MasterClass in Bladder Cancer 2026

New molecules and mechanisms of action in preclinical development

Organized by:
HENDERE HEALTHCARE

#BladderMasterClass26

Hospital Universitario 12 de Octubre
SaludMadrid

My Disclosures

- **Compensated Advisory Boards:**
  - MSD, BMS, Roche-Genentech, Astellas, PYCYC, IPSEN, Novartis, Bayer, Astra-Zeneca, Grey Wolf Therapeutics
- **Research Funding [institution]:**
  - Roche-Genentech, Astra-Zeneca
- **Cover of Travel expenses:**
  - Roche-Genentech, IPSEN, Astra-Zeneca, Bayer
- **Clinical Trials [collaboration]:**
  - BMS, Roche-Genentech, PYCYC, EISAI, MSD, Tahio Oncology, Gilead, Exelixis, Bicycle Therapeutics,
- **Compensated Lectures:**
  - EUSA pharma, MSD, BMS, Roche-Genentech, IPSEN, Jansen, Astellas, Bayer, Astra-Zeneca
- **Clinical trial [lead]:** Gilead [PI of PRISMA-1 study]

Learning objectives

To review potential mechanisms of resistance to currently utilized drugs in advanced urothelial cancer and from those understand the development of new strategies in this context

Outline

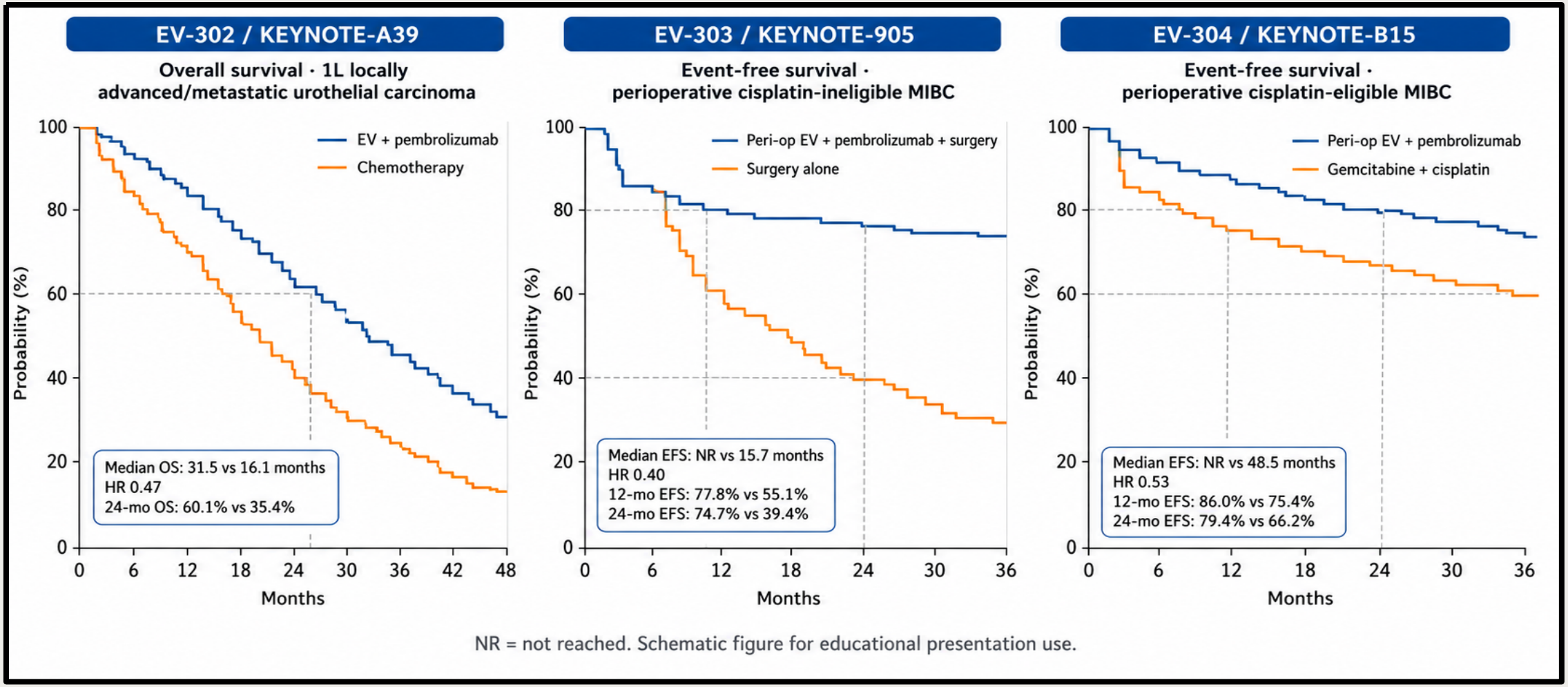
- The evolution of treatment of urothelial carcinoma
- Current therapeutic approaches
- ADCs: Structure and MoA
- Resistance to ADCs based combos
- Drug Development according to the mechanisms of resistance
- New strategies around immunotherapy
- Summary
- Q&A

Where do we stand today?

- The therapeutic landscape of urothelial carcinoma has been absolutely transformed over the last decade.

- **Checkpoint inhibitors**, **FGFR inhibition,** and especially **ADCs** such as enfortumab vedotin have reshaped the treatment scenario…and more to come

ADCs + CPIs have succeeded in bladder cancer at different clinical settings



…But today's success creates tomorrow's resistance population

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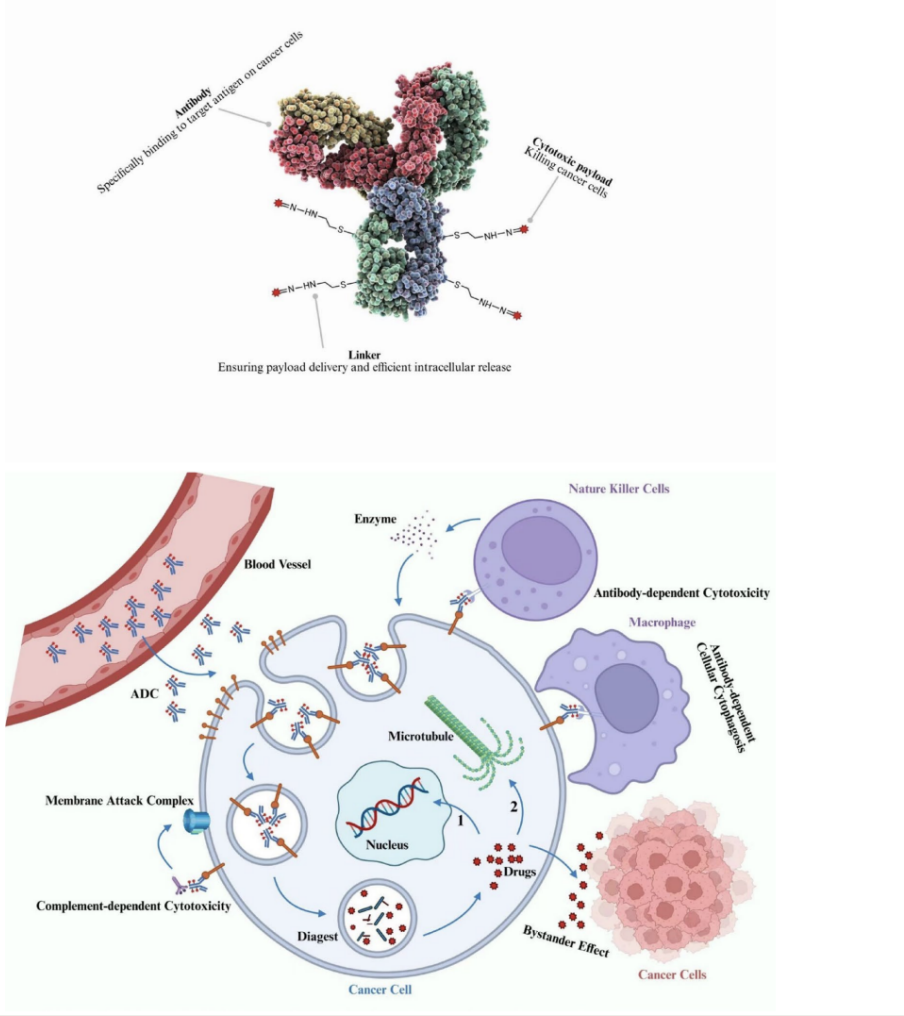
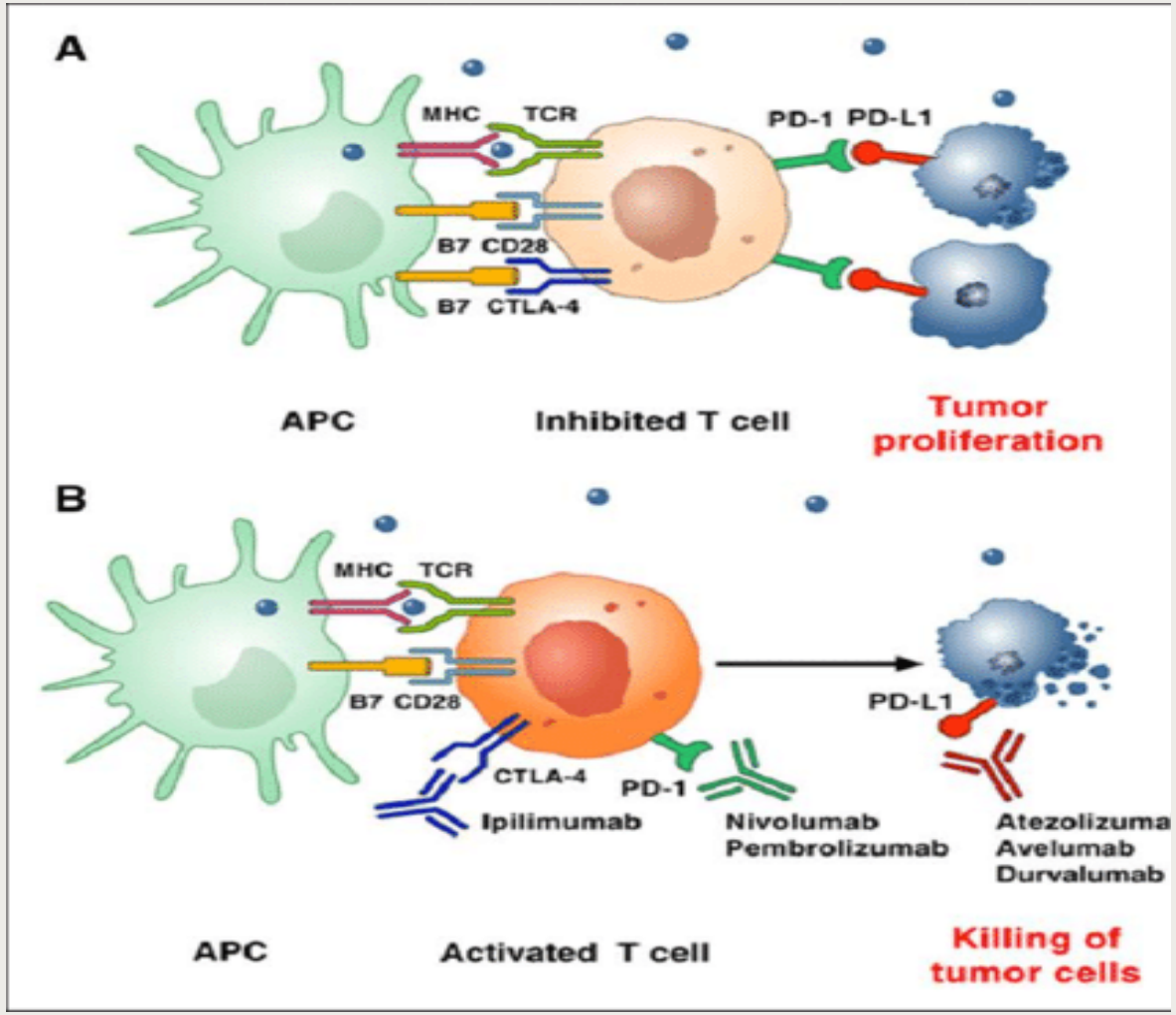
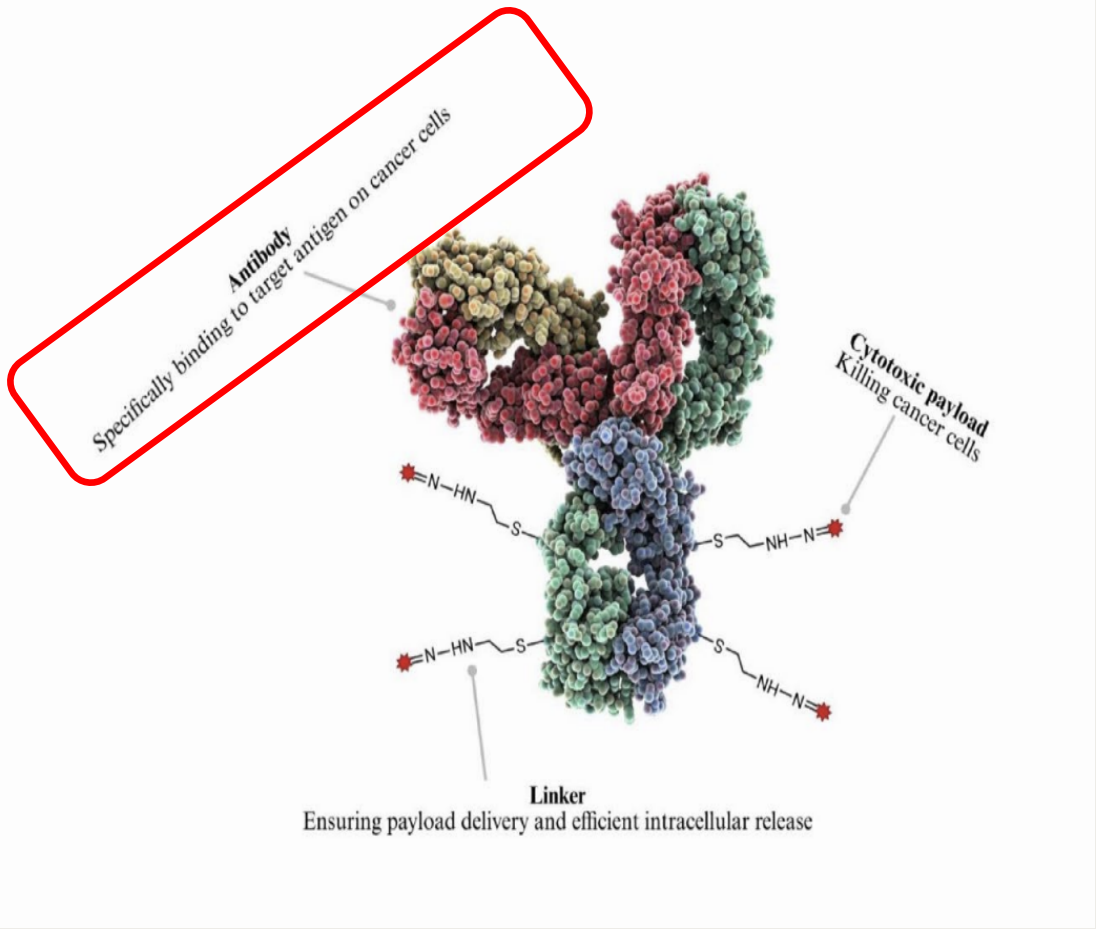
The mechanism of action





- Image of ADC from Zhou et al. Journal of Hematology & Oncology (2025) 18:96 : : image of CPI MoA from Circulation. 2017;136:1989–1992.

THE ANTIBODY



The antibody provides **SPECIFICITY** by selectively **TARGETING TUMOR ANTIGENS**, thus minimizing the impact on normal tissues and **OPTIMIZING THE DELIVERY** of the **CYTOTOXIC AGENT** directly to **CANCER CELLS**

Zhou et al. Journal of Hematology & Oncology (2025) 18:96

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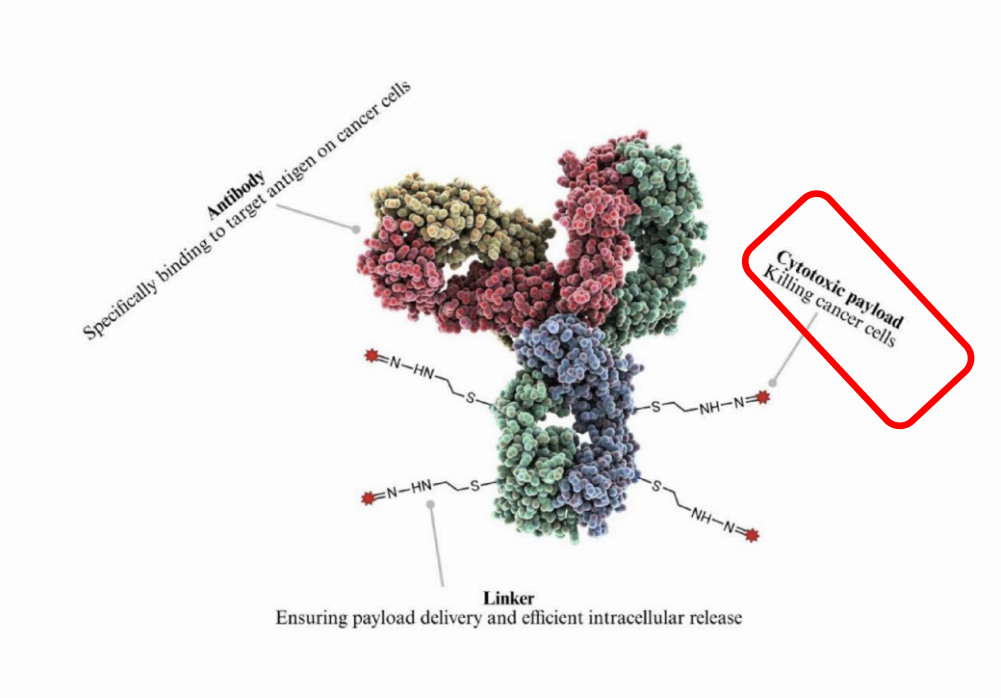
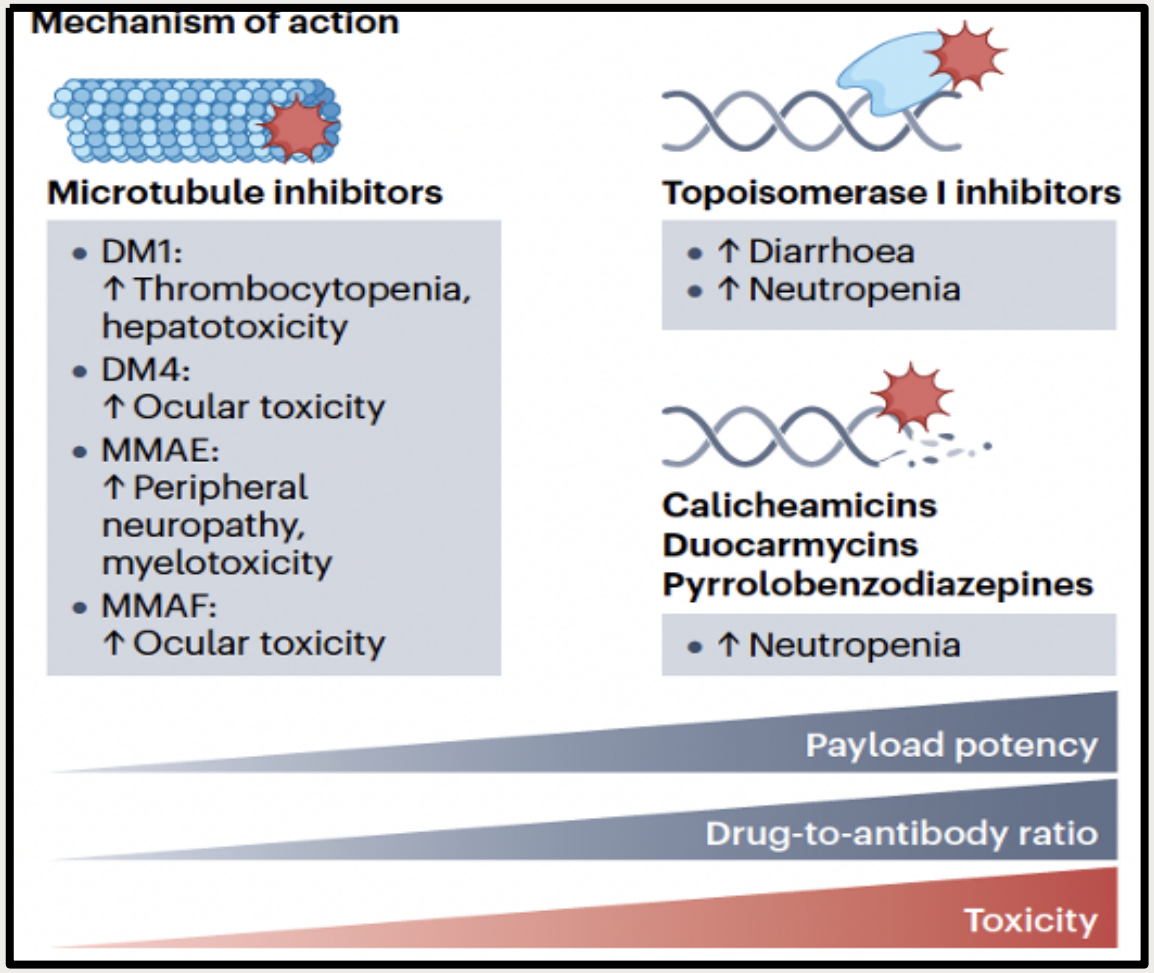
THE PAYLOAD

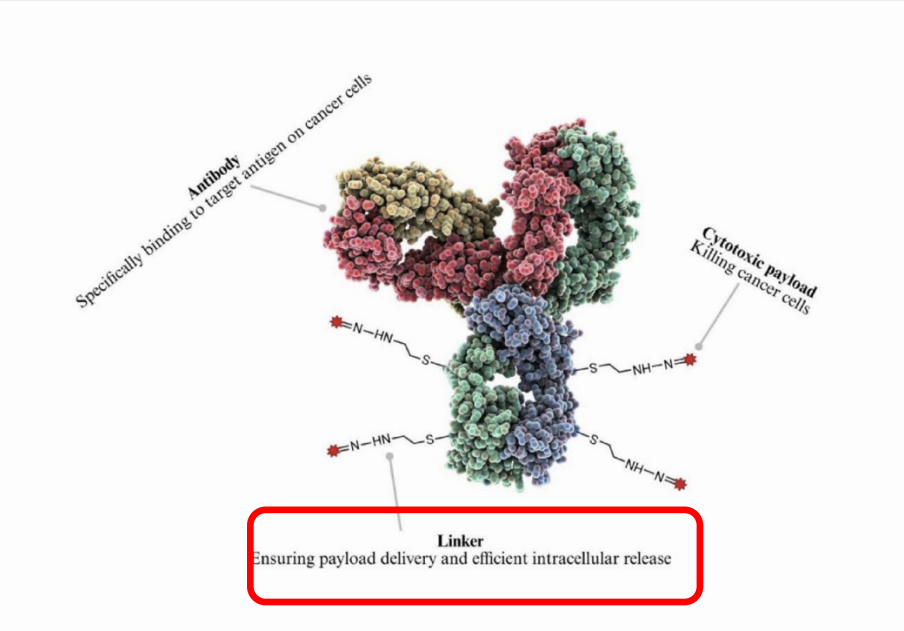


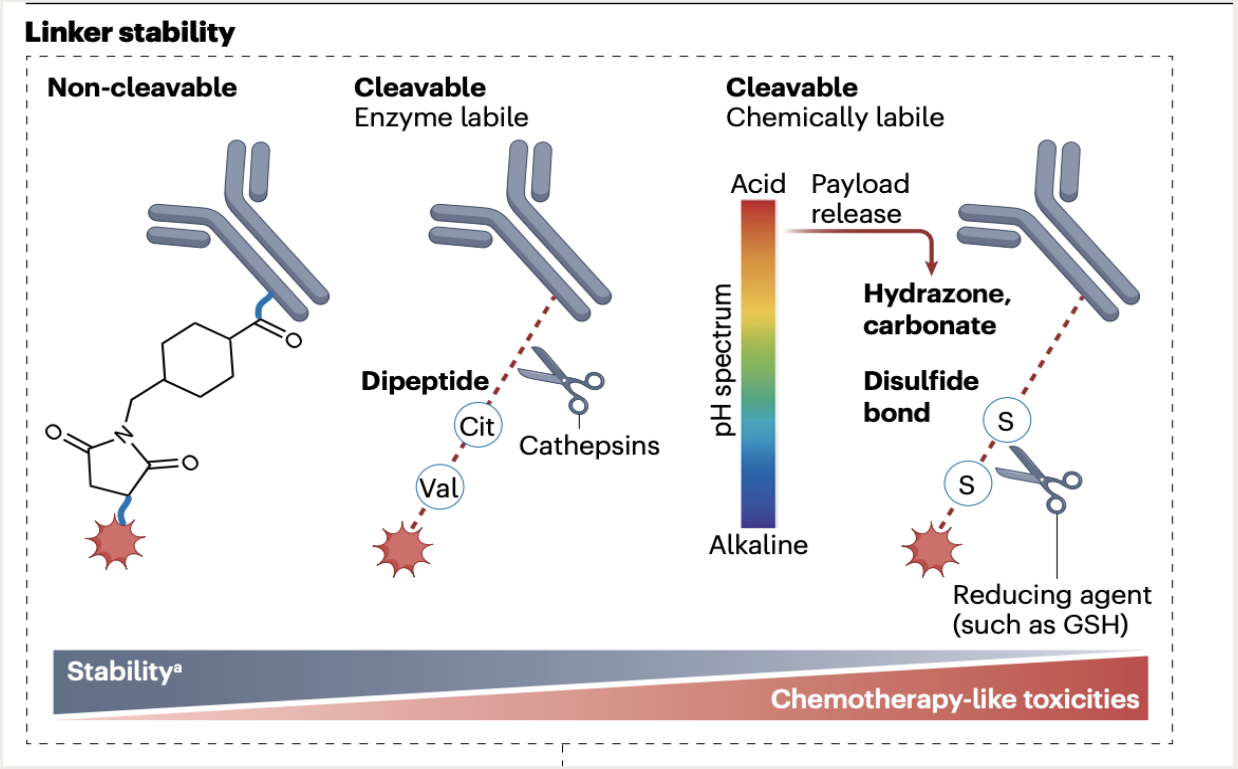


- **CORE DRIVER OF ADC EFFICACY,** designed to be **EXTREMELY POTENT,** [100 to 1000 times stronger than chemo.
- Most fall into **TWO MAIN CATEGORIES**: **tubulin inhibitors** which block microtubule assembly and disrupt cell division
- or **DNA-damaging agents** which cause DNA breaks or interfere with replication
- A key design parameter is the **drug-to-antibody ratio** (DAR), which defines the number of payload molecules per antibody.

Tarantino P, Ricciuti B, Pradhan SM, Tolaney SM.“Optimizing the safety of antibody-drug conjugates for patients with solid tumours.” N*at Rev Clin Oncol.* 2023;20(8):558-576. Curr. Oncol. 2026, 33, 103

THE LINKER

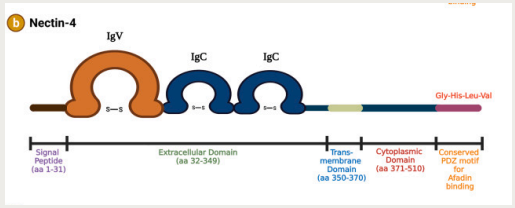




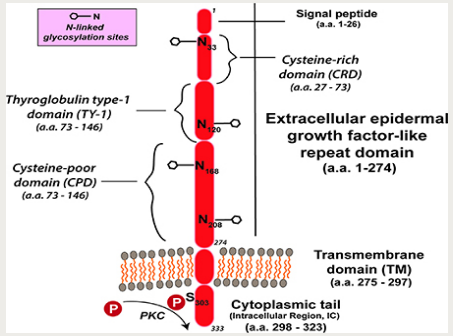
- The linker enables spatiotemporal control of payload delivery
- **CLEAVABLE** designs exploit **TME-specific triggers** (acidic pH, cathepsins, or other enzymes), whereas **NON-CLEAVABLE** linkers depend on lysosomal processing to release the cytotoxic agent

Tarantino P, Ricciuti B, Pradhan SM, Tolaney SM.“Optimizing the safety of antibody-drug conjugates for patients with solid tumours.” N*at Rev Clin Oncol.* 2023;20(8):558-576.

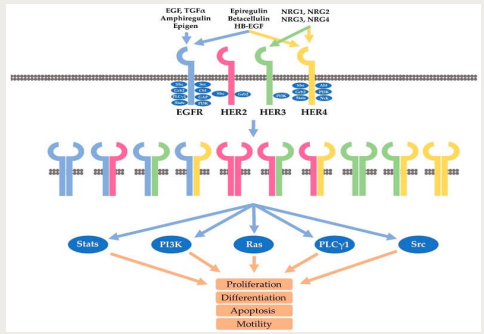
THE TARGET



- **Nectin-4** is a cell-adhesion protein with limited expression in normal adult tissues but frequent overexpression in cancer.
- Its overexpression is linked to tumor progression, proliferation, angiogenesis, epithelial–mesenchymal transition, metastasis, relapse, and poor prognosis.



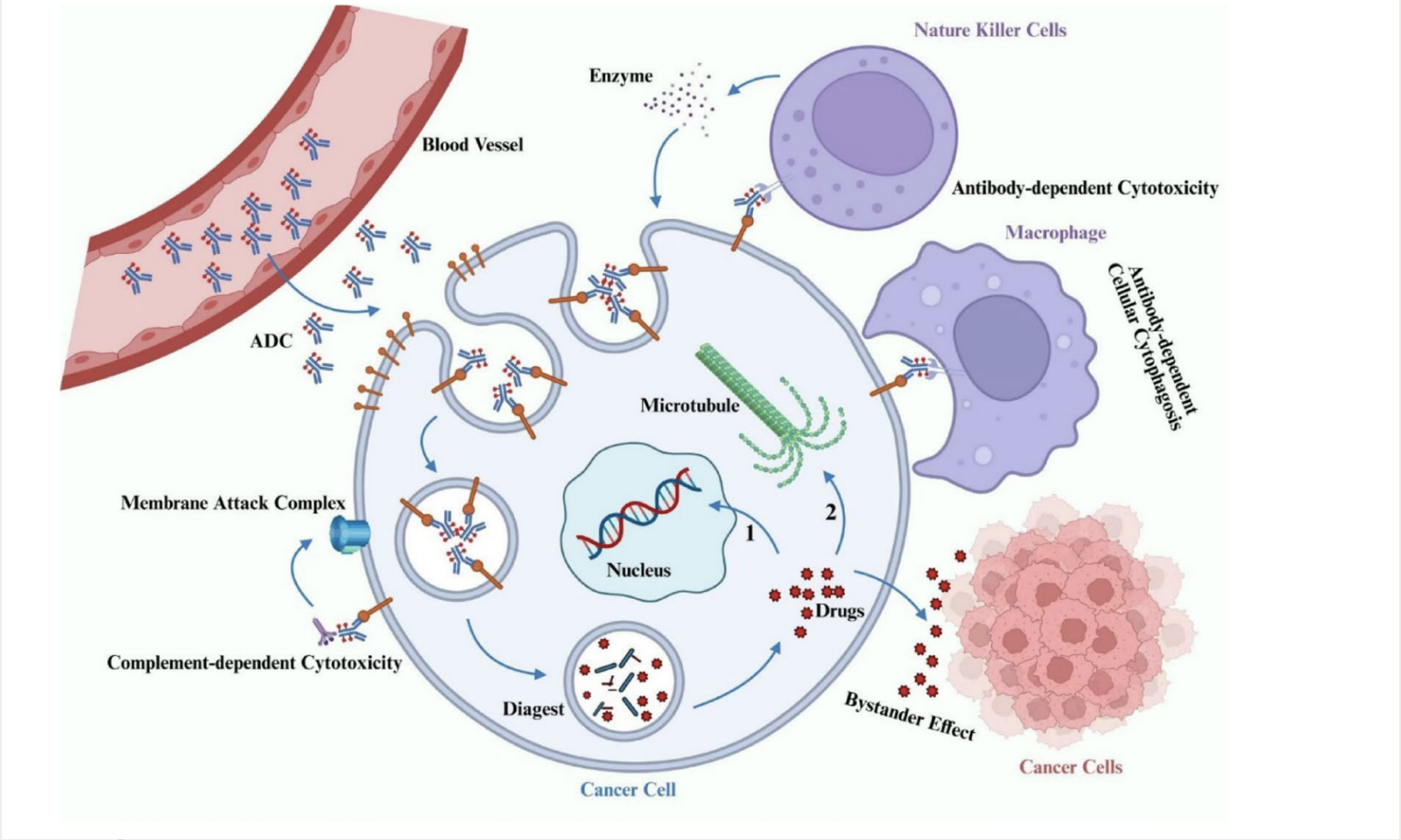
- **Trophoblast surface antigen 2** (Trop-2) is a type I transmembrane glycoprotein involved in Ca2+ signaling in tumor cells.
- It is highly expressed in various tumor tissues and represents a novel and promising molecular target for cancer targeted therapy.



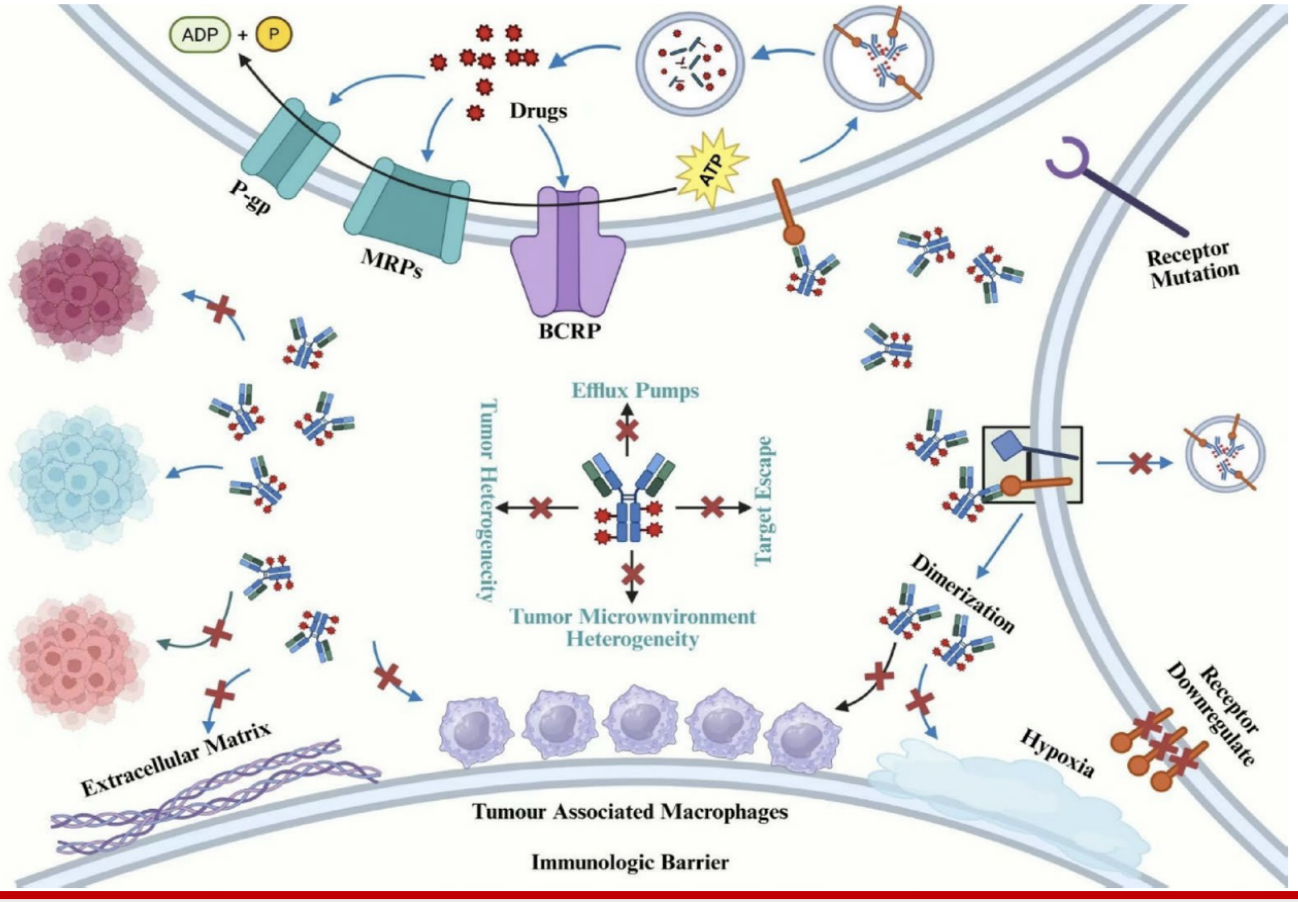
- **HER2** is one of the most mature emerging ADC targets beyond Nectin-4 and TROP-2. In urothelial carcinoma, HER2 may be altered through ERBB2 amplification, mutation, or protein overexpression,

Huang J et al Curr Oncol. 2026 Feb 5;33(2):103.

ADC: MoA


Nature Killer Cells
Enzyme
Blood Vessel
Antibody-dependent Cytotoxicity
Macrophage
Antibody-dependent Cellular Cytophagosis
ADC
Microtubule
Membrane Attack Complex
Nucleus
1
2
Drugs
Complement-dependent Cytotoxicity
Diagest
Bystander Effect
Cancer Cells
Cancer Cell

MAIN CHALLENGE: RESISTANCE

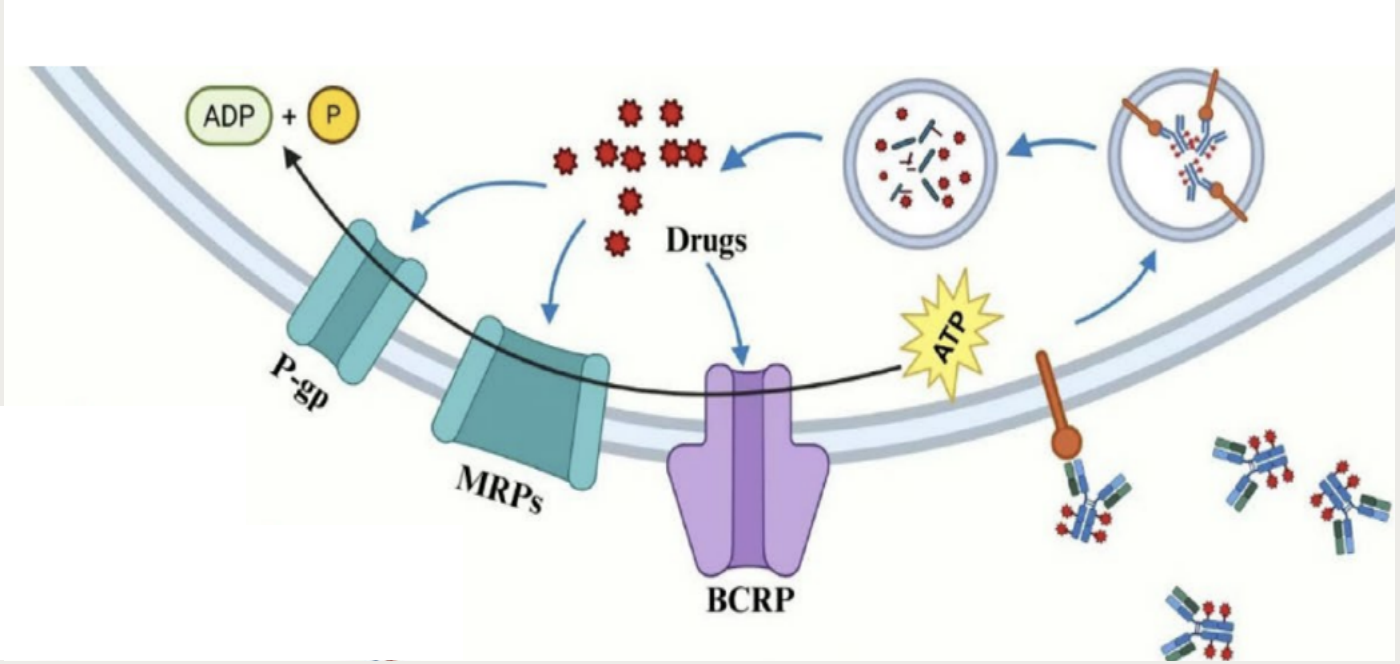


The resistance to ADCs are multifactorial and include:

1. **EFFLUX PUMP SYSTEM**
2. **TARGET ESCAPE**
3. **TME HETEROGENEITY**

Efflux pump system

- ATP-dependent transmembrane transporters actively export cytotoxic agents out of tumor cells, thereby diminishing intracellular drug accumulation and attenuating the efficacy of ADCs.

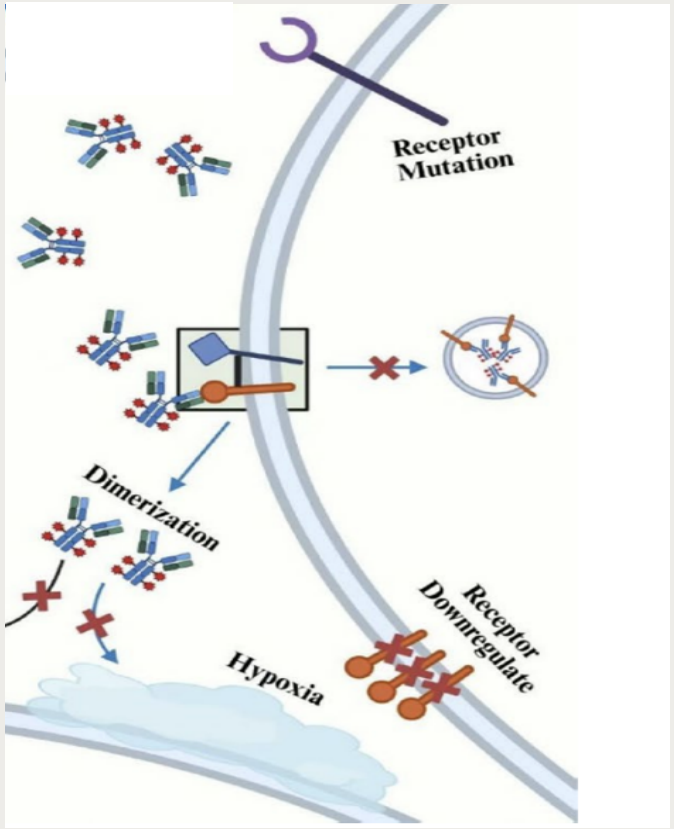


- Several frequently used payloads, including calicheamicin gamma 1, monomethyl auristatin E (MMAE), DM1, and DM4, have been identified as P-gp substrates

- P-gp functions as a **pan-ADC resistance determinant** as shown in preclinical models

THE TARGET

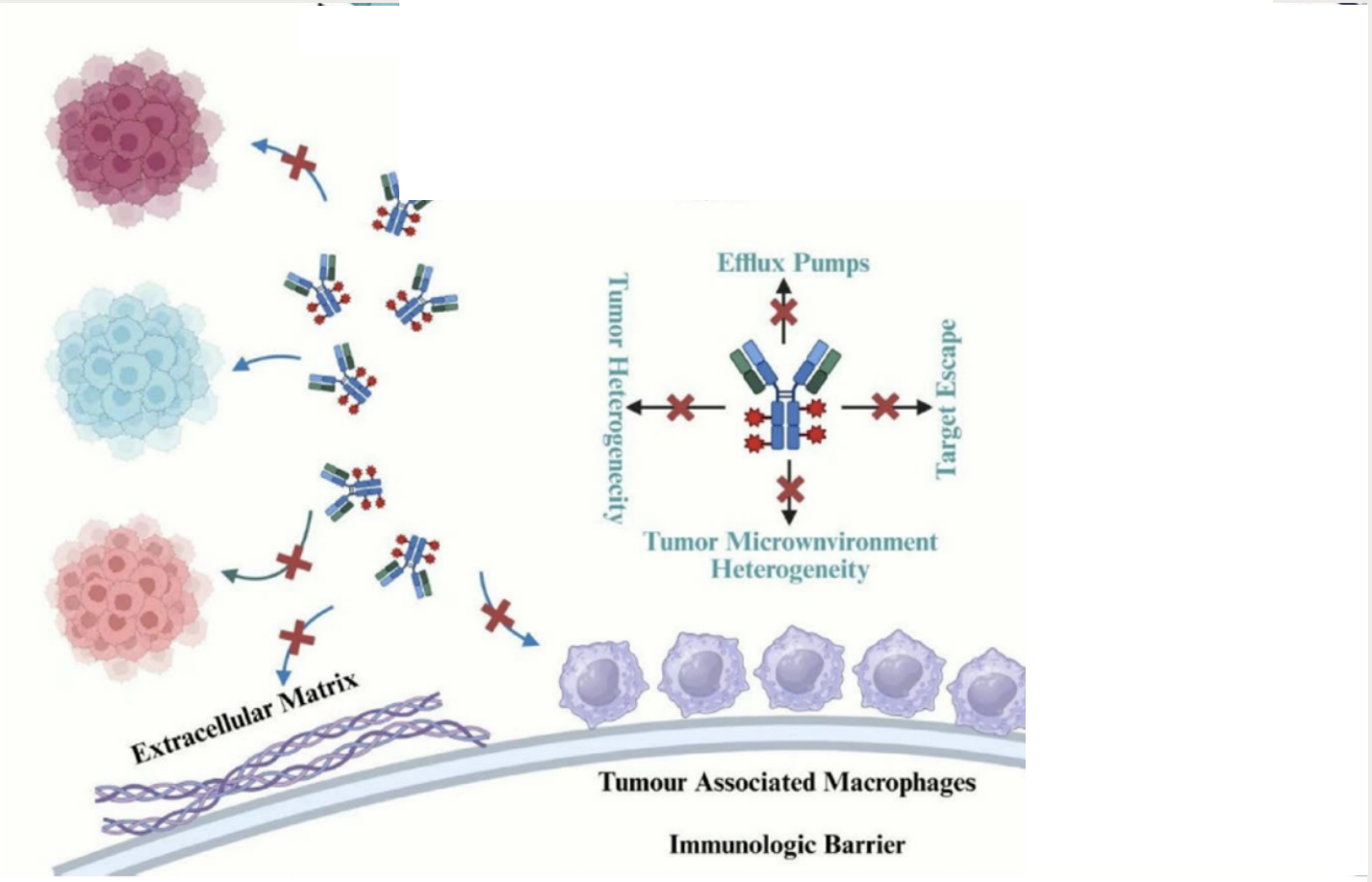
- The therapeutic efficacy of ADCs is primarily governed by the **HIGH-AFFINITY BINDING TO TUMOR-SPECIFIC ANTIGENS**, enabling delivery of cytotoxic payloads to malignant cells



- A primary mechanism underlying resistance to ADCs involves **GENETIC ALTERATIONS OF THE TARGET ANTIGENS.**
  - **Mutations** [i.e. mutations in TROP-2 (missense mutation T256R) associates with resistance to Saci Govitecan
  - **Downregulation** of the target
  - **Structural changes** in the target antigen that impair payload internalization
  - **Aberrant interaction** of the target with other molecules

Coates JT, Sun S, Leshchiner I, Thimmiah N, Martin EE, McLoughlin D, et al. Parallel genomic alterations of antigen and payload targets mediate polyclonal acquired clinical resistance to sacituzumab Govitecan in triplenegative breast cancer. Cancer Discov. 2021;11(10):2436–45

THE TUMOR MICROENVIROMENT



Resistance to ADCs mediated by the TME involves complex biological pathways that contribute to treatment failure at multiple levels.

SO HOW CAN WE OVERCOME THIS MECHANISM OF RESISTANCE?

Current research is focused on three complementary strategies:

- Inhibiting tumor cell defense mechanisms (Efflux Pumps)
- Engineering next-generation ADC constructs
- Employing rational combination therapies that target cancer through multiple pathways.

OVERCOMING P-GP MEDIATED RESISTANCE

- Several approaches are being explored focusing on :
  - **DISRUPTING ITS FUNCTION**
  - **MODULATING ITS EXPRESSION**
  - **DEVELOPING PAYLOADS WITH REDUCED P-GP AFFINITY**.

OVERCOMING P-GP MEDIATED RESISTANCE

- **DISRUPTING ITS FUNCTION,**
- **Pharmacological inhibition of P-gp**

  - Third-generation P-gp inhibitors, including TARIQUIDAR, ZOSUQUIDAR, and LANIQUIDAR, have shown potential in preclinical models to enhance intracellular drug retention by targeting the ATPase or substrate-binding domains of P-gp

  - However, **the clinical utility of systemic P-gp inhibitors remains constrained by their off-target effect**s on physiological barriers such as the blood-brain barrier (BBB), liver, and kidneys

OVERCOMING P-GP MEDIATED RESISTANCE

- **MODULATING ITS EXPRESSION**

  - **Gene-silencing strategies,** particularly small interfering RNA (siRNA)-mediated targeting of P-gp, have demonstrated promising preclinical results in overcoming drug resistance but **difficult to translate to therapeutics.**

  - **Emerging technologies, including CRISPR/Cas9-based gene editing**, offer additional strategies to suppress P-gp expression. [in development]

OVERCOMING P-GP MEDIATED RESISTANCE

- **PAYLOADS WITH REDUCED P-GP AFFINITY**.
  - **Exatecan,** a potent topoisomerase Inhibitor, is not a preferred substrate for P-gp and does not require metabolic activation
    - OBI-992, a TROP2-targeted ADC employing exatecan and an enzymatically cleavable linker, which demonstrated potent anti-tumor activity in vivo
    - OBI-992 retained efficacy in P-gp- overexpressing cells, as exatecan showed markedly lower efflux compared to conventional payloads such as DXd and 7-ethyl-10-hydroxycamptothecin (SN-38)

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- Engineering next-generation ADC constructs
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Engineering next-generation ADC constructs

The three core components of an ADC, the **antibody**, **payload** and **linker** can be modified

Jang, A.; Brown, J.R. Strategies to Overcome Resistance to Enfortumab Vedotin and Pembrolizumab for Patients with Urothelial Carcinoma: Harnessing Present Knowledge for Future Advances. Explor. Target. Anti-Tumor Ther. 2025, 6, 1002307

Engineering next-generation ADC constructs

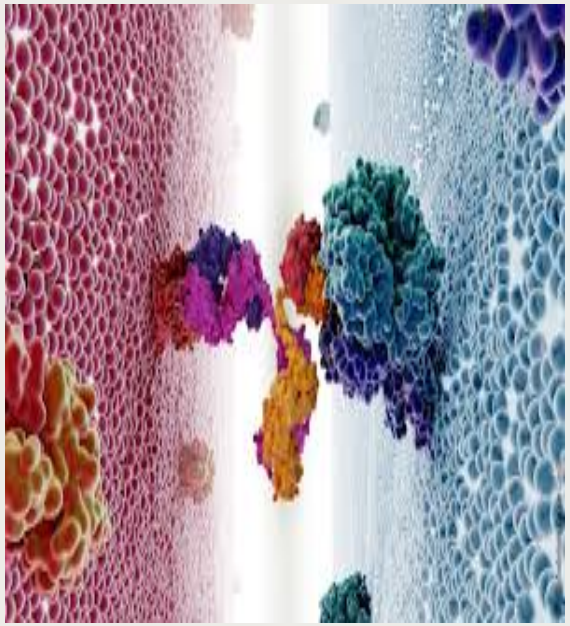
The three core components of an ADC, the **antibody**, **payload** and **linker** can be modified :

- **ANTIBODY**
  - **Bispecific ADCs** capable of binding to two distinct epitopes or targets have the potential to enhance tumor selectivity and reduce antigen escape
  - **Miniaturized conjugates**, such as bicycle toxin conjugates (BTCs)
  - **Nanoparticle-based delivery systems**

Jang, A.; Brown, J.R. Strategies to Overcome Resistance to Enfortumab Vedotin and Pembrolizumab for Patients with Urothelial Carcinoma: Harnessing Present Knowledge for Future Advances. Explor. Target. Anti-Tumor Ther. 2025, 6, 1002307

A NEW APPROACH: BI-SPECIFICs

- Bispecific approaches in urothelial cancer are another innovative approach.
- The most advanced is the EGFR × HER3 bispecific ADC **izalontamab brengitecan**/BL-B01D1, which combines **dual HER-family** targeting with a **Topo-I payload** and is now being tested in randomized development after immunotherapy.
- Other bispecific strategies include :
  - **immune-modulating constructs** such as bintrafusp alfa, which showed limited activity in platinum-refractory UC
  - checkpoint bispecifics such as **cadonilimab** in combination with HER2 ADCs.
- T-cell–redirecting bispecifics are less developed in classical urothelial carcinoma, although DLL3 × CD3 targeting may become relevant for neuroendocrine/small-cell bladder cancer.



SUMMARY OF BI-SPECIFICS?

Agent / platform	Bispecific target	Type	Development status / relevance in UC
Izalontamab brengitecan / Iza-bren / BL-B01D1	**EGFR × HER3**	**Bispecific ADC** with Topo-I payload	Phase II data in pretreated la/mUC showed encouraging activity. **IZABRIGHT-Bladder01** is a randomized phase II/III trial comparing Iza-bren vs platinum chemotherapy after progression on/after immunotherapy
Bintrafusp alfa / M7824	**PD-L1 × TGF-β trap**	Bifunctional immunotherapy fusion protein	Tested in platinum-refractory advanced UC. Phase Ib showed **ORR 20%**, but accrual was stopped because meaningful benefit beyond available therapies was considered unlikely; further development in this setting was halted.
Cadonilimab / AK104	**PD-1 × CTLA-4**	Dual-checkpoint bispecific antibody	Not a major standalone UC program, but it has been studied in combination with **disitamab vedotin** in urothelial carcinoma. This represents a HER2 ADC + bispecific checkpoint strategy rather than a UC-specific bispecific target program. (American Society of Clinical Oncology)
Tarlatamab	**DLL3 × CD3**	Bispecific T-cell engager	Not conventional urothelial carcinoma development, but potentially relevant for **small-cell/neuroendocrine bladder cancer** if DLL3-positive.
Preclinical Nectin-4 × CD3 CAB bispecifics	**Nectin-4 × CD3**	Conditional T-cell engager	Preclinical concept only. Designed to redirect T cells to Nectin-4–expressing tumor cells with conditional activity in the tumor microenvironment; not yet a mature clinical UC program.

Engineering next-generation ADC constructs

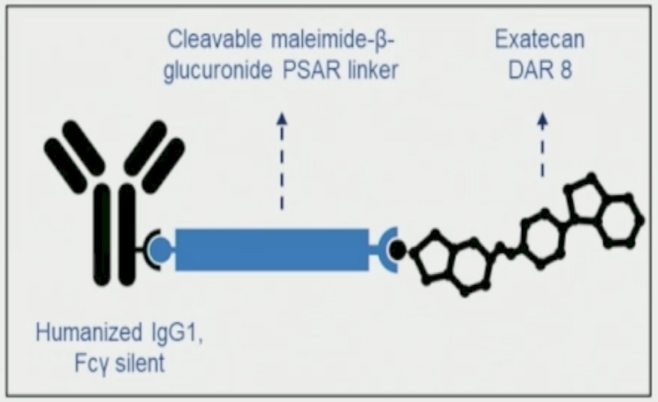
The three core components of an ADC, the **antibody**, **payload** and **linker** can be modified :

- **PAYLOAD**
  - **Payload substitution** [switching from a tubulin inhibitor to a DNA damaging agent can circumvent resistance linked to prior payload exposure]
  - **Dual-payload ADCs**, engineered to deliver two distinct cytotoxic agents, are also under development to minimize the likelihood of single mechanism resistance

Jang, A.; Brown, J.R. Strategies to Overcome Resistance to Enfortumab Vedotin and Pembrolizumab for Patients with Urothelial Carcinoma: Harnessing Present Knowledge for Future Advances. Explor. Target. Anti-Tumor Ther. 2025, 6, 1002307

LY4101174: NEW PAYLOAD SAME TARGET

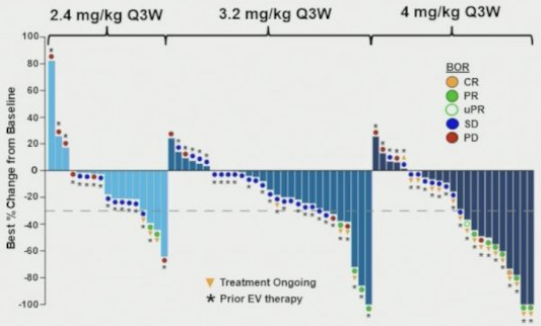
- LY4101174 / ETx-22 is a next-generation Nectin-4 ADC designed to extend Nectin-4 targeting beyond enfortumab vedotin by **replacing the MMAE payload with the Topo-I inhibitor exatecan.**



	All Participants (n=143)	mUC (n=86)
Median age, years (range)	68 (30-85)	70 (35-85)
Race, n (%)		
White	94 (66)	57 (66)
Asian	19 (13)	9 (11)
Black or African American	6 (4)	4 (5)
Other	24 (17)[c]	16 (19)[d]
ECOG PS, n (%)		
0	56 (39)	33 (38)
1[a]	87 (61)	53 (62)
Tumor type, n (%)		
mUC	86 (60)	86 (100)
non-mUC[b]	57 (40)	-
CrCl mL/min, n (%)		
30-49	9 (6)	8 (9)
50-59	24 (17)	16 (19)
≥60	110 (77)	62 (72)

Disease Characteristics of Special Interest in mUC (n=86)	
Metastatic disease site[e], n (%)	
Visceral metastases	76 (88)
Liver metastases	27 (31)
Lymph node only	8 (9)
Median prior regimens for mUC (range)	3 (1-8)
Prior Therapy, n (%)	
Platinum chemotherapy	76 (88)
EV with or without pembrolizumab	79 (92)
EVP	26 (30)
ICI[f]	86 (100)
ADC – Topo-I	18 (21)
Reason for EV discontinuation	
Toxicity	15 (19)

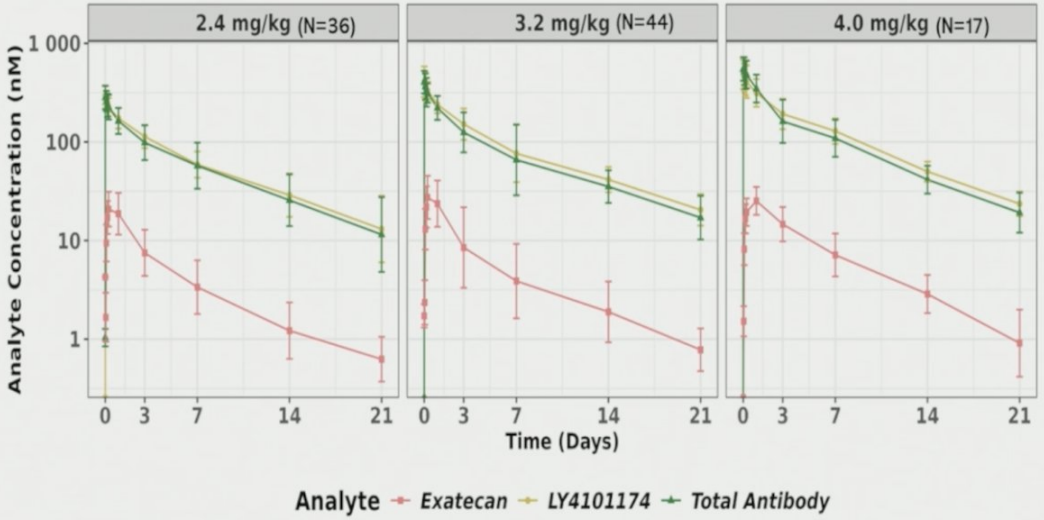
Efficacy Evaluable Participants[a]	Total Q3W (n=76)	2.4 mg/kg Q3W (n=19)	3.2 mg/kg Q3W (n=32)	4 mg/kg Q3W (n=25)
ORR, % (n)	**20 (15)**	**11 (2)**	**13 (4)**	**36 (9)**
CR, n (%)	1 (1)	-	-	1 (4)
PR, n (%)	14[b] (18)	2 (11)	4 (13)	8[b] (32)
SD, n (%)	40 (53)	9 (47)	21 (66)	10 (40)
DCR, % (n)	**72 (55)**	**58 (11)**	**78 (25)**	**76 (19)**



Grade ≥3 Hematologic TEAEs by DL, (All Q3W Doses)			
Hematologic TEAEs, %	**2.4 mg/kg (n=37)**	**3.2 mg/kg (n=47)**	**4 mg/kg (n=25)**
Anemia	41	53	68
Neutropenia[b]	14	43	36
Thrombocytopenia[c]	5	26	48
Febrile neutropenia[f]	3	13	16
Dose reductions due to AEs[h], %	14	40	48

Gao X. et al. Initial results from EXCEED, a phase 1 study of LY4101174… *Journal of Clinical Oncology*, ASCO 2026 abstract 4517

EXCEED DID NOT EXCEED EXPECTATIONS



There was an **elevated plasma payload release** (~8%), consistent with the observed systemic toxicities.

Additionally, the maleimide-beta-glucuronide **linker may be susceptible to cleavage by normal tissue proteases:**

- Tolerability of LY4101174 was primarily limited by grade 3+ hematologic toxicity, in particular neutropenia and febrile neutropenia, which persisted despite G-CSF prophylaxis
- The EXCEED study did not identify a dose that was both tolerable and sufficiently efficacious in participants with previously treated metastatic urothelial carcinoma
- Without a clear therapeutic window, development was discontinued

Engineering next-generation ADC constructs

The three core components of an ADC, the **antibody**, **payload** and **linker** can be modified :

- **LINKER**
- New designs aimed at **exploiting novel cleavage mechanisms**, including those activated by **radiation** or **tumor-specific enzymes.**
  - Radiation-activated ADCs represent a new strategy
    - In these constructs, the linker is designed to remain stable in circulation and release the payload only after exposure to ionizing radiation.
    - This could allow radiotherapy to “switch on” payload release selectively within irradiated tumor sites, potentially reducing off-tumor toxicity and enabling combinations with local radiation
  - The best-described platform is called **RAMP-ADC**, for **radiation-amplified antibody–drug conjugate**.

Quintana JM et al. Radiation Cleaved Drug-Conjugate Linkers Enable Local Payload Release. *Bioconjugate Chemistry*. 2022.

SO HOW CAN WE OVERCOME THIS MECHANISM OF RESISTANCE?

Current research is focused on three complementary strategies:

- Inhibiting tumor cell defense mechanisms (Efflux Pumps)
- Engineering next-generation ADC constructs
- Employing rational combination therapies that target cancer through multiple pathways.

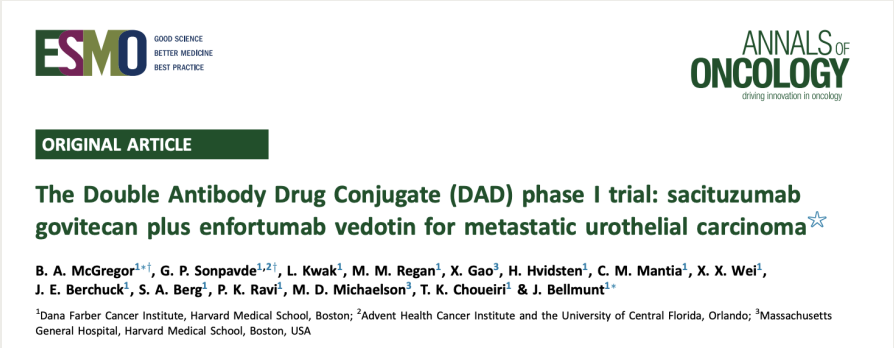
Rational combination therapy

Combining ADCs with agents that act through non-overlapping mechanisms can achieve synergistic effects and prevent resistance:

- Dual antibody drug conjugate (DAD) trial: EV + SG
- DAD-IO: Combining dual ADC + IO
- ANTI-TIGIT ANTI LAG-3 based combos
- SAC TMT + EV
- ADCs + Chemo
- ADCs + TKIs

Brown, J.T.; Nazha, B.; Liu, Y.; Lozada, K.; Smith, J.D.; Hartman, C.; McClintock, G.R.; Kucuk, O.; Carthon, B.C.; Harvey, R.D.; et al. Updated Interim Analysis of a Phase I/Ib Study of Enfortumab Vedotin plus Cabozantinib in Patients with Metastatic Urothelial Carcinoma. J. Clin. Oncol. 2024, 42, 4586

DAD/DAD-IO


ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

The Double Antibody Drug Conjugate (DAD) phase I trial: sacituzumab govitecan plus enfortumab vedotin for metastatic urothelial carcinoma☆

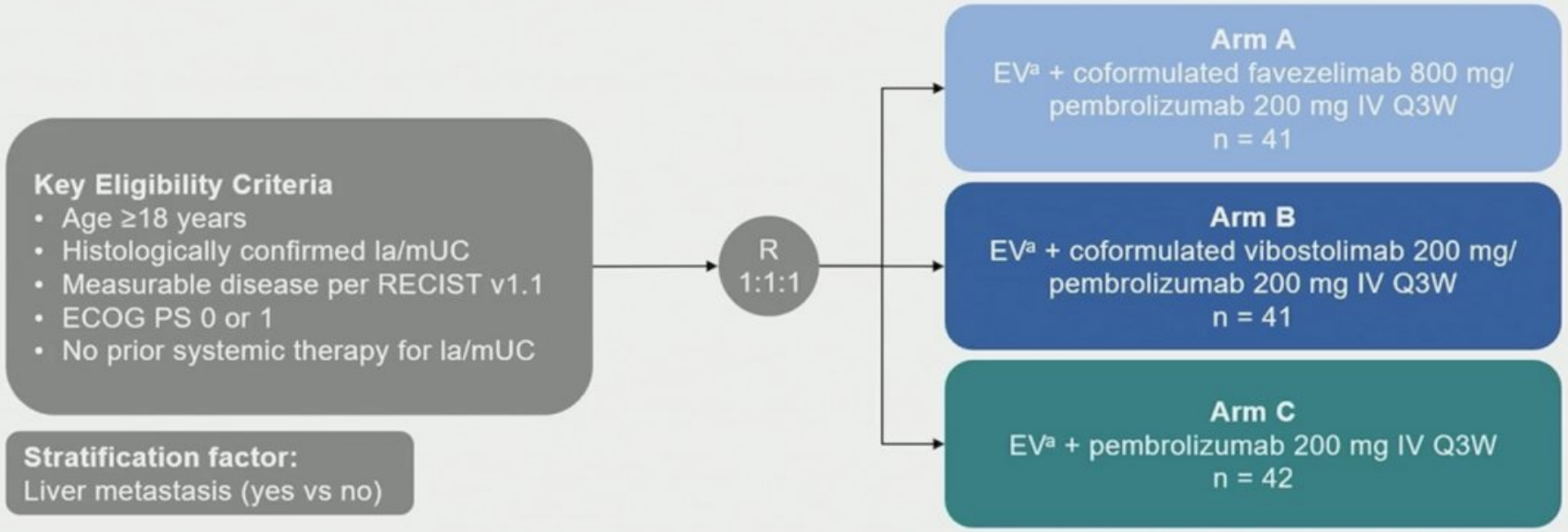
B. A. McGregor[1,*,†], G. P. Sonpavde[1,2,†], L. Kwak[1], M. M. Regan[1], X. Gao[3], H. Hvidsten[1], C. M. Mantia[1], X. X. Wei[1], J. E. Berchuck[1], S. A. Berg[1], P. K. Ravi[1], M. D. Michaelson[3], T. K. Choueiri[1] & J. Bellmunt[1,*]

[1]Dana Farber Cancer Institute, Harvard Medical School, Boston; [2]Advent Health Cancer Institute and the University of Central Florida, Orlando; [3]Massachusetts General Hospital, Harvard Medical School, Boston, USA

DAD/DAD-IO explores whether dual ADC targeting can intensify treatment in metastatic urothelial carcinoma.

- In the DAD phase I cohort, SG + EV produced a high ORR of 70% in heavily pretreated mUC, with durable responses and no unexpected delayed toxicity.
- DAD-IO builds on this by adding pembrolizumab to SG + EV in the first-line setting, but mature efficacy data for the triplet have not yet been publicly reported.
    - The study will enroll patients with treatment-naive metastatic urothelial carcinoma,
    - The phase 2 portion of the study will enroll approximately 42 patients who will receive EV at 1.25 mg/kg and SG at 7.5 mg/kg on days 1 and 8, every 21 days, in addition to pembrolizumab
    - During the expansion phase of the study, granulocyte colony-stimulating factor support will be strongly mandated

ADCs doublets: KEYMAKER-U04 Substudy 04B



End points
- **Primary:** ORR per RECIST v1.1 by investigator and safety
- **Secondary:** DOR and PFS per RECIST v1.1 by investigator

Median study follow-up[b]:
- **EV + fave/pembro:** 11.9 months (range, 9.7-17.0)
- **EV + vibo/pembro:** 11.7 months (range, 9.7-16.3)
- **EV + pembro:** 11.8 months (range, 9.8-16.8)

OTHER DOUBLETS: KEYMAKER-U04 substudy 04C

KEYMAKER-U04 substudy 04C — NCT06483334

This is a phase 1/2 umbrella substudy in locally advanced or metastatic urothelial carcinoma. It is specifically designed to test **dual-ADC therapy** using:

Sac-TMT / MK-2870 — TROP2-directed ADC with a belotecan-derived Topo-I payload

plus **Enfortumab vedotin** — Nectin-4-directed ADC with an MMAE payload

The study has two parts: Part 1 evaluates safety and preliminary efficacy of **Sac-TMT + EV;** Part 2 is intended to evaluate **Sac-TMT + EV + pembrolizumab**, depending on Part 1 results.

SAC-TMT is also being delivered in other context as a single agent

TROP-2 WITH TOPO 1: Datopotamab deruxtecan with platinum-based chemo

TROPION-Urothelial03: A phase 2/3 study of datopotamab deruxtecan (Dato-DXd) + platinum chemotherapy (CT) vs gemcitabine + platinum CT in participants with locally advanced or metastatic urothelial carcinoma (la/mUC) with progression on or after enfortumab vedotin (EV) + pembrolizumab (pembro).

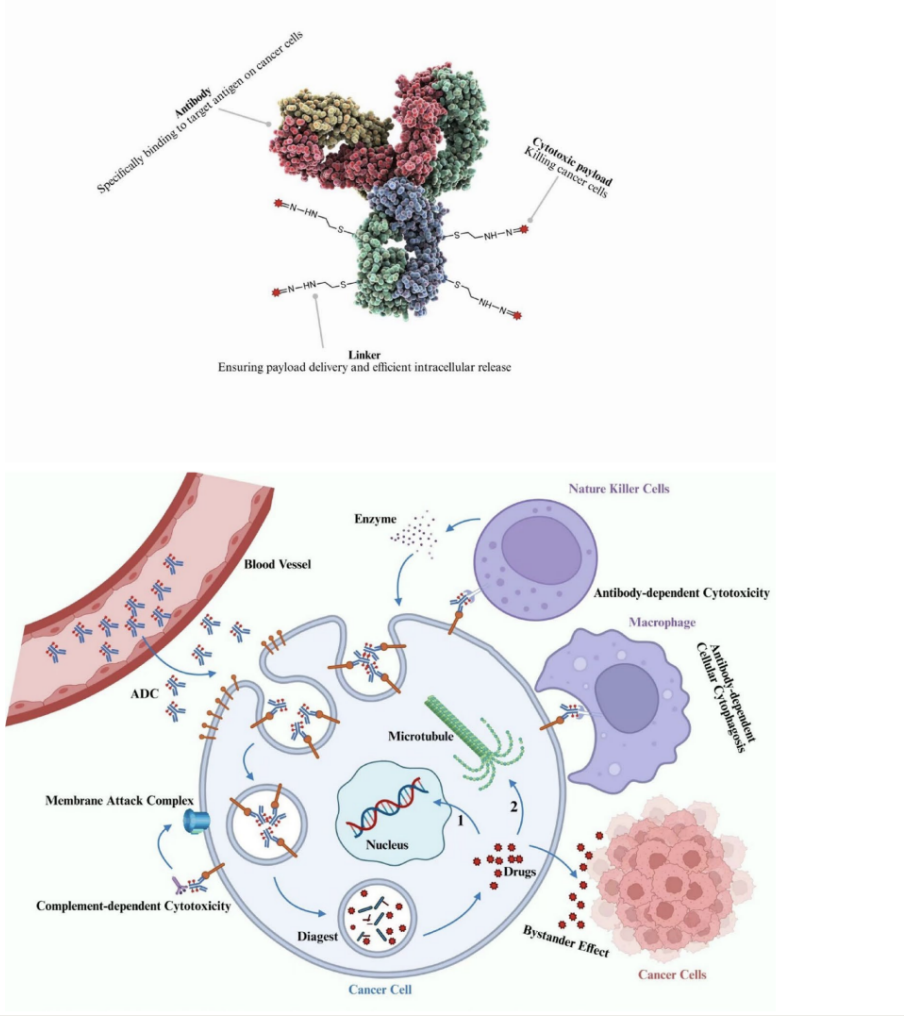
Matthew D. Galsky, Alexandra Drakaki, Arnab Basu, Bradley Alexander McGregor, Jens Bedke, Yohann Loriot, Eiji Kikuchi, Jun Guo, Benjamin Garmezy, Srikala S. Sridhar, Gunnar Klauss, Daisy Lin, Chelsea Liu, Andrea B. Apolo, Thomas Powles; Icahn School of Medicine at Mount Sinai, Tisch Cancer Institute, New York, NY; UCLA Health, Los Angeles, CA; Division of Hematology and Oncology, Mayo Clinic Florida, Jacksonville, FL; Dana-Farber, Harvard Cancer Center, Boston, MA; Klinikum Stuttgart Katharinen Hospital, Stuttgart, Germany; Gustave Roussy Cancer Institute, Paris, France; St. Marianna University School of Medicine, Kawasaki, Japan; Peking University Cancer Hospital and Research Institute, Beijing, China; Genitourinary Research Program, Sarah Cannon Research Institute, Nashville, TN; Princess Margaret Cancer Centre, Toronto, ON, Canada; Daiichi Sankyo, Inc., Basking Ridge, NJ; National Cancer Institute, Bethesda, MD; Barts Cancer Institute, Queen Mary University of London, London, United Kingdom

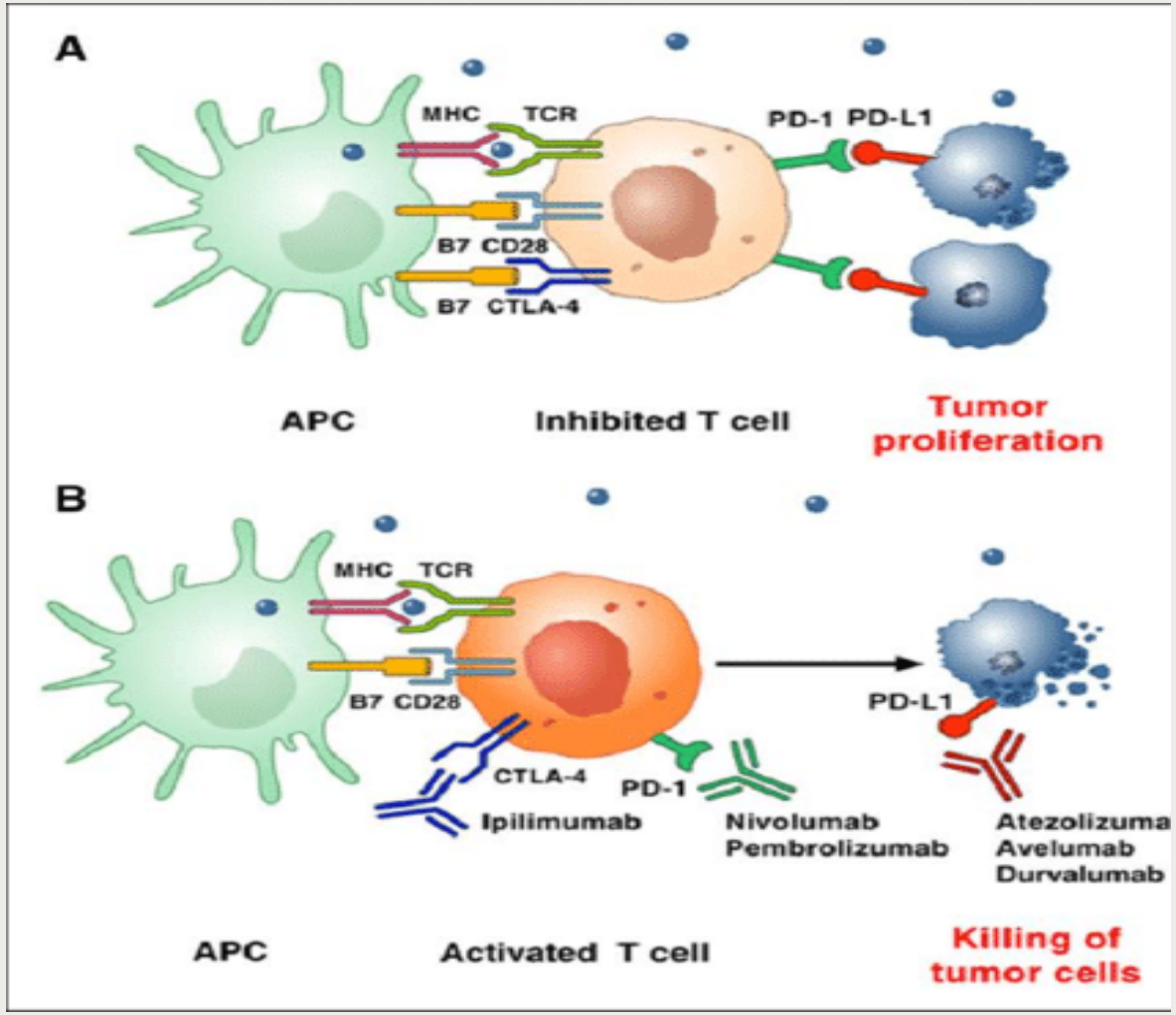
A phase 2/3 trial comparing the efficacy and safety of Dato-DXd + platinum CT (carboplatin or cisplatin) vs gemcitabine + platinum CT in participants with la/mUC with disease progression on or after EV + pembrolizumab.

- 60 participants will be randomized 1:1 to receive Dato-DXd 4 or 6 mg/kg + platinum CT.
- In part B (phase 3), ~570 participants will be randomized 1:1 to receive Dato-DXd at the recommended phase 3 dose (determined using part A data) + platinum CT vs gemcitabine + platinum CT.


TIME LEFT

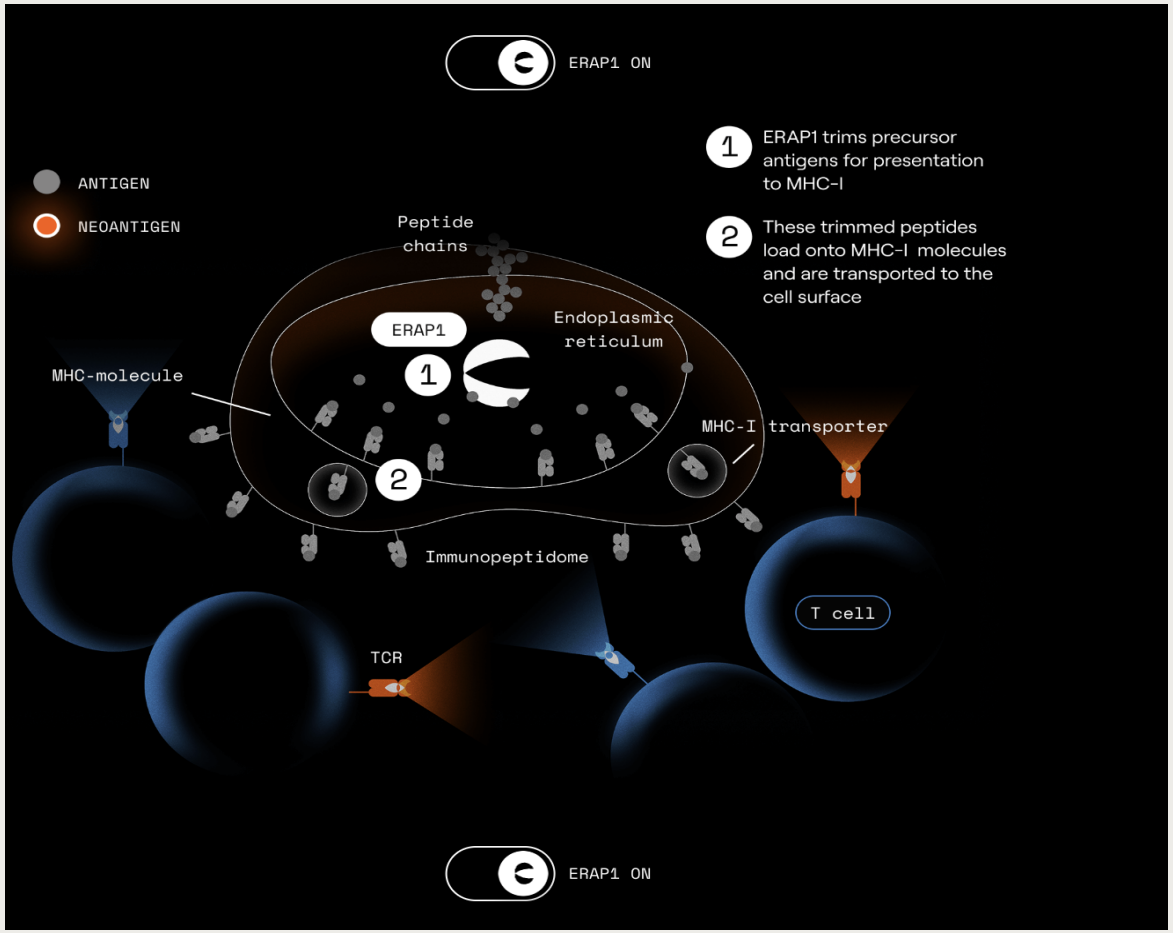
The mechanism of action

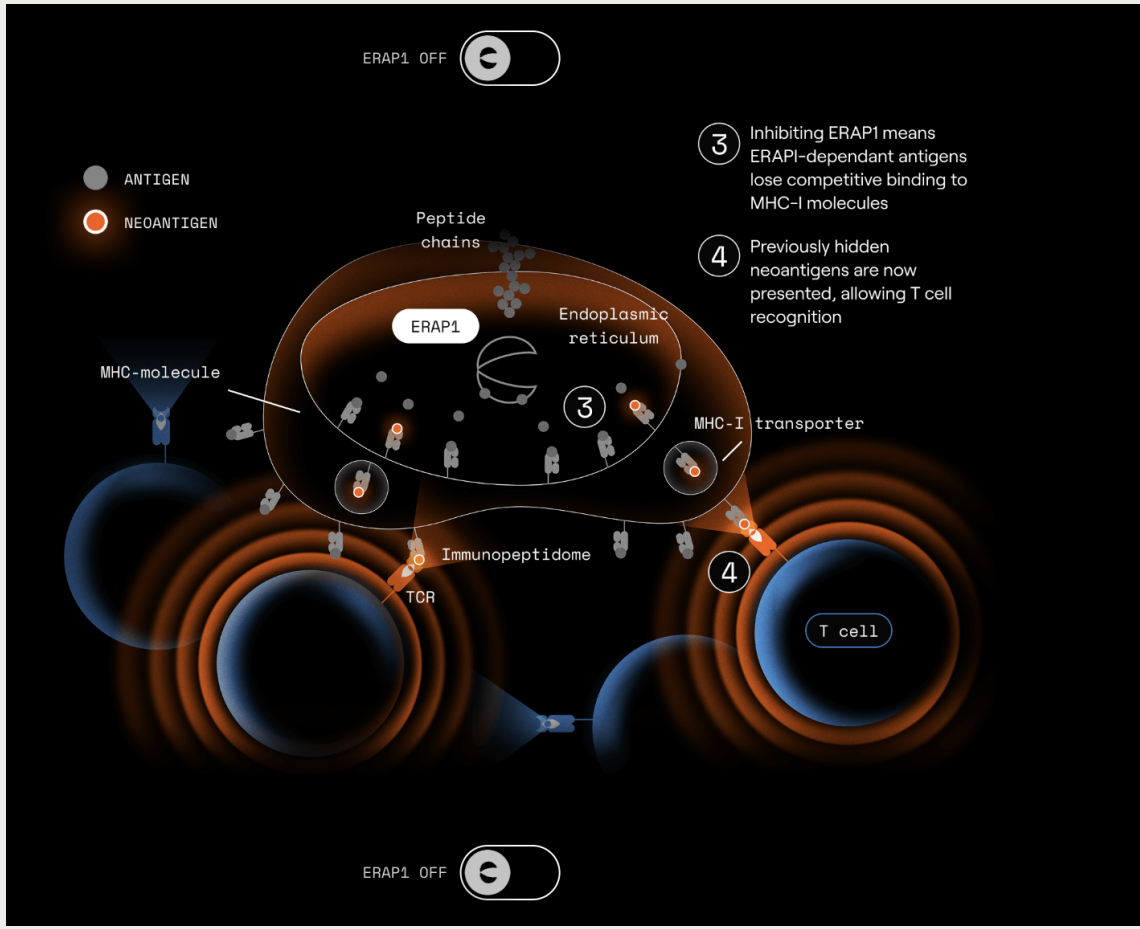




- Image of ADC from Zhou et al. Journal of Hematology & Oncology (2025) 18:96 : : image of CPI MoA from Circulation. 2017;136:1989–1992.

ERAP-1

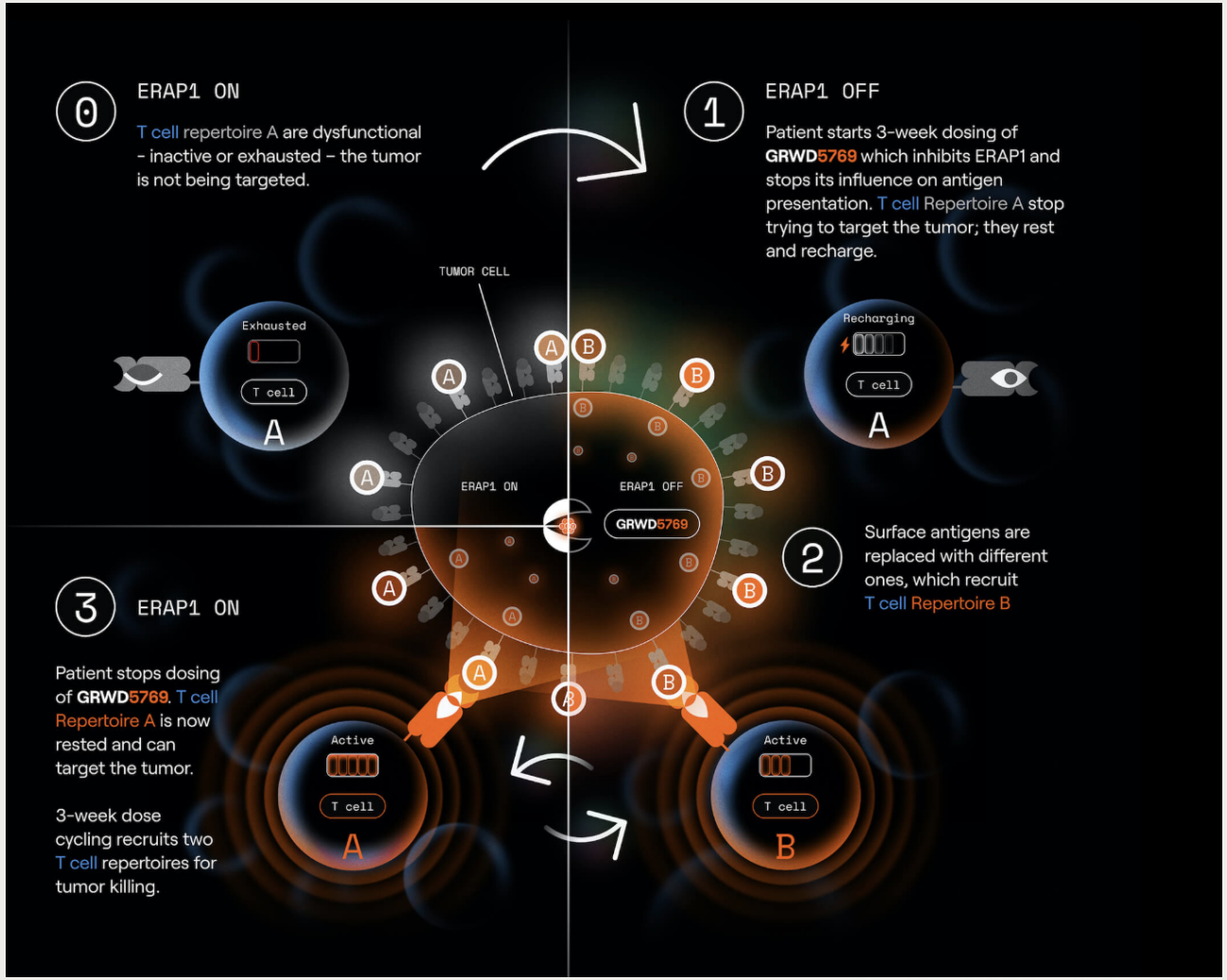

ERAP1 ON
ANTIGEN
NEOANTIGEN
Peptide chains
ERAP1
Endoplasmic reticulum
MHC-molecule
MHC-I
transporter
Immunopeptidome
T cell
TCR
ERAP1 ON
1
ERAP1 trims precursor antigens for presentation to MHC-I
2
These trimmed peptides load onto MHC-I molecules and are transported to the cell surface


ERAP1 OFF
ANTIGEN
NEOANTIGEN
Peptide chains
ERAP1
Endoplasmic reticulum
MHC-molecule
MHC-I
transporter
Immunopeptidome
TCR
T cell
ERAP1 OFF
3
Inhibiting ERAP1 means ERAPI-dependant antigens lose competitive binding to MHC-I molecules
4
Previously hidden neoantigens are now presented, allowing T cell recognition

ERAP-1 : A new way of restoring T cell exhaustion

ERAP1 inhibition cycling replaces tumor surface antigens to cycle T cell repertoires

- Re-sensitizes tumors after acquired resistance, enabling renewed responses to checkpoint inhibitor rechallenge
- Potential to improve response to first-line immunotherapy by:
  - Preventing T cell exhaustion from occurring
  - Expanding T cell breadth and activity



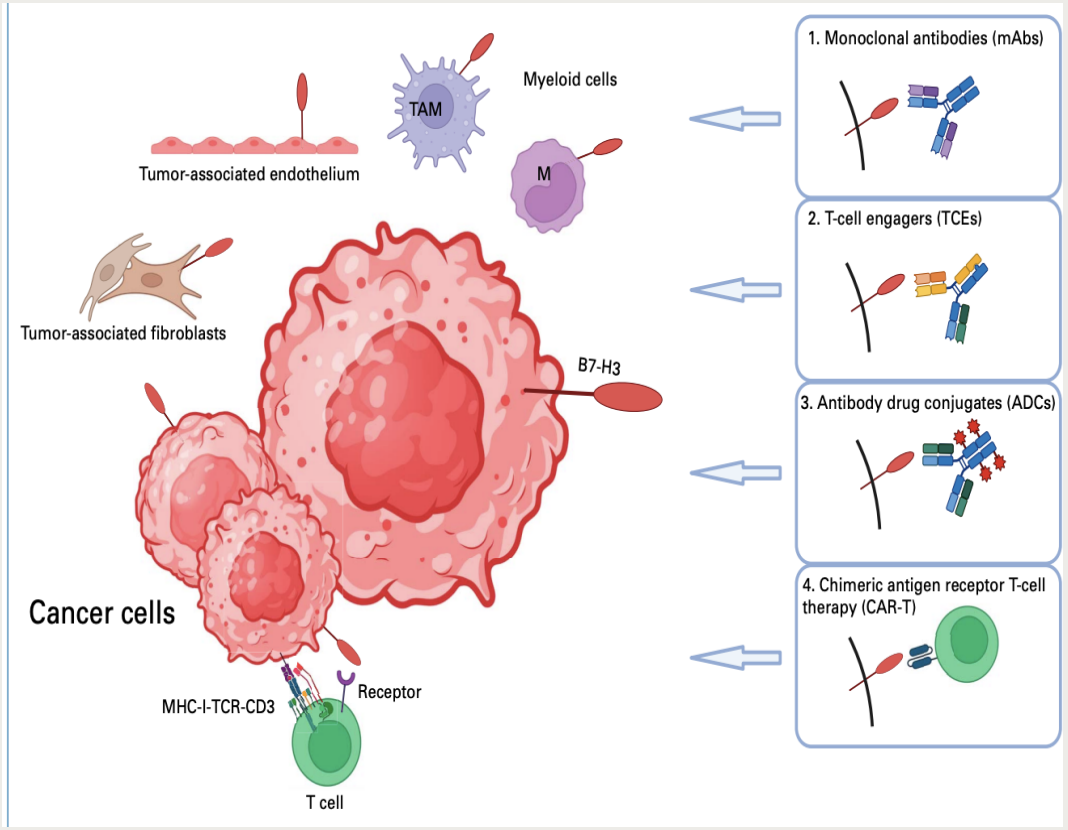
GRWD5769 is a ERAP-1 inhibitor

https://www.greywolftherapeutics.com/

B7-H3

B7-H3/CD276 is attractive because of **broad expression in solid tumors**, **immune-regulatory biology**, and **ongoing development of B7-H3 ADCs** such as **IFINATAMAB DERUXTECAN** in advanced solid tumors including urothelial cancer.

It is highly upregulated in cancer cells and stromal and hematopoietic components within the tumor microenvironment



ONE STEP BEYOND

FOCUS ON MOLECULAR IMAGING

Nectin-4–Targeted Radiotheranostics for Personalized Cancer Therapy: A Systematic Review

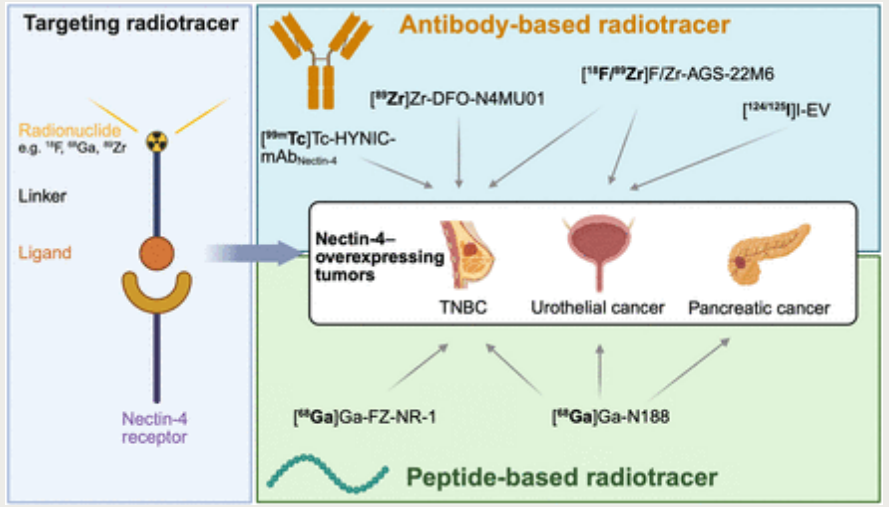
Laura Schäfer[1], Betül Altunay[1], Agnieszka Morgenroth[1], Andreas Vogg[1], Yvonne Derks[2], Twan Lammers[3,4], Quim Peña[3], Felix Manuel Mottaghy[1,4,5], and Susanne Lütje[1,4]

[1]Department of Nuclear Medicine, University Hospital RWTH Aachen, Aachen, Germany; [2]Department of Medical Imaging, Nuclear Medicine, Radboudumc, Nijmegen, The Netherlands; [3]Institute for Experimental Molecular Imaging, University Hospital RWTH Aachen, Aachen, Germany; [4]Center for Integrated Oncology, University Hospital RWTH Aachen, Aachen, Germany; and [5]Department of Radiology and Nuclear Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

Preclinical studies of nectin-4–targeted radiotracers such as [^{89}Zr]Zr-AGS-22M6, [^{68}Ga]Ga-N188, and [^{68}Ga]Ga-NOTA-PEG$_{12}$-BP have shown high specificity and strong correlation of uptake with immunohistochemistry scores.

PEGylation of bicyclic peptides improved tumor uptake and imaging contrast, particularly in liver and bone metastases.

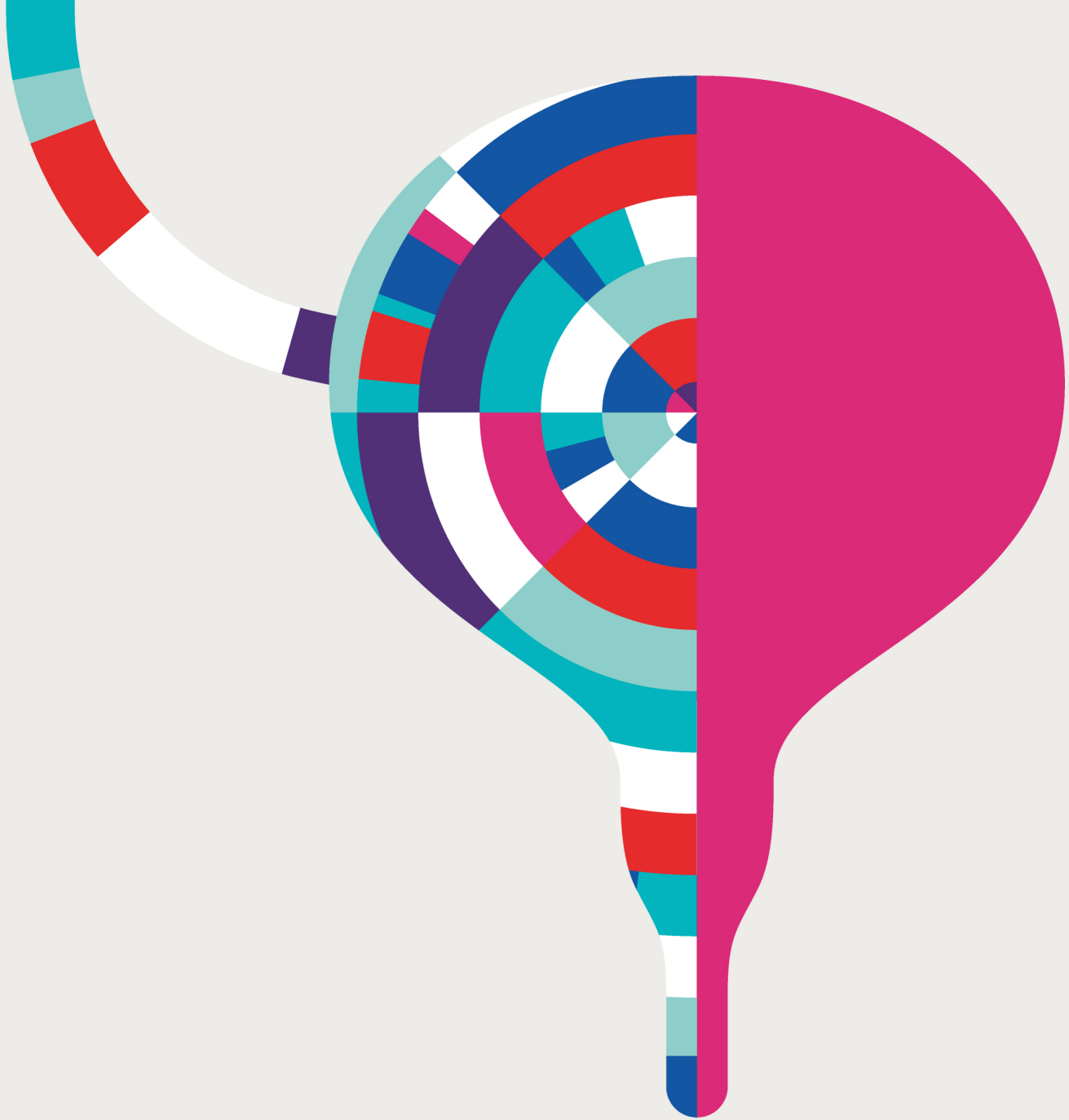
These tracers demonstrated favorable pharmacokinetics, with rapid clearance from nontarget tissues and minimal toxicity in preclinical models, supporting their safety for clinical use.



SUMMARY

- In the current era ADCs + CPI are becoming SOC in urothelial cancers in different clinical settings.
- Nevertheless, resistance to these agents will happen and new drugs/new MoA are needed
- Rotating Payloads, combos of ADCs and bispecifics result interesting strategies
- New strategies around the modulation of the immune response result also appealing approaches

MasterClass in
Bladder Cancer 2026



¡Gracias!

Organized by:
HENDERE HEALTHCARE

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12 de Octubre
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