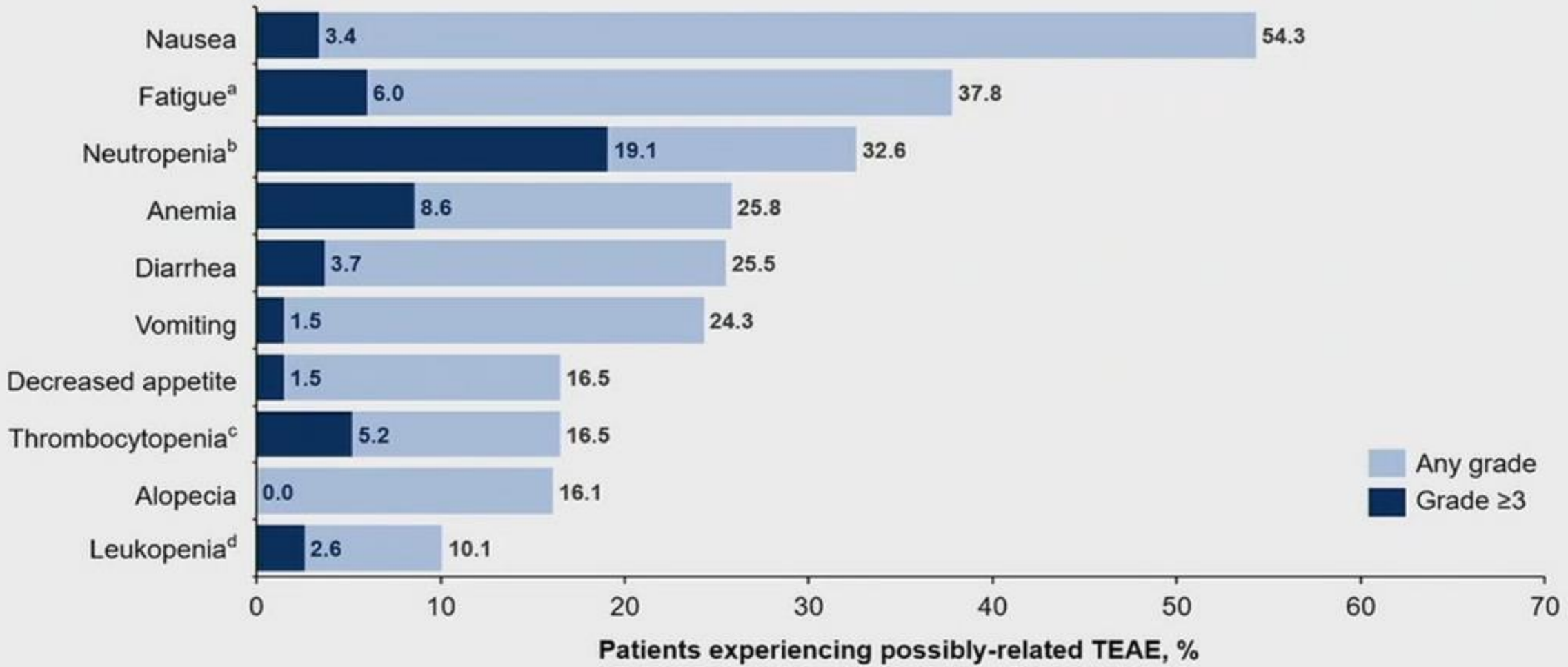
Incidence of ILD over time

	2016 (n=74)	2017 (n=168)	2018 (n=569)	2019 (n=179)	2020 (n=160)
Any Grade ILD, n (%)	18 (24.3)	33 (19.6)	87 (15.3)	28 (15.6)	11 (6.9)
Grade ≥3 ILD, n (%)	2 (2.7)	6 (3.6)	21 (3.7)	8 (4.5)	3 (1.9)
Grade 5 ILD, n (%)	1 (1.4)	5 (3.0)	12 (2.1)	5 (2.8)	2 (1.3)

Patients grouped by year of enrollment, based on a data snapshot from **December 2020**.

Patients enrolled in 2020 (after implementation of toxicity management guidelines) appear to have had lower rates of all grade (6.9%), grade > 3 (1.9%) and grade 5 ILD (1.3%) compared with those enrolled in previous years

Drug-Related TEAEs in ≥10% of Patients



Analyses were performed in patients who received ≥1 dose of T-DXd (n=267). [a]This category includes the preferred terms fatigue, asthenia, and malaise. [b]This category includes the preferred terms neutrophil count decreased and neutropenia. [c]This category includes the preferred terms platelet count decreased and thrombocytopenia. [d]This category includes the preferred terms white blood cell count decreased and leukopenia.
TEAE, treatment-emergent adverse event; T-DXd, trastuzumab deruxtecan.

Meric-Bernstam et al. ASCO 2023 LBA 3000

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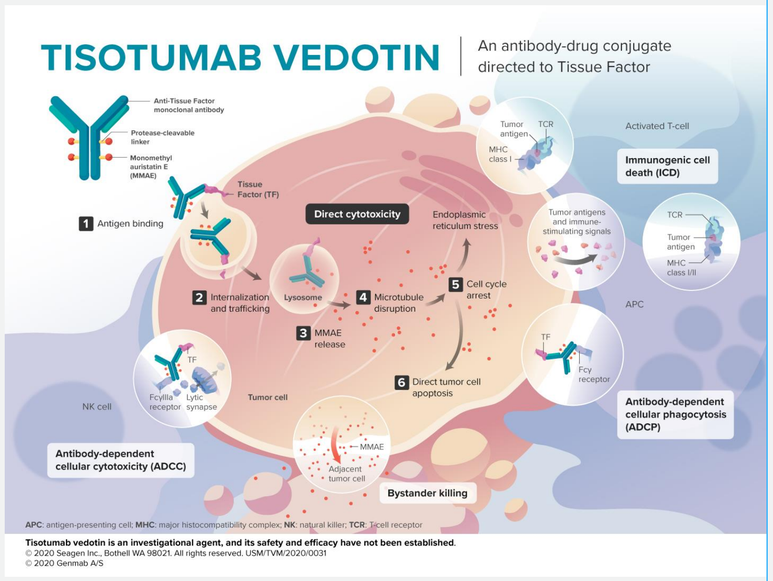
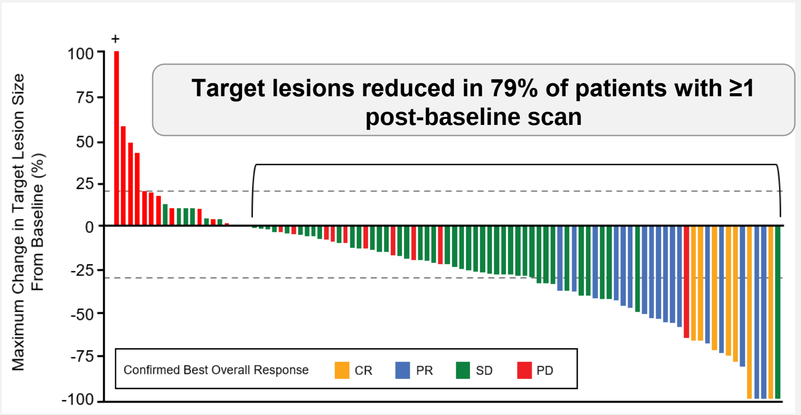
Antibody Drug Conjugates (ADCs) Are Emerging as Highly Active Therapeutics in Gynecologic Cancers: Tisotumab Vedotin

Tisotumab vedotin: MOA



ADC targeting tissue factor (TF) conjugated with Monomethyl auristatin E (MMAE), a microtubule-disrupting agent

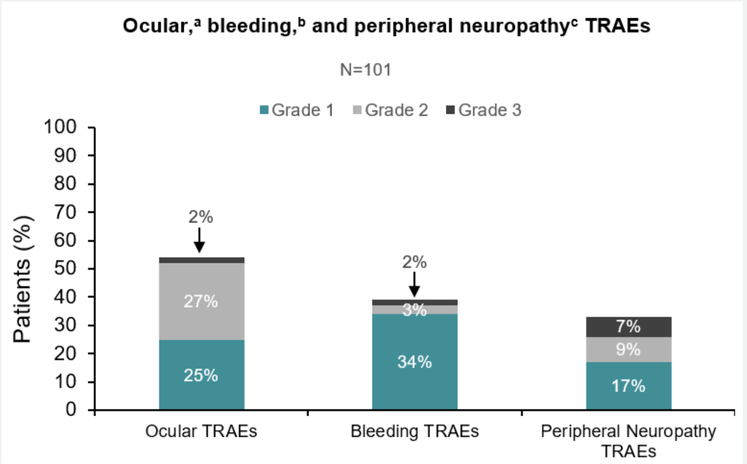
Efficacy- Cervical Cancer



	N=101
Confirmed ORR (95% CI),[a] %	**24 (15.9–33.3)**
CR, n (%)	7 (7)
PR, n (%)	17 (17)
SD, n (%)	49 (49)
PD, n (%)	24 (24)
Not evaluable, n (%)	4 (4)

Coleman RL, et al. Presented at ESMO Congress 2020, virtual. Abstract LBA24.

Key TRAEs



	Ocular	Bleeding	Peripheral Neuropathy
Time to onset (median, months)	1.4	0.3	3.1
Events resolved, %	86	90	21
Time to resolution[d] (median, months)	0.7	0.5	0.6

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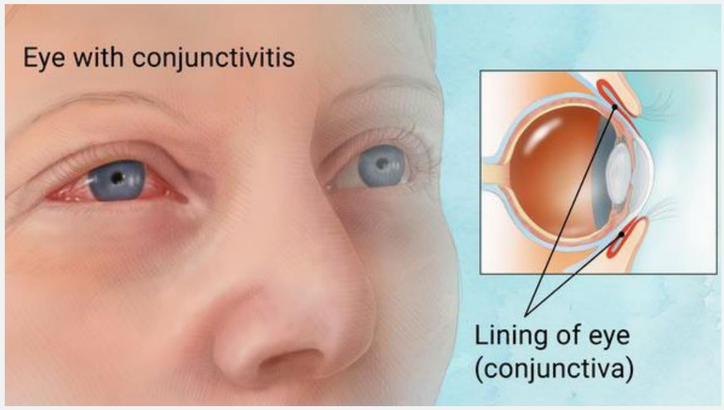
Antibody Drug Conjugates (ADCs)
Mitigation of Treatment Related Adverse Events: Ocular

Tisotumab vedotin:
Ocular TRAEs: Conjunctivitis

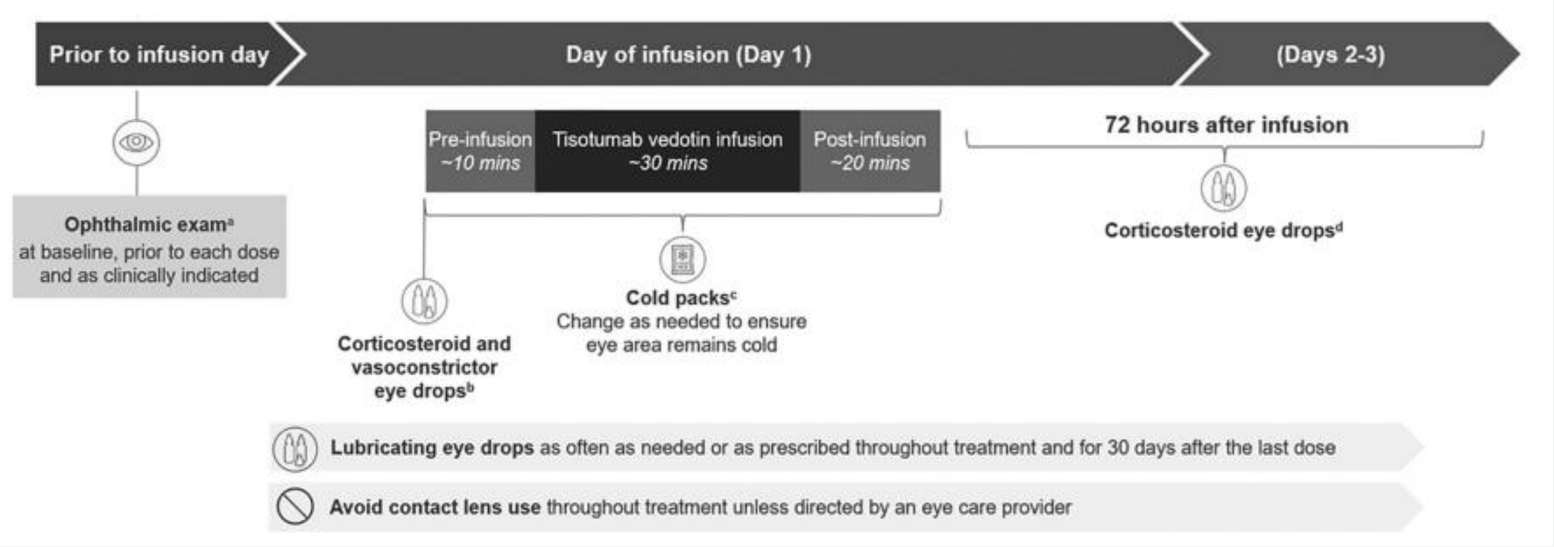


Ocular adverse events regardless of causality		
Incidence, n (%)	**N=101**	
	Any grade	**Grade 3**
Patients with ≥1 ocular AE	55 (54)	3 (3)
Ocular AE in ≥5 patients		
Conjunctivitis	31 (31)	0
Dry eye	25 (25)	0
Keratitis	11 (11)	0
Blepharitis	7 (7)	0
Punctate keratitis	6 (6)	0

Coleman et al. Lancet Oncol 2021

Mitigation

- 5% of patients discontinued treatment due to ocular TEAEs
- 20% of patients required dose reductions due to ocular TEAEs
- The only Grade 3 ocular TEAE was ulcerative keratitis (3%)



Kim et al. Gynecol Onc 2022

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Mitigation and management strategies for ocular events associated with tisotumab vedotin

Stella K. Kim [a,*], Paul Ursell [b], Robert L. Coleman [c], Bradley J. Monk [d], Ignace Vergote [e]

CTCAE term	Definition	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Conjunctivitis	A disorder characterized by inflammation, swelling and redness to the conjunctiva of the eye	Asymptomatic or mild symptoms; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best correct visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); limited self-care ADL	Best corrected visual acuity of 20/200 or worse in the affected eye	–
Dry eye	A disorder characterized by dryness of the cornea and conjunctiva	Asymptomatic; clinical or diagnostic observations only; symptoms relieved by lubricants	Symptomatic; moderate decreased in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decreased in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline; up to 20/200); limiting self-care ADL	–	–
Keratitis	A disorder characterized by inflammation to the cornea of the eye	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; moderate decrease in visual acuity (best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline)	Symptomatic with marked decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200); corneal ulcer; limiting self-care ADL	Perforation; best corrected visual acuity of 20/200 or worse in the affected eye	–
Eye disorders, other	–	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated	Moderate; minimal, local or noninvasive intervention indicated; limiting instrumental ADL; best corrected visual acuity 20/40 and better or 3 lines or less decreased vision from known baseline	Severe or medically significant but not immediately sight-threatening; limiting self care ADL; decrease in visual acuity (best corrected visual acuity worse than 20/40 or more than 3 lines of decreased vision from known baseline, up to 20/200	Sight-threatening consequences; urgent intervention indicated; best corrected visual acuity of 20/200 or worse in the affected eye	–

Grade 1 ocular disorders are without symptoms – no change in therapy is necessary

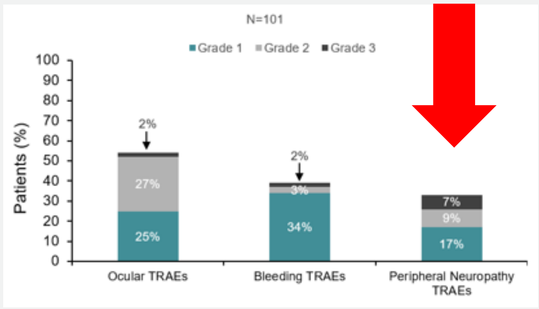
Grade 2 ocular disorders have symptoms and treatment should be held until symptoms resolved (grade 1) and then can restart at same dose

Second occurrence of Grade 2 or Grade 3 requires does hold and dose reduction

Grade 4 should result in permanent d/c

Antibody Drug Conjugates (ADCs)
Treatment Related Adverse Events: Neuropathy & Fever

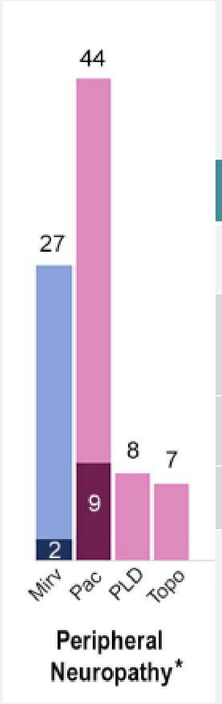
Tisotumab vedotin



	Ocular	Bleeding	Peripheral Neuropathy
Time to onset (median, months)	1.4	0.3	3.1
Events resolved, %	86	90	21
Time to resolution[d] (median, months)	0.7	0.5	0.6

Coleman et al. Lancet Oncol 2021

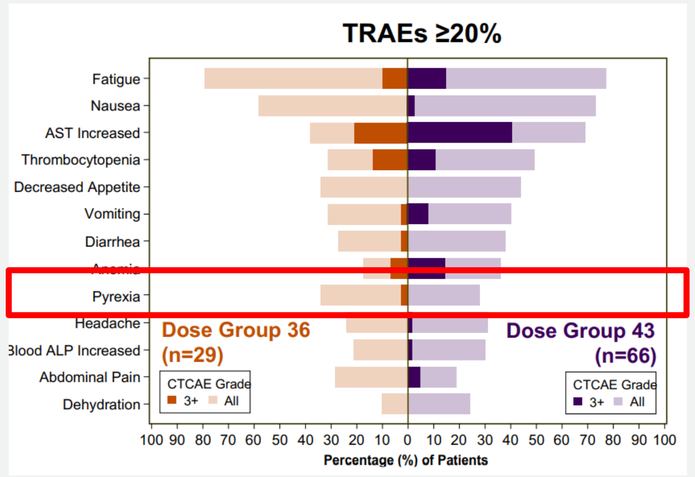
Mirvetuximab soravtansine



	All Grades n(%)	Grade >3, n(%)
Neuropathy peripheral	64(14)	4(<1)
Peripheral sensory neuropathy	36(8)	4(<1)
Peripheral motor neuropathy	4(<1)	1(<1)
Paresthesia	21(5)	0

Moore et al. ASCO 2022, Moore et al. Ann Oncol 2021

Upifitamab rilsdotin



Premedication with an anti-pyretic (Tylenol or ibuprofen is recommended

Richardson et al. 2022 SGO

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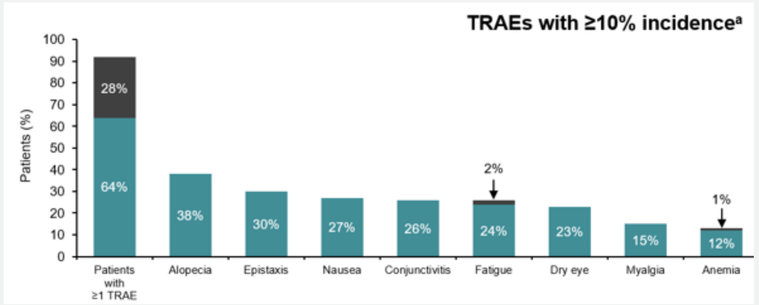
Antibody Drug Conjugates (ADCs)
Differentiated Safety Profile

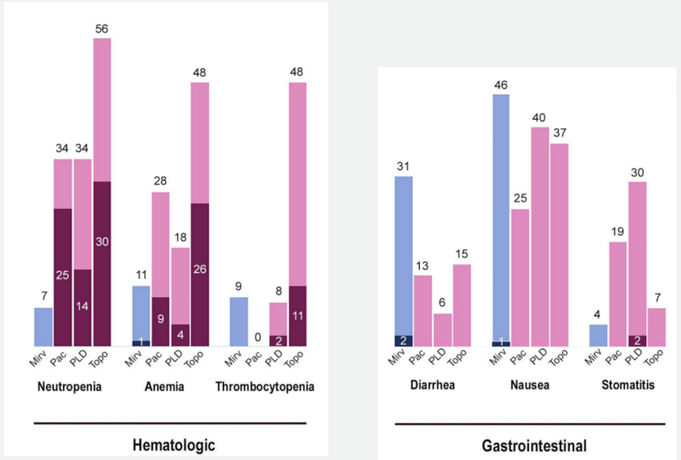
Tisotumab vedotin



Negligible heme tox (1% G3)
Epistaxis (G1-2) 30%
Alopecia (G1-2) 38%
Nausea 27%

Coleman et al. Lancet Oncol 2021

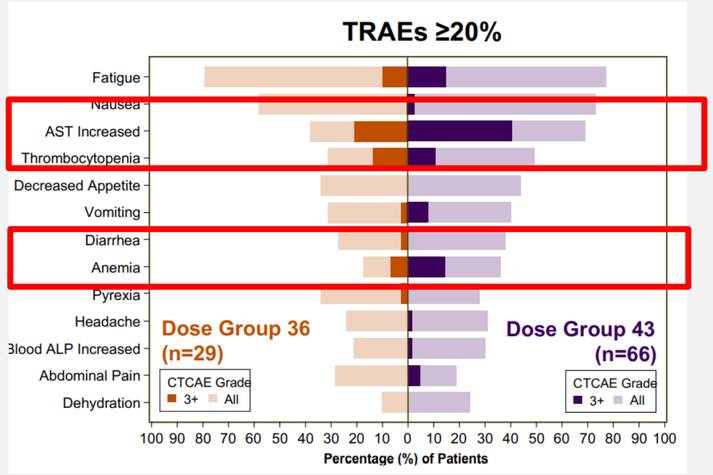
Mirvetuximab soravtansine



Negligible heme tox (1% G3)
Diarrhea (46%) and Nausea (31%)

Moore et al. ASCO 2022, Moore et al. Ann Oncol 2021

Upifitamab rilsdotin



Thrombocytopenia is more common here
AST elevation (transient)
Nausea 50%

Richardson et al. 2022 SGO

Nausea, vomiting and fatigue can be common across agents and standard pre-medications are recommended for mitigation

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Conclusions

- The approval of antibody drug conjugates for the treatment of Her2+ breast cancer and Hodgkins lymphoma has created great enthusiasm for the technology as a proven paradigm.
- Antibody drug conjugates against novel targets are in development for a large number of solid tumors and blood cancers.
- The possibilities for developing and utilizing these agents are limited only by the discovery of suitable targets, both highly expressed on and relatively specific to cancer cells.
- ADCs allow more precise delivery of chemotherapy to cancer cells, which should improve effectiveness relative to toxicity.