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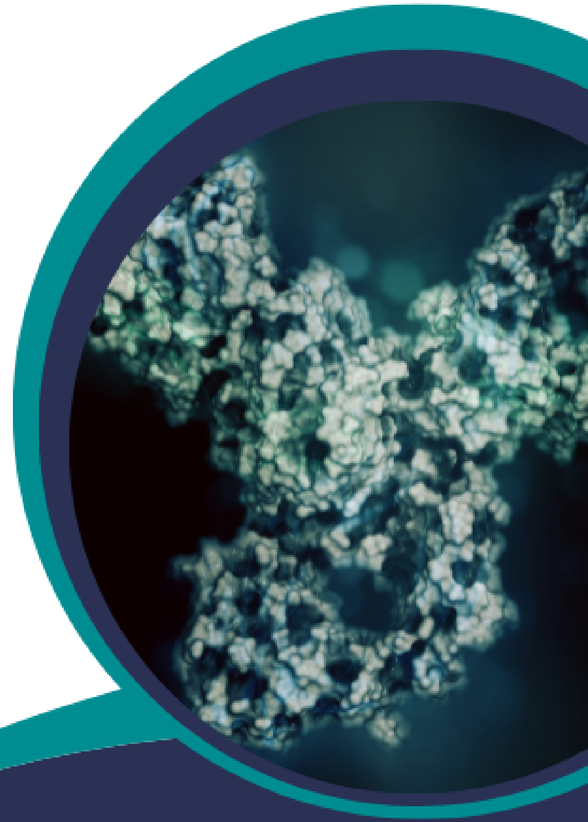
SEOUL IGCS 2023

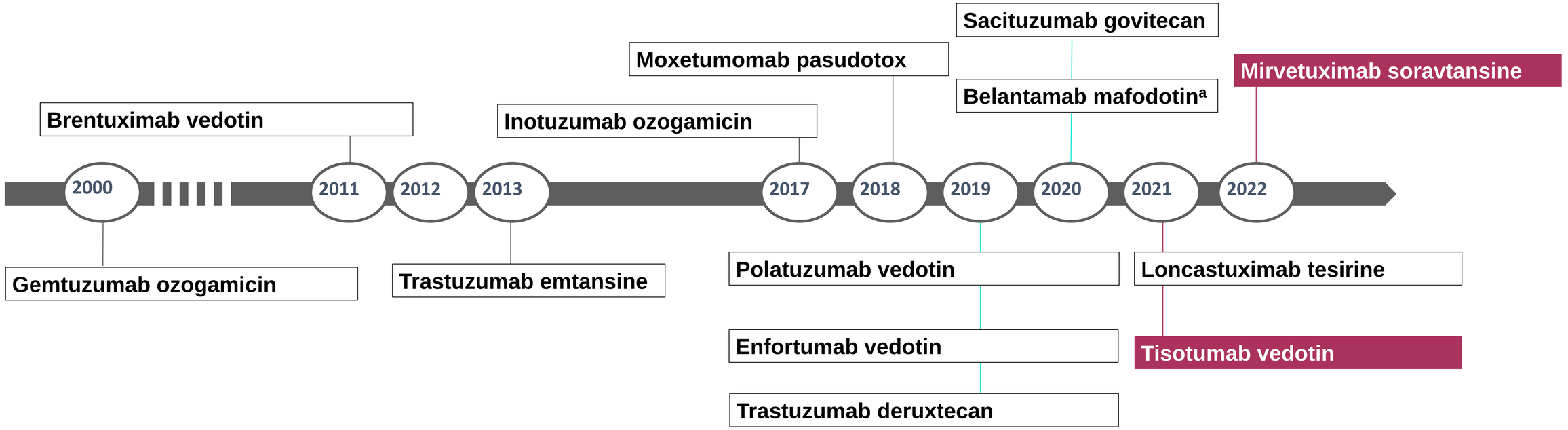
Important Advancements in Clinical Trial Development: How Lessons Learned Influence and Shape Future Opportunities



Róisín O'Cearbhaill, MD

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

Thirteen FDA-approved ADCs currently on the market



Two ADCs approved for gynecologic cancers[2]

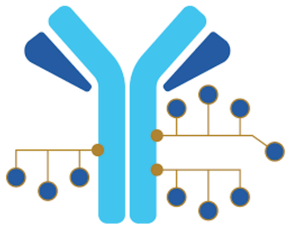
[a]Belantamab mafodotin was approved in 2020 for the treatment of relapsed or refractory multiple myeloma; however, withdrawal of this indication was initiated in November 2022 at the request of the US Food and Drug administration.[3,6 b] Trastuzumab deruxtecan received accelerated approval in 2019 for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

ADC, antibody-drug conjugate; FDA, US Food and Drug Administration.

Perez HL et al. *Drug Discov Today*. 2014;19(7):869-881.

Learnings from negative trials: Upifitamab rilsodotin (UpRi), ADC targeting NaPi2b

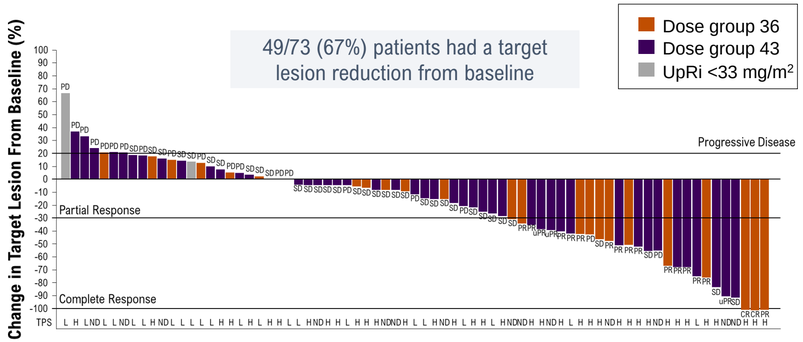
Upifitamab rilsodotin[1]

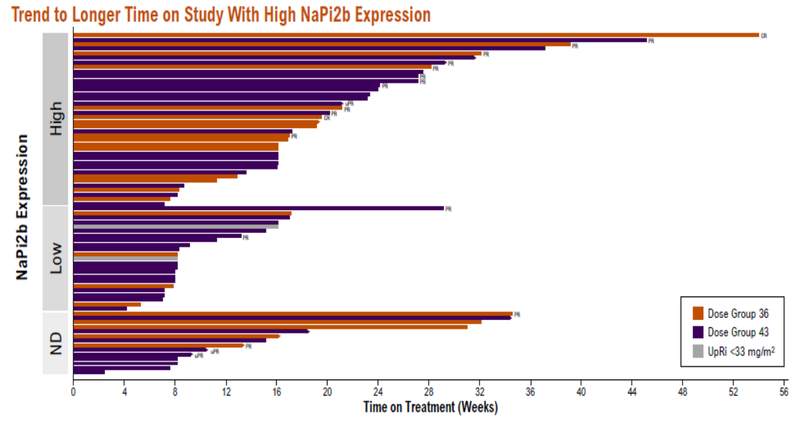


UpRi

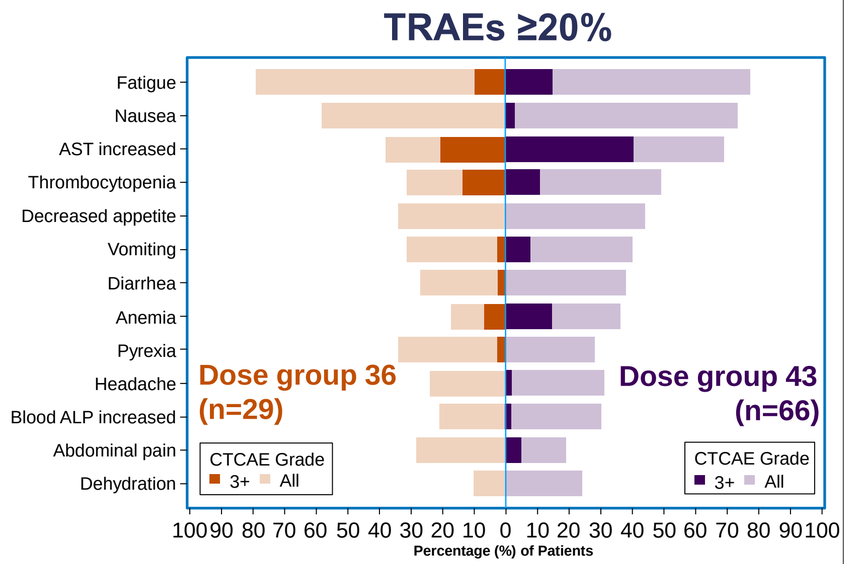
Target	NaPi2b
Linker	Polymer scaffold conjugated (cleavable ester)
Antibody	humanized monoclonal anti-NaPi2b
DAR	~10
Payload	AF-HPA/AF (DolaLock-controlled bystander effect)
Bystander effect	Controlled bystander effect
Disease of interest	Ovarian cancer

Efficacy[2,a-c]





Safety[2]



- Dose group 36 pneumonitis:
  - Grade 1–2 (n=2), Grade 3+ (n=0)
- Dose group 43 pneumonitis:
  - Grade 1–2 (n=5), Grade 3+ (n=4)

[a]2 patients not included in waterfall plot as tumor measurement data missing in the database as of data cut, both patients had BOR of PD due to new lesions. [b]Unconfirmed response, BOR per RECIST v1.1 is SD. [c]CR of target lesions and non-CR/non-PD of nontarget lesions, BOR per RECIST v1.1 is PR.

ADC, antibody-drug conjugate; AF-HPA, auristatin f-hydroxypropylamide; ALP, alkaline phosphatase; AST, aspartate transferase; BOR, best overall response; CR, complete response; CTCAE, common terminology criteria for adverse events; H, higher NaP/2b expression; L, lower NaP/2b expression; NaPi2b, sodium- dependent phosphate transporter; ND, NaP/2b expression not yet determined or tissue not available; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumors; SD, stable disease; TRAE, treatment-related adverse event; UpRi, upifitamab rilsodotin.

1. Moore et al. SGO Annual Meeting on Women's Cancer 2023. 2. Mersana Therapeutics. FORM 8K. Accessed October 13, 2023.

Upifitamab rilsodotin (UpRi) failed to meet expectations

The phase 1/2 UPLIFT trial (NCT03319628) evaluating UpRi in patients with platinum-resistant ovarian cancer failed to meet its primary endpoint of investigator-assessed ORR in the NaPi2b-positive population[1,2]

NaPi2b-positive population (n=141)[2]

	Investigator Assessment	IRR Assessment
ORR, n (%) [95% CI]	22 (15.6%) [10.0%, 22.7%]	23 (16.3%) [10.6%, 23.5%]
Partial Response, n (%)	20 (14.2%)	16 (11.3%)
Complete Response, n (%)	2 (1.4%)	7 (5.0%)
Median DOR, months	7.4	NR

Total population (n=268)[2]

	Investigator Assessment	IRR Assessment
ORR, n (%)	35 (13.1%)	35 (13.1%)
Partial Response, n (%)	32 (11.9%)	24 (9%)
Complete Response, n (%)	3 (1.1%)	11 (4.1%)
Median DOR, months	7.4	10.7

Grade 5 (fatal) bleeding events were observed in 560 patients treated with UpRi.[3] Grade 3 pneumonitis was observed as well.[4]

ADC, antibody-drug conjugate; DOR, duration of response; IRR, independent radiology review; NaPi2b, sodium- dependent phosphate transporter; NR, not reached; ORR, objective response rate; UpRi, upifitamab rilsodotin.

1. ClinicalTrials.gov, NCT04907968. Accessed October 13, 2023. 2. Mersana press release. Published July 27, 2023. Accessed September 29, 2023. https://ir.mersana.com/news-releases/news-release-details/mersana-therapeutics-announces-topline-data-uplift-clinical. 3. Mersana press release. Published June 15, 2023. Accessed October 13 29, 2023. https://ir.mersana.com/news-releases/news-release-details/mersana-therapeutics-announces-partial-clinical-hold-next-and. 4. Richardson DL. Interim data from ovarian cancer expansion cohort of the UpRi phase 1 study. Published September 10, 2021. https://ir.mersana.com/static-files/f50f16b7-c8bf-4268-903c-8f9860ccc3f5

Other ADCs explored in ovarian cancer

Folate receptor α	Toxin (DAR)	Best Response
STRO-002[1]	3-aminophenyl hemiasterlin; SC209 (4) MTT	ORR: 7.7%
MORAb-202[2,3]	Eribulin mesylate (4) MTT	ORR: 37.5%

MUC16	Toxin (DAR)	Best Response
Sofituzumab vedotin (DMUC5754A)[5]	MMAE (3.5) MTT	ORR: 17%
Anti-MUC16 TDC (DMU4C064A)[1,6]	MMAE (2) MTT	ORR: 45%

CDH6	Toxin (DAR)	Best Response
DS-6000a[11,12]	ND (8)	cORR: 53%

Mesothelin	Toxin (DAR)	Best Response
Anetumab ravtansine[2]	Ravtansine DM4 (3.2) MTT	ORR: 9%
DMOT4039A[2,6]	MMAE (3.5) MTT	ORR: 30%
BMS-986148[4,6]	Duocarmycin-related (1.4) DNA alkylator	ORR: 9%

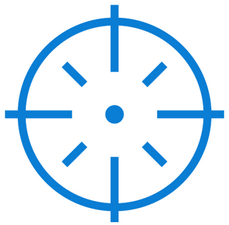
HER2	Toxin (DAR)	Best Response
SYD985[7,8]	vc-seco-DUBA (2.7)	ORR: 17%
T-DXd[9,10]	Topo I inhibitor/DXd (7–8)	ORR: 45%

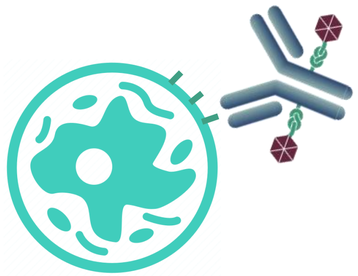
Tissue Factor	Toxin (DAR)	Best Response
Tisotumab vedotin[13,14]	MMAE (4) MTT	ORR: 13.9%

ADC, antibody-drug conjugates; cORR, confirmed overall response rate; DAR, drug-to-antibody ratio; DM4, maytansine 4; MMAE, monomethyl auristatin E; MTT, 3-[4, 5- dimethylthiazolyl-2]-2, 5diphenyltetrazolium bromide; ND, not determined; ORR, overall response rate.

1. Manzano A and Ocana A. *Cancers (Basel)*. 2020;12(8): 2223. 2. Nerone M et al. *Explor Target Antitumor Ther*. 2022;3(2):149-171. 3. Cheng X et al. *Mol Cancer Ther*. 2018;17(12):2665-2675. 4. Rottey S et al. *Clin Cancer Res*. 2022;28(1):95-105. 5. Ponte JF et al. *Mol Cancer Ther*. 2021;20(1):203-212. 6. Yeku O. Poster presentation at NRG Oncology Summer Meeting 2022; 7. Yao. *Drug Discov Today*. 2021;26(8):1857–1874. 8. Tymon-Rosario J, et al. *Curr Opin Obstet Gynecol*. 2021;33(1):26-33. 9. Takegawa N et al. *Int J Cancer*. 2017;141(8):1682–1689. 10. Meric-Bernstam F et al. Poster presented at ESMO Annual Meeting 2023. LBA 34. 11. Moore KN et al. Poster presented at ESMO 2023; Abstract 3002. 12. ClinicalTrials.gov. NCT04707248. Accessed March 1, 2023. 13. Fu Z et al. *Signal Transduct Target Ther*. 2022;7(1):93; 14. Manzano A, Ocaña A. *Cancers (Basel)*. 2020;12(8):2223.

Important antibody and antigen characteristics in ADC design





High <u>specificity</u> between antibody and antigen	High <u>affinity</u> between antibody and antigen	Antibody-antigen complex internalization	Lack of antigen downregulation
Essential to prevent uptake of the ADC by healthy cells, which could result in systemic toxicity before reaching antitumor efficacy[1] **Antigen should be highly expressed by tumor cells, with limited or no expression in healthy tissues[1]**	Antibody must bind the target antigen with high affinity for efficient uptake into cancer cells[1]	Receptor-mediated endocytosis of the antigen–ADC complex is important for maximal release of antitumor drug into cancer cells[1]	Target antigen should not be downregulated by endocytosis or repeated stimulation during treatment[2] **Downregulation and/or mutation of the target antigen can lead to resistance to the antibody component of the ADC[3]**

ADC, antibody-drug conjugate.

1. Panowski S et al. *MAbs*. 2014;6(1):34–45. 2. Hoffmann RM et al. *Oncoimmunology*. 2018;7(3):e1395127. 3. Collins DM et al. *Cancers (Basel)*. 2019;11(3):394.

Pharmacokinetic properties of ADC are important to achieve a longer half-life with slower clearance in plasma

Specific ADC features may influence pharmacokinetic parameters such as maximum plasma concentration, clearance, elimination half-life, and distribution[1,2]

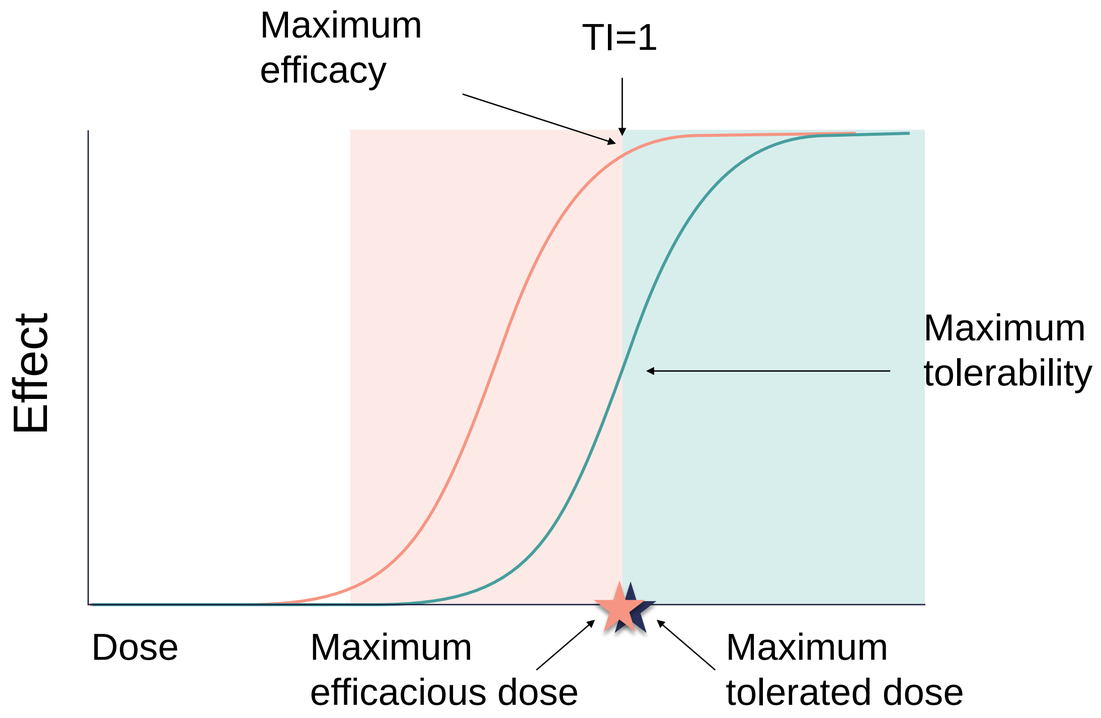
Antibody structure[1]	Linker design[3]	Conjugation site[4]
		
Regulates serum half-life and recognition of different activating and inhibitory immune effector cells that can influence bioavailability, sequestration to tissues, trafficking to tumors, antigen targeting, and immune functions	May prevent premature release of drugs in circulation, **limiting systemic toxicity and increasing the therapeutic window**	Site-specific conjugation of the payload at defined sites on the antibody **minimizes heterogeneity of ADC batches and allows for precise control of drug-to-antibody ratio (DAR)**

ADC, antibody-drug conjugate.

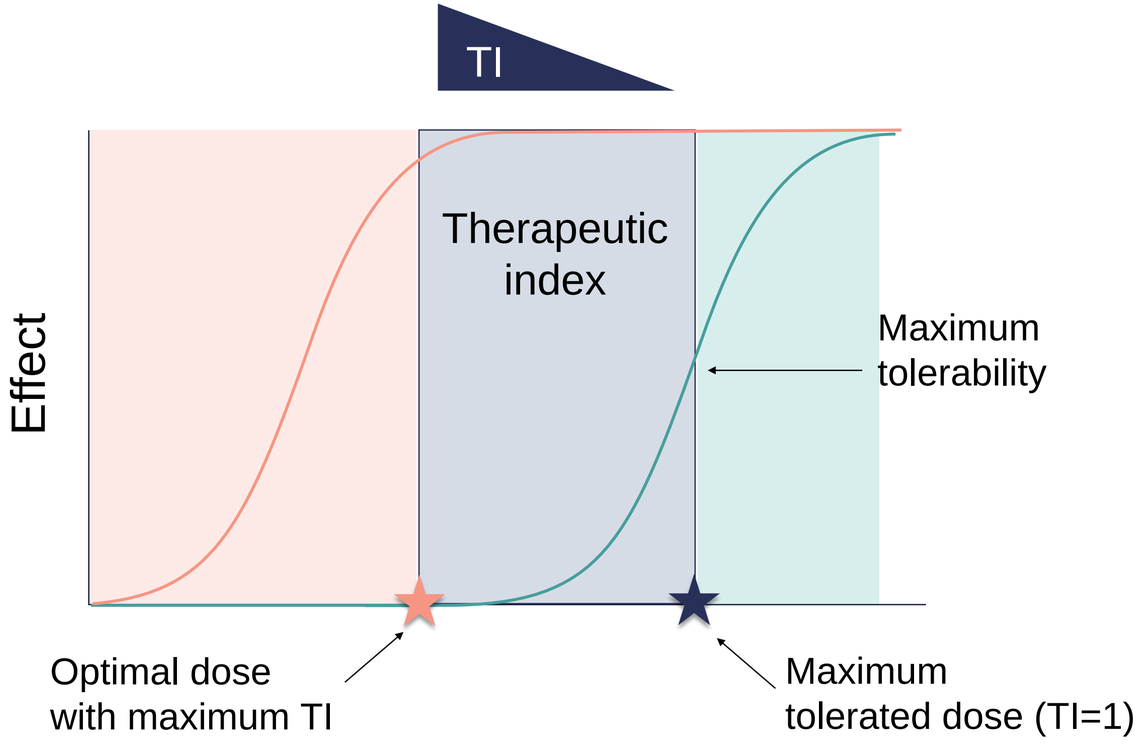
1. Hoffmann RM et al. *Oncoimmunology*. 2018;7(3):e1395127. 2. Mahmood I. *Antibodies (Basel)*. 2021;10(4):40. 3. Khongorzul P et al. *Mol Cancer Res*. 2020;18(1):3–19. 4. Panowski S et al. *MAbs*. 2014;6(1):34–45.

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

Small-molecule chemotherapy (narrow therapeutic index)



ADC-targeted therapy (expanded therapeutic index)



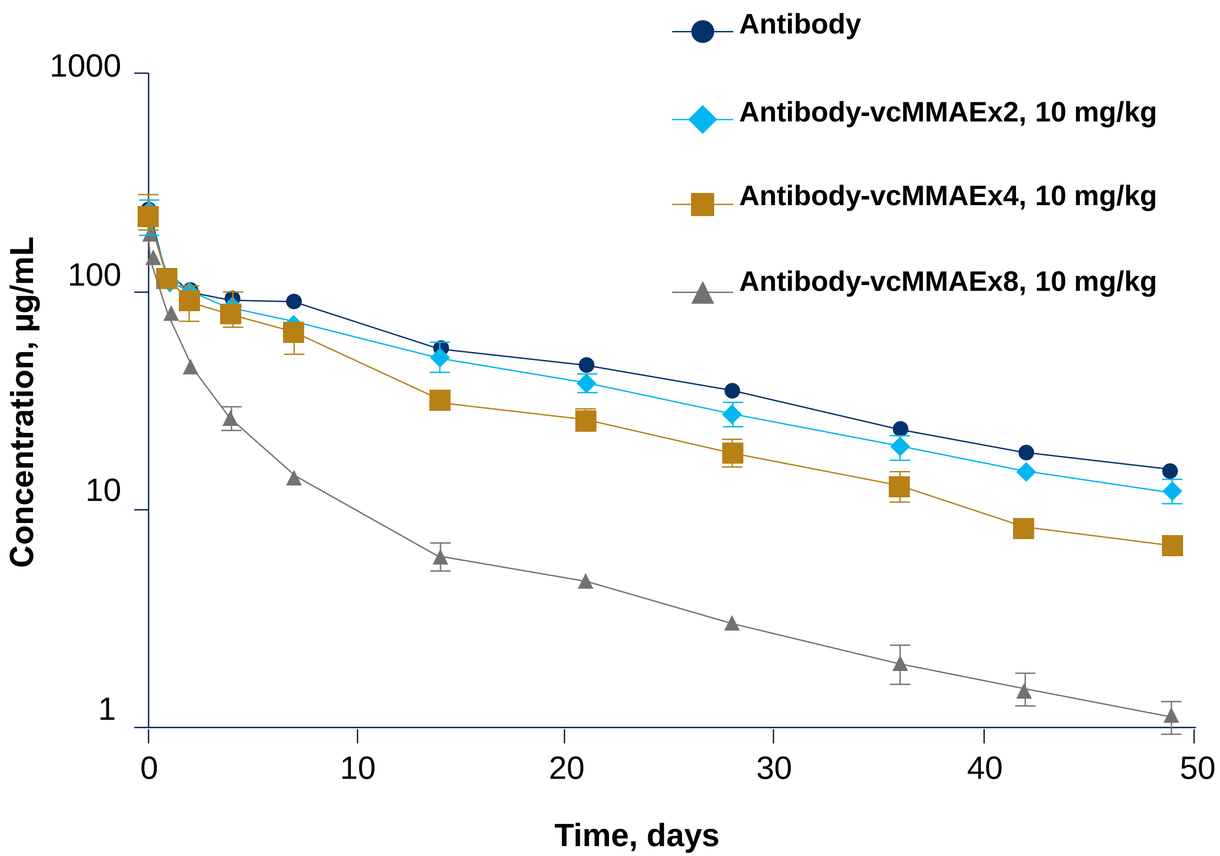
[a]Therapeutic index is the ratio between the toxic dose and the dose at which the drug becomes effective.[2]

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 limited to **DAR 2–4** to maintain physiochemical and pharmacokinetic properties[3,4]
- High DAR delivers greater concentration of antitumor drugs to tumor cells but may result in off-target cytotoxicity, aggregation, and increased plasma clearance[1,3]
- Potential to use novel linkage strategies to deliver the payload



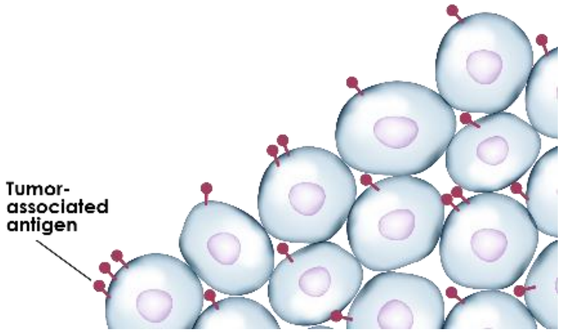
Traditional ADCs with a DAR >3–4 experience a decline in the drug's physiochemical properties[5]

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

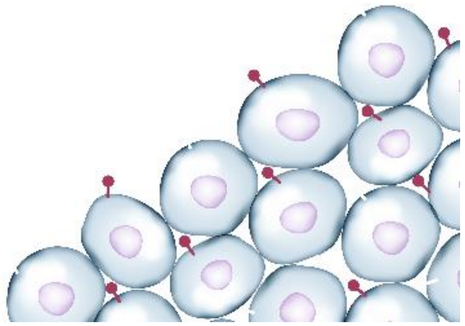
1. Wakankar A et al. *MAbs*. 2011;3(2):161–172. 2. Perez HL et al. *Drug Discov Today.* 2014;19(7):869–881. 3. Yurkovetskiy AV et al. *Mol Cancer Ther*. 2021;20(5):885–895. 4. Lyon RP et al. *Nat Biotechnol*. 2015;33(7):733–735. 5. Hamblett KJ et al. *Clin Cancer Res*. 2004;10(20):7063–7070.

Heterogeneous and low tumor expression of the target antigen may hinder the therapeutic effect of ADCs

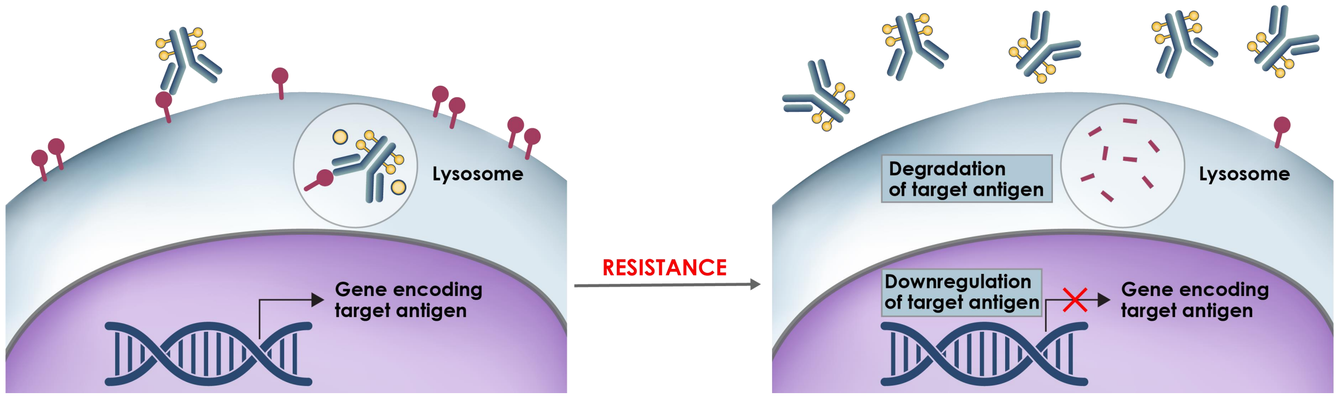
Heterogeneous and low expression of the target antigen plays a key role in the efficacy of, as well as mechanisms of resistance against, ADCs[1-3]



Heterogeneity in target expression throughout tumor



Low expression of target in tumor



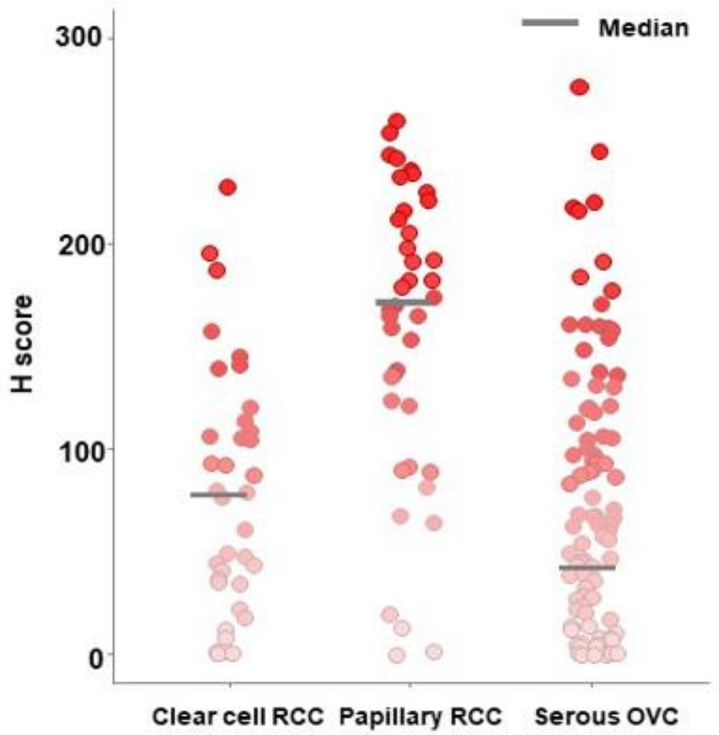
Preclinical studies have shown that improvements in the design of ADCs, such as cleavable linkers, payloads with high permeability, and an increase of DAR, may overcome limitations around low or no antigen expression[2-5]

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

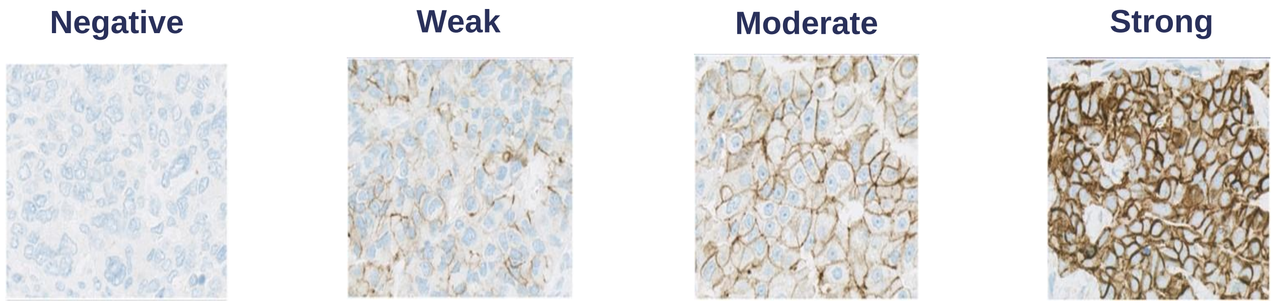
1. Drago JZ et al. *Nat Rev Clin Oncol*. 2021;18(6):327–344. 2. Ocaña A et al. *Breast Cancer Res*. 2020;22(1):15. 3. Ogitani Y et al. *Cancer Sci*. 2016;107(7):1039–1046. 4. Erickson HK et al. *Cancer Res*. 2006;66(8):4426–4433. 5. Yurkovetskiy AV et al. *Mol Cancer Ther*. 2021;20(5):885–895.

CDH6 expression in renal cell carcinoma/serous ovarian cancer

CDH6 expression in RCC/serous OVC[1]



CDH6 expression in human tissue factor by IHC assay



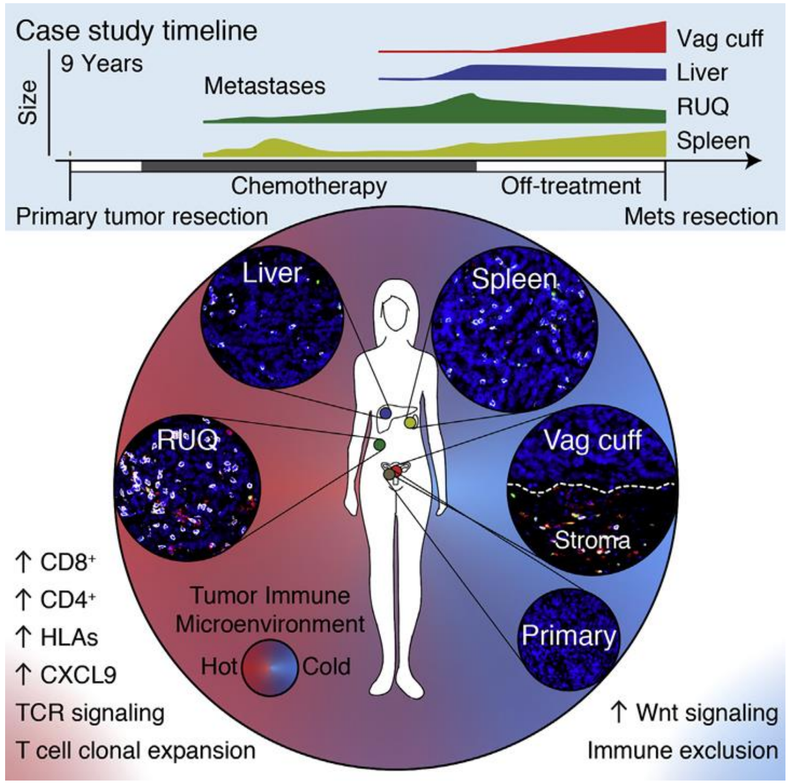
Tumor type	n	CDH6 H-score (n, %)							
		0		1-100		101-200		201-300	
Clear cell RCC	39	0	0%	25	64%	13	33%	1	3%
Papillary RCC	41	1	2%	9	22%	18	44%	13	32%
Serous OVC	118	18	15%	71	60%	24	20%	5	4%

- 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
- Expression of CDH6 is observed in ~65–85% of patients with OVC[2,3]

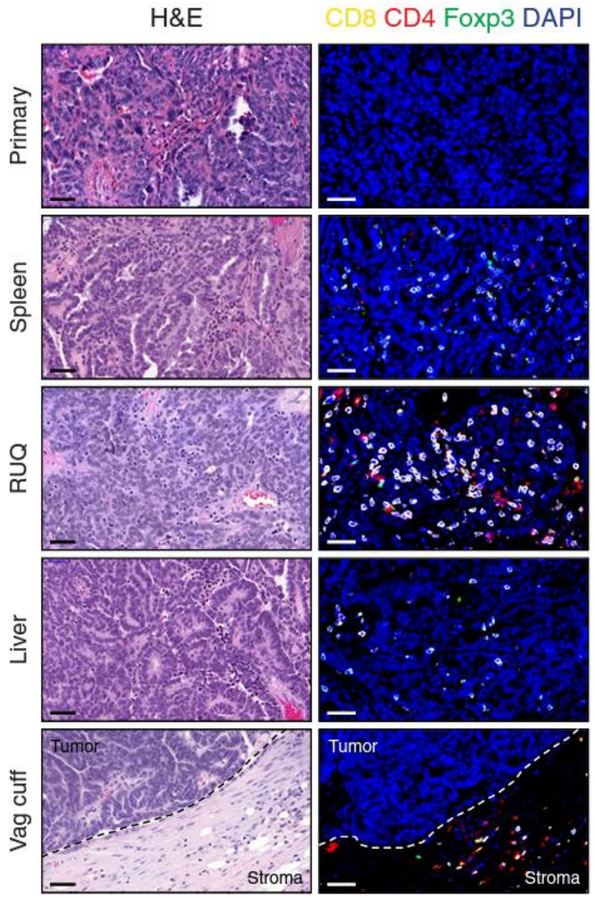
CDH6, cadherin-6; IHC, immunohistochemistry; OVC, serous ovarian cancer; RCC, renal cell carcinoma;

1. Hirokazu S, et al. Presented at ESMO 2021. Abstract 10P. 2. Bartolomé RA, et al. Mol Oncol. 2021;15:1849–1865; 3. Shintani D, et al. *Gynecol Oncol.* 2022;166(Suppl. 1):S116

Intratumor and intertumor heterogeneity: different tumor microenvironments and antigen expression within the same patient



Intersite immune heterogeneity represents an important clinical challenge in developing treatment modalities to address the diversity of tumors within the same patient



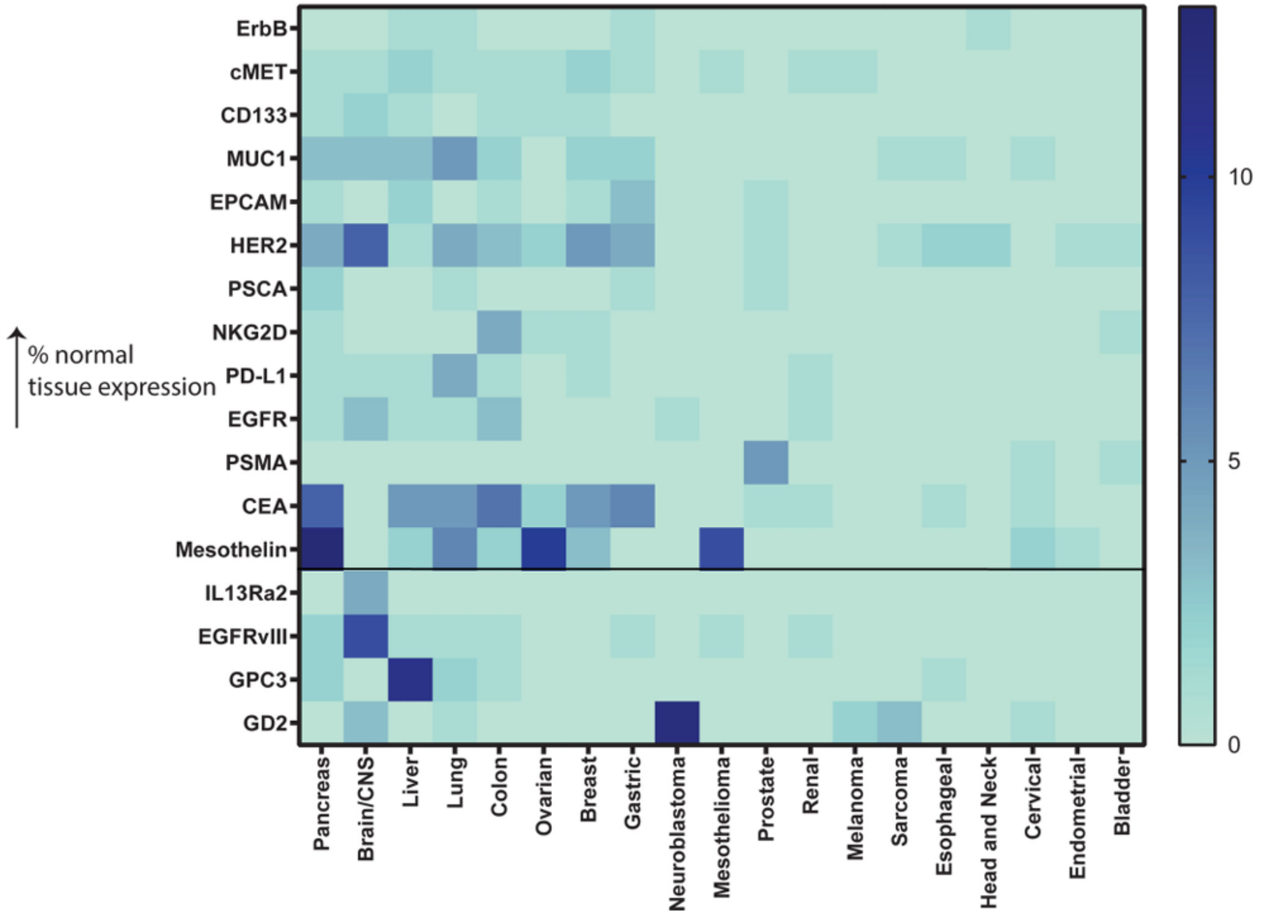
Heterogenous microenvironments across tumor samples
H&E staining of tumor samples and immunofluorescence staining for DAPI, cytotoxic T cells (CD8+), helper T cells ($CD4^+FOXP3^-$), T-regs ($CD4^+$ $FOXP3^+$)

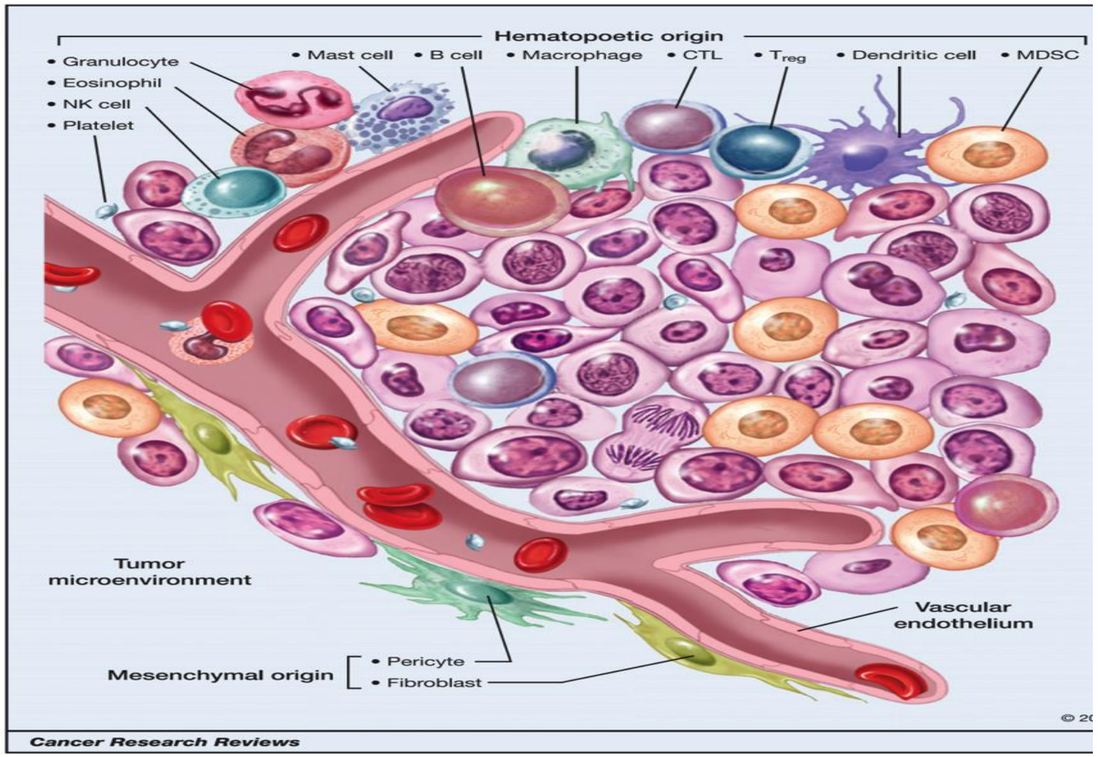
CD4, cluster of differentiation 4; CD8, cluster of differentiation 8; CXCL9, C-X-C motif chemokine ligand 9; DAPI, 4′,6-diamidino-2-phenylindole; FOXP3, forkhead box P3; H&E, hematoxylin and eosin stain; HLA, human leukocyte antigen; TCR, T cell receptor; T-regs, regulatory T-cells; RUQ, right upper quadrant; Vag cuff, vaginal cuff; Wnt, Wingless and Int-1.

Jimenez-Sanchez A et al. *Cell*. 2017;170(5):927-938.e20.

Additional potential targets

Landscape of potential target surface antigens





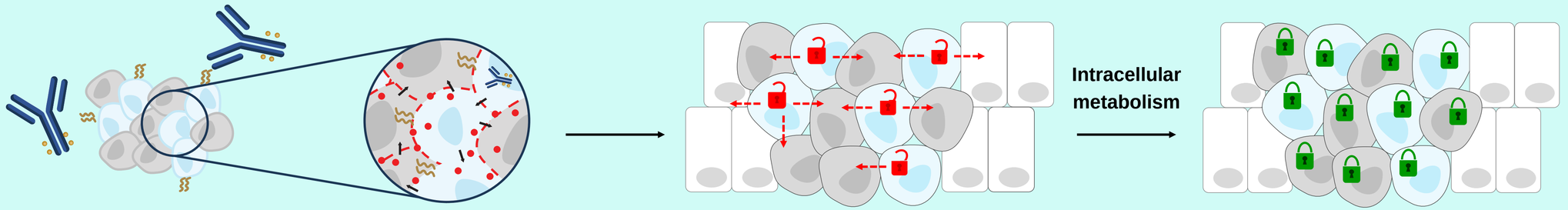
CAR, chimeric antigen receptor; CD133, cluster of differentiation 133; CEA, carcinoembryonic antigen; cMET, mesenchymal-epithelial transition factor; CNS, central nervous system; EGFR, epidermal growth factor receptor; Erb**B**, Erb-B2 receptor tyrosine kinase 2; EPCAM, epithelial cell adhesion molecule; GD2, ganglioside G2; GPC3, glypican-3; HER2, human epidermal receptor 2; IL13Ra2, interleukin 13 receptor, alpha 2; MUC1, mucin 1; KLRK1 (NKG2D), killer cell lectin like receptor K1; PD-L1, programmed death-ligand 1; PSCA, prostate stem cell antigen; PSMA, prostate-specific membrane antigen;

Schoenfeld AJ and O'Cearbhaill RE. *Cancer J.* 2021;27(2):134–142. Kerkar SP, Restifo NP Cancer Res 2012;72:3125-3130.

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[2]



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

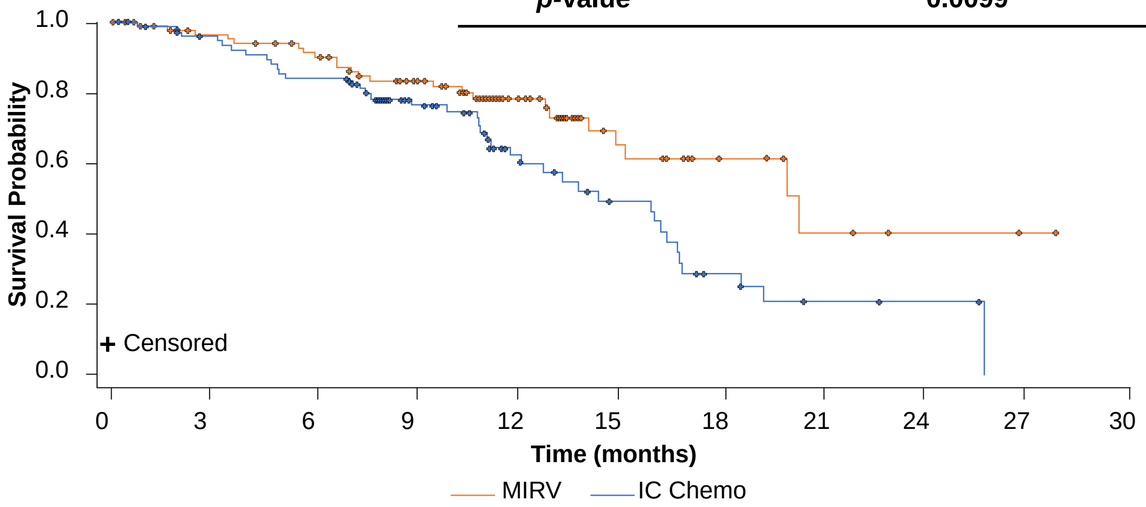
ADC, antibody-drug conjugate; DAR, drug-to-antibody ratio.

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.

Should we use ADCs earlier in disease course?

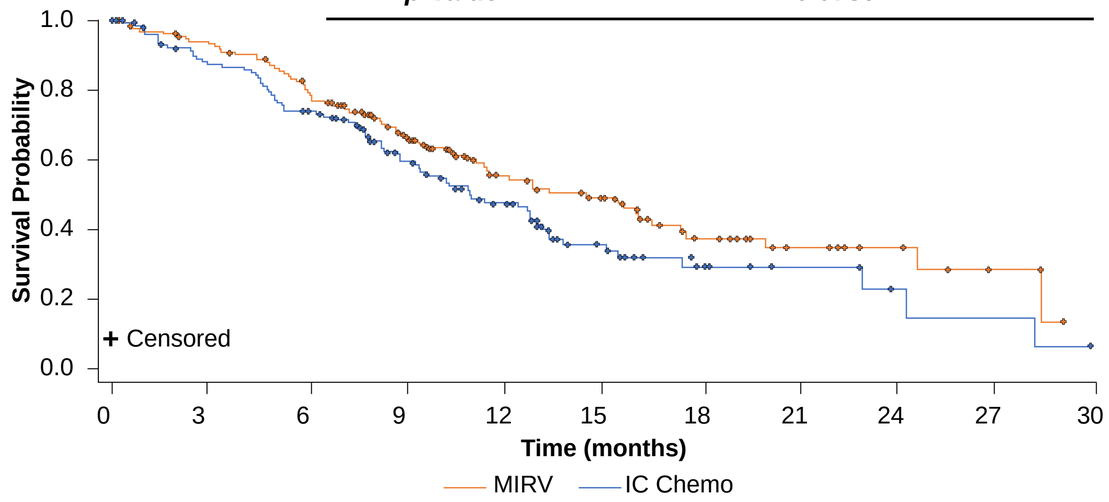
Bevacizumab-naïve

	Mirvetuximab	Chemotherapy
Events, n (%)[a]	23 (10.1)	39 (17.3)
mOS (95% CI)	20.2 (14.8-NE)	14.4 (11.8-16.7)
HR (95% CI)	0.51 (0.31-0.86)	
p-value	0.0099	



Bevacizumab-treated

	Mirvetuximab	Chemotherapy
Events, n (%)[a]	67 (29.5)	75 (33.2)
mOS (95% CI)	15.4 (11.3-17.5)	10.9 (9.4-13.3)
HR (95% CI)	0.74 (0.54-1.04)	
p-value	0.0789	



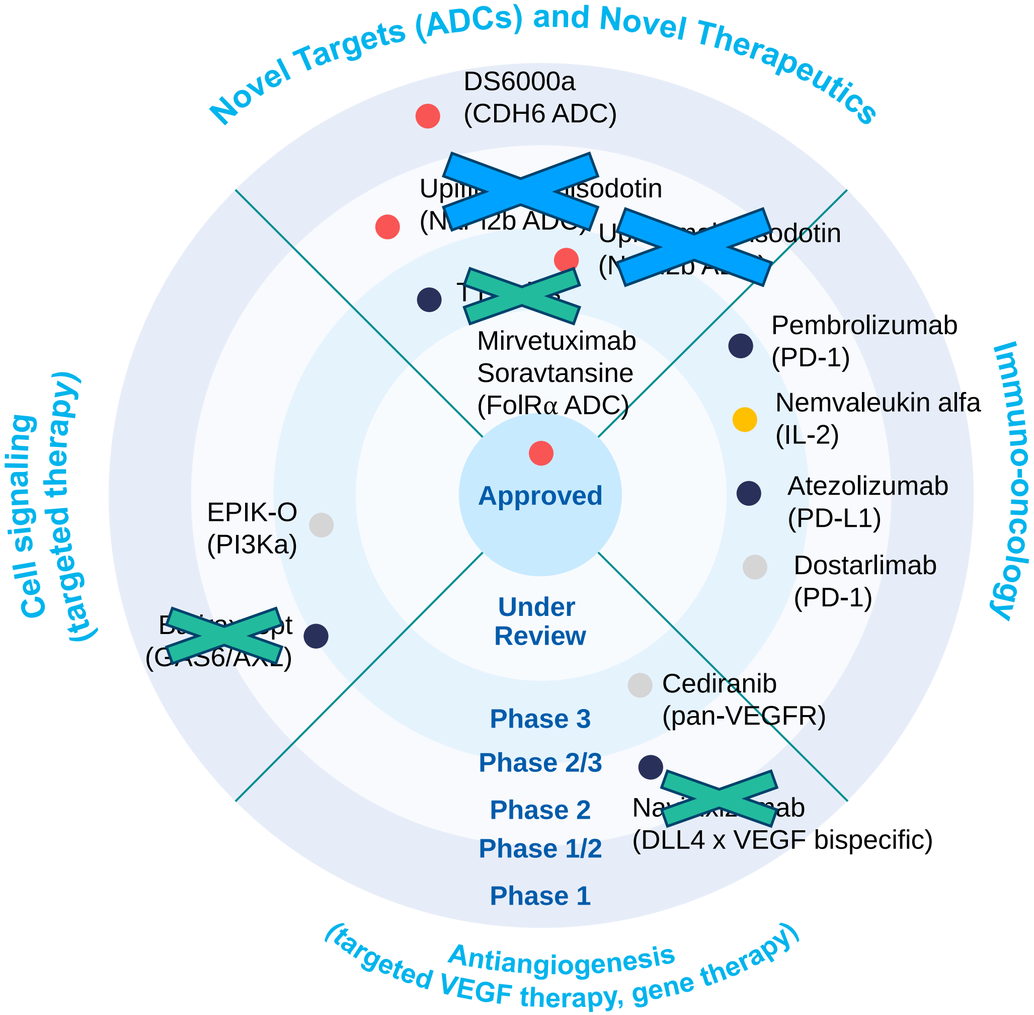
Data cutoff: March 6, 2023.

[a]Percentage of events was calculated out of the total number of patients in each treatment arm: n=227 for MIRV and n=226 for IC Chemo.

ADC, antibody-drug conjugate; IC chemo, investigator-chosen chemotherapy; MIRV, mirvetuximab soravtansine; mOS, median overall survival.

Moore KN et al. Presented at ASCO Annual Meeting 2023. LBA5507

Fast moving landscape: pivotal trials in platinum resistant ovarian cancer



Regimen

- Monotherapy
- Chemo combo
- IO combo
- PARP inhibitor combo

Competition/Drug	Approved (est)
ImmunoGen/mirvetuximab soravtansine	2022
Novartis/PIQRAY	2024
AstraZeneca/cediranib (NCI study)	2024
Aravive/AVB-500	2024
Roche/Tecentriq	2024
Novocure/TTFields	2024
OncXerna/navicixizumab	2024
Alkermes/nemvaleukin alfa	2026
Merck/Keytruda	2026

Rationale combinations with ADCs will be the next logical step

Updated October 2023.

ADC, antibody-drug conjugate; CDH6, human cadherin-6; Chemo, chemotherapy; DLL4, delta-ligand 4; FolRα, folate receptor a; GAS6, growth arrest specific 6; IL, interleukin; IO, Immuno-oncology; NCI, National Cancer Institute; PARP, poly-ADP ribose polymerase; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein 1; PI3Ka, phosphoinositide 3-kinases; TNFR1, tumor necrosis factor receptor 1; TTFields, tumor treating fields; VEGFR, vascular endothelial growth factor receptor.

Combination approaches: ADCs and Immunotherapy

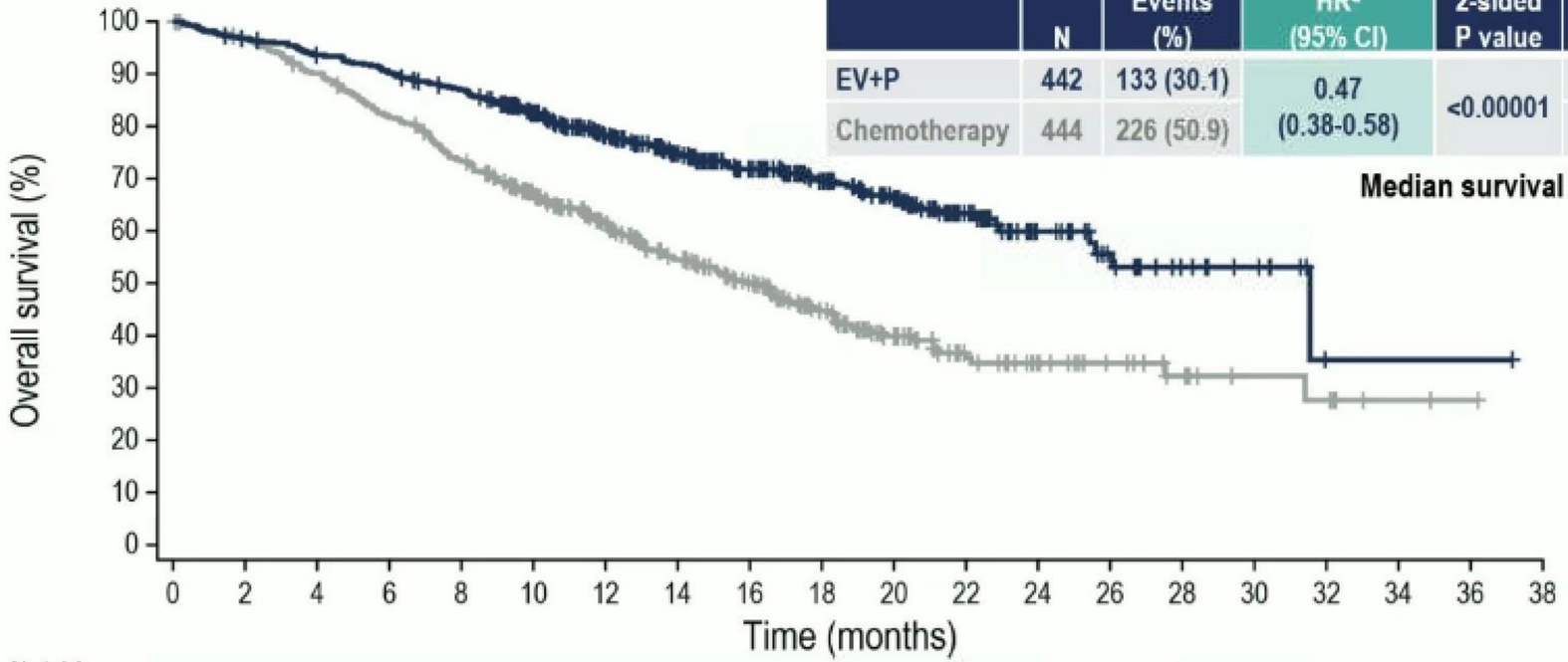
Limited Overlapping Toxicity

Overall Survival

Risk of death was reduced by 53% in patients who received EV+P

	N	Events (%)	HR[a] (95% CI)	2-sided P value	mOS (95% CI), months
EV+P	442	133 (30.1)	0.47 (0.38-0.58)	<0.00001	31.5 (25.4-NR)
Chemotherapy	444	226 (50.9)			16.1 (13.9-18.3)

Median survival follow-up: 17.2 months



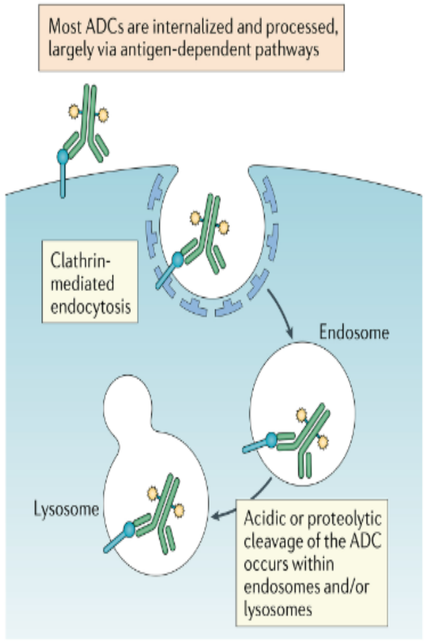
OS at 12 and 18 months was estimated using Kaplan-Meier method
mOS, median overall survival; NR, not reached
[a]Calculated using stratified Cox proportional hazards model. A hazard ratio <1 favors the EV+P arm

Powles et al.

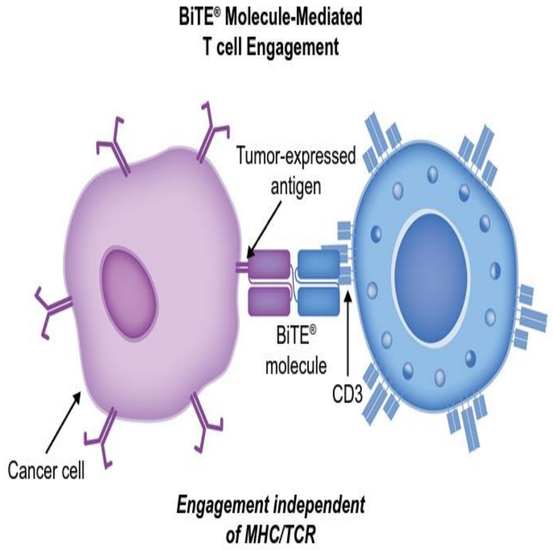
1. Powles T. et al. *ESMO Annual Meeting 2023*

Future treatment landscape: potential non-chemotherapy approaches

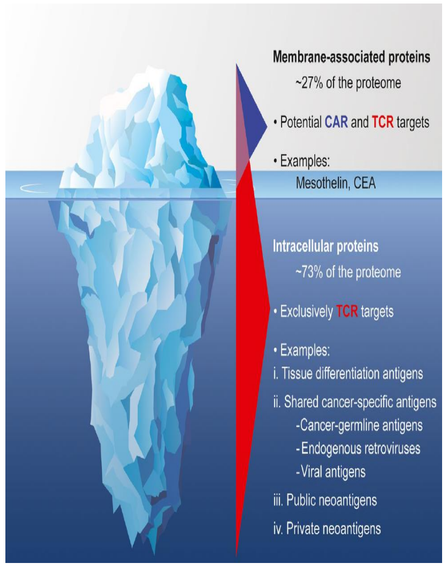
ADCs[1]



Bispecific antibodies[2]



Cellular therapies[3]



Vaccines

Combination approaches will be the key to the solution

KEYNOTE-A39 is an open-label, randomized phase III trial comparing enfortumab vedotin (Nectin-4–directed ADC) and pembrolizumab versus chemo in previously untreated locally advanced/metastatic urothelial cancer[4]

ADC, antibody-drug conjugate; CAR, chimeric antigen receptor; CD3, cluster of differentiation 3; CEA, carcinoembryonic antigen; MHC, major histocompatibility complex; TCR, T-cell receptor.

1. Drago et al. *Nat Rev Clin Oncol*. 2021;18(6):327–344; 2. Einsele H et al. *Cancer*. 2020;126(14):3192-3201; 3. Chandran SS and Klebanoff CA. *Immunol Rev.* 2019;290(1):127-147; 4. Powles et al. Presented at ESMO 2023. Abstract LBA6

ADC future developments

Different regimens and combinations of ADCs are being explored to enhance their effectiveness and broaden their applications[1]

Diversifying ADC payload development is crucial for advancing cancer therapy[2]

Although ADCs are “targeted,” we see toxicities like peripheral neuropathy, pneumonitis, eye toxicity, hematologic toxicity, and gastrointestinal toxicity

Key considerations for development strategies:

1. Is it better to retrospectively confirm target expression on archival tissue, or is screening patients a priority?
2. Should treatment with ADCs be moved up earlier in the disease course?
3. A validated assay and robust scoring system are necessary to develop companion diagnostics
4. Some ADCs may not require high target expression
   (T-DXd in HER2 low breast cancer, DESTINY-Breast04)

ADC, antibody-drug conjugate. HER2, human epidermal growth factor receptor; T-DXd, trastuzumab deruxtecan.

1. Marei HE et al. *Cancer Cell Int*. 2022;22(1):255. 2. Conilh L et al. *J Hematol Oncol*. 2023;16(1):3.