Introduction to ADCs, Understanding the Mechanism of Action with a Case Presentation

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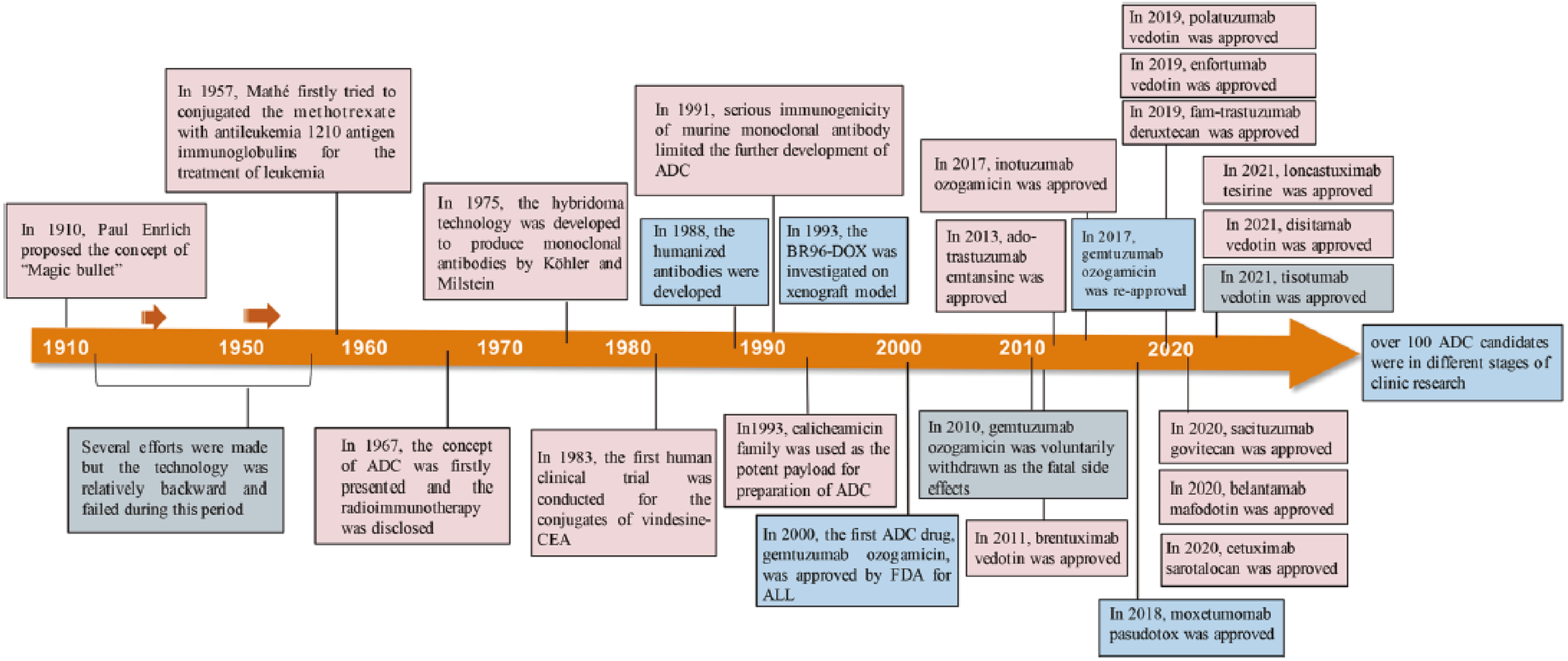
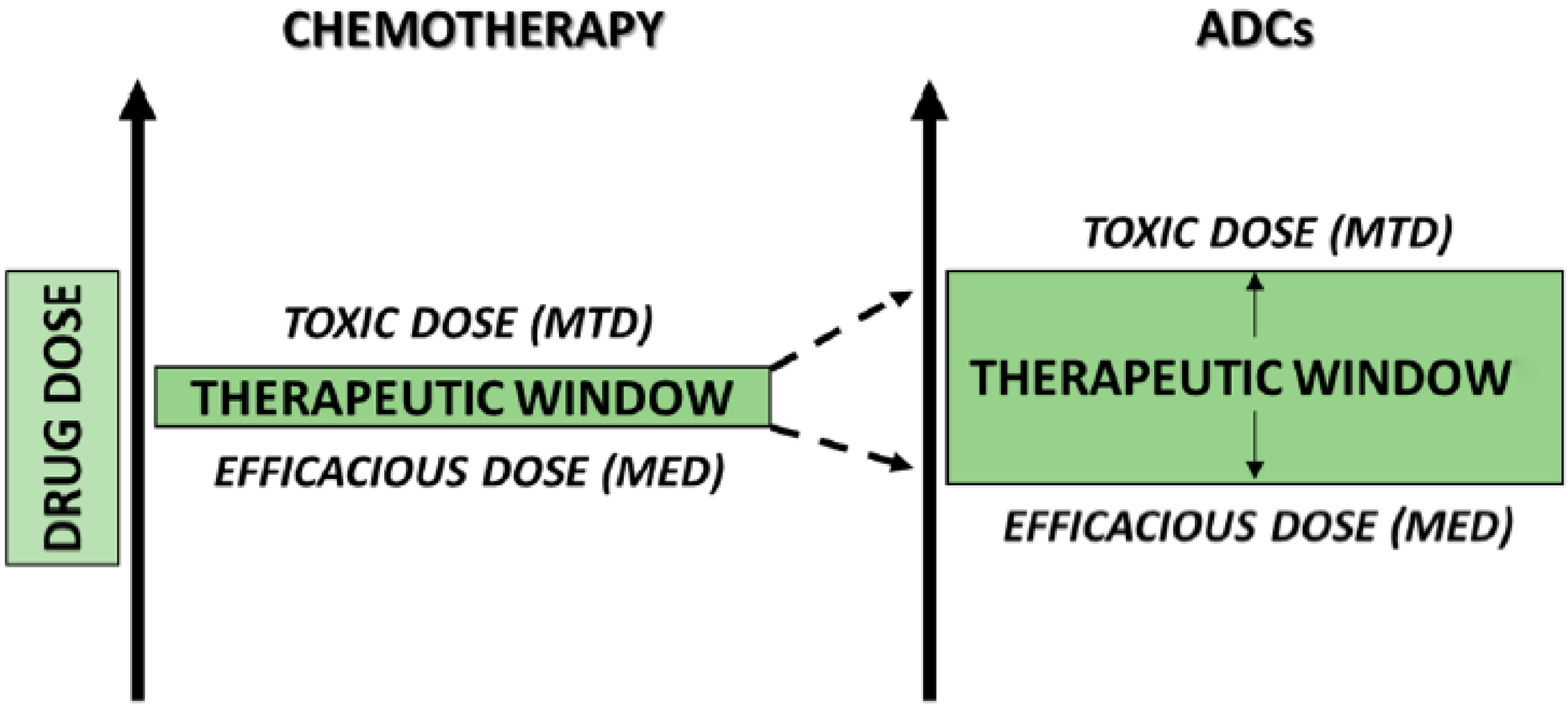
History of ADC Development

Timeline depicting important events in the development and approval of ADC drugs over the past century since the “magic bullet” was proposed by Paul Enrlich 1910



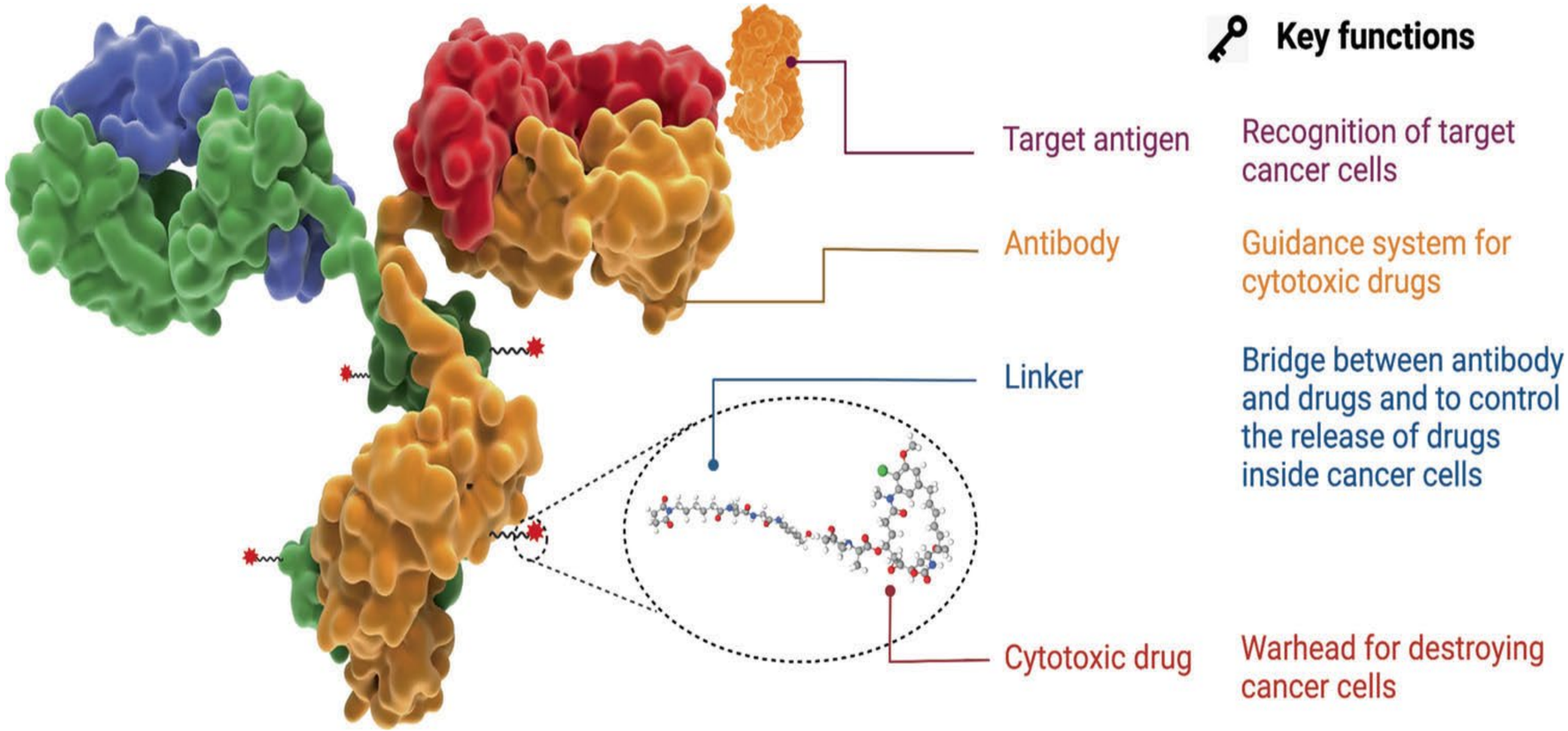
Fu Z et al Signal Transduction and Targeted Therapy 2022

Theoretical increase in the therapeutic window through the use of ADCs compared with chemotherapy



Antibody Drug Conjugate Design

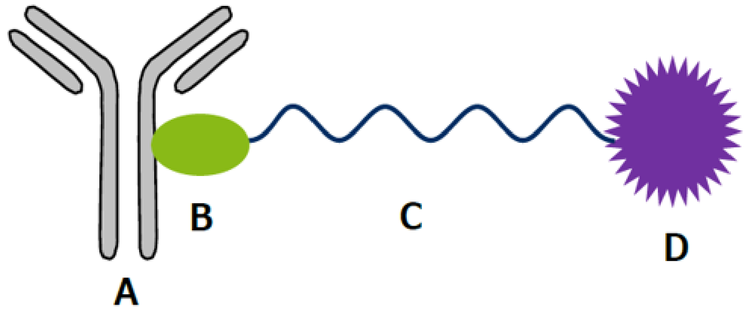
The structure and characteristic of an ADC drug.
The core components including target antigen, antibody, linker, cytotoxic drug



Fu Z et al Signal Transduction and Targeted Therapy 2022c

ADC Design

Each component and their interactions have a crucial role in determining efficacy and toxicity profiles of an ADC



A : Antibody
B : Attachment site
C : Linker
D : Drug

Antibody:
1. Tumor selective and high expression antigens
2. Internalization to target cell
3. Minimized non-specific binding

Linker:
1. Cleavable and non-cleavable
2. Release active substance in target cell

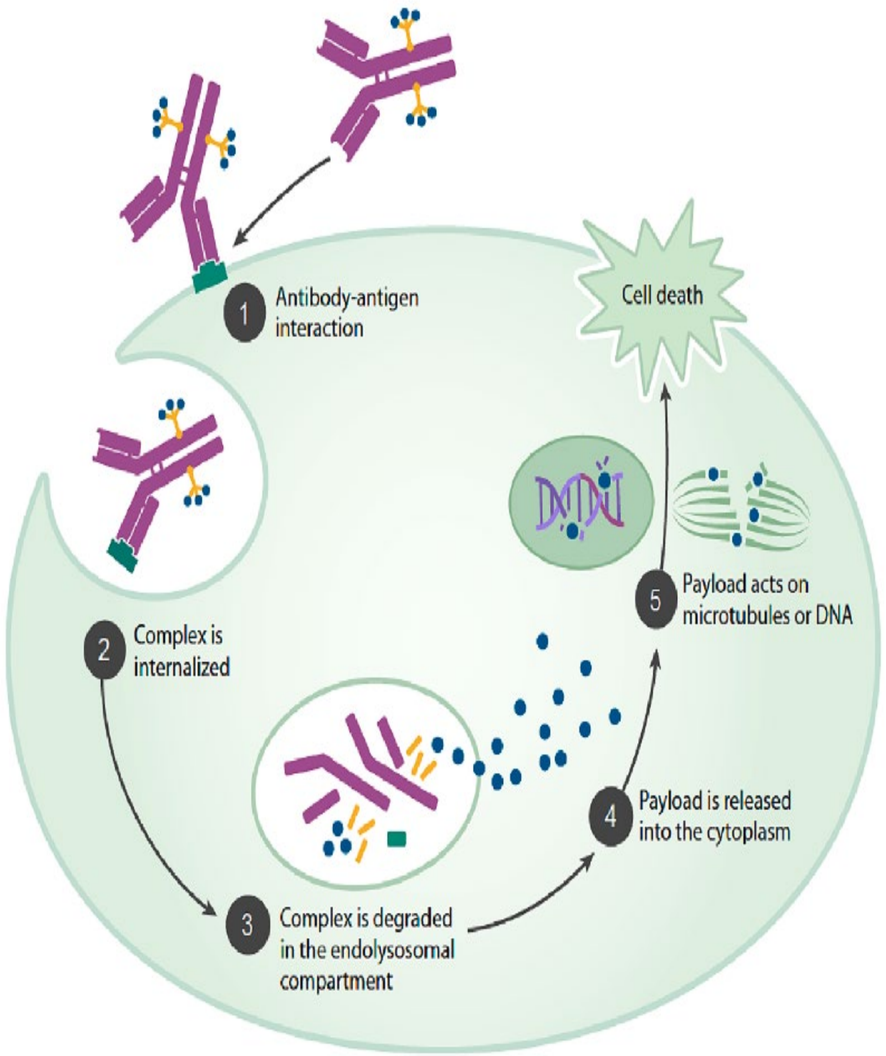
Attachment site:
1. Typically cysteine or lysine residue on antibody
2. Control of drug to antibody ratio
3. Control of drug distribution

Drug:
1. Should have potent efficacy
2. Available linker binding site

Key Terminology

- **Drug to antibody ratio (DAR):** is the average number of drugs conjugated to the antibodies
- **De-conjugation:** is the release of the small molecule (payload) from the ADC by chemical or enzymatic process
- **Bystander effect:** escape of the released toxin from the targeted cancer cells allow toxins to affect neighboring cells and cause subsequent killing

Canonical Mechanism of Action of ADCs



Antibody binds to the target antigen at the surface of the cancer cell.

ADC-antigen complex is internalized and trafficked through the endolysosomal compartment.

Payload is released in the endolysosomal compartment

Drug payload enters the cytoplasm

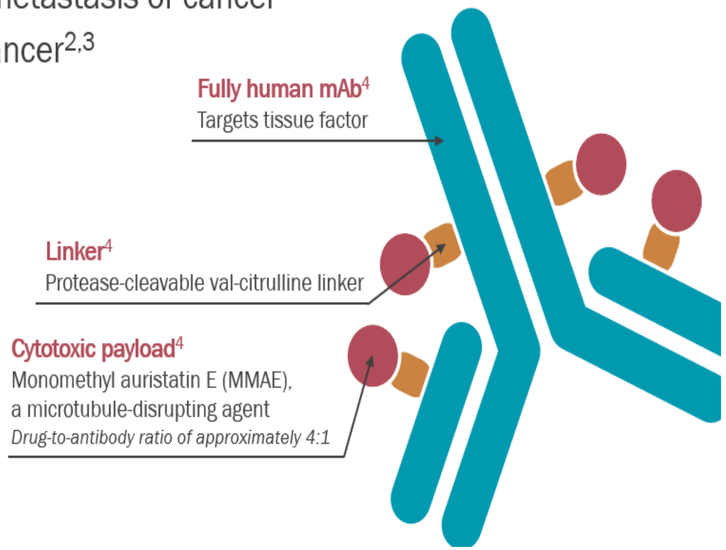
Drug payload acts on microtubules or DNA, resulting in cell death.

Tolcher AT, et al. Cancer Treatment Reviews 2023

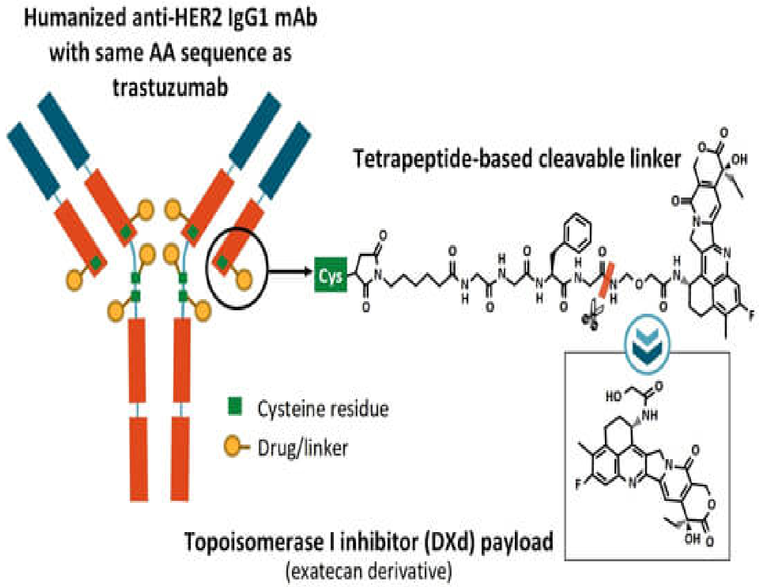
ADCs: Cervical Cancer

Tisotumab Vedotin (TV): A Tissue Factor-Directed ADC

- Tissue factor
  - Transmembrane protein that is the primary initiator of coagulation[1]
  - Involved in angiogenesis and metastasis of cancer[1]
  - Highly expressed in cervical cancer[2,3]



HER2-Targeted ADC: Trastuzumab Deruxtecan

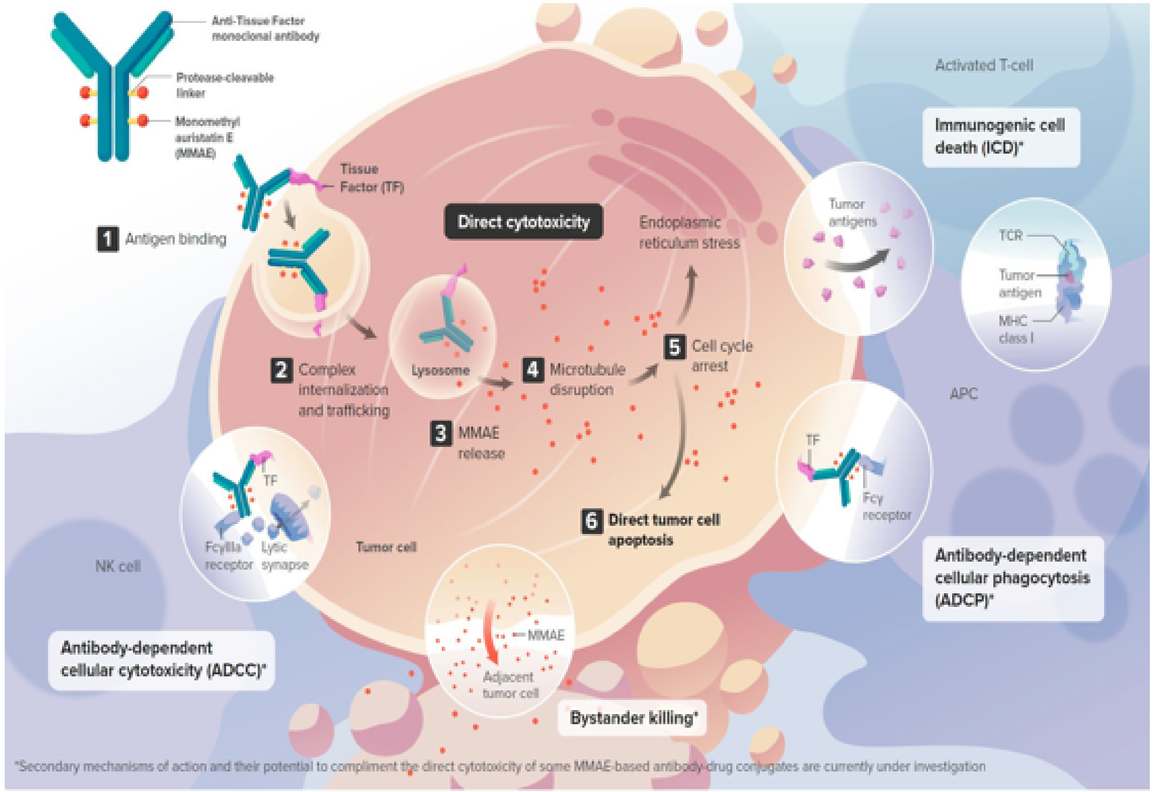


- High drug:antibody ratio: ~8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

Nakada. Chem Pharm Bull (Tokyo). 2019;67:173, Trail, Pharmacol Ther. 2018:181:156, Ogitani Cancer Sci. 2016 2016;107:1039

Tisotumab Vedotin: Mechanism of Action

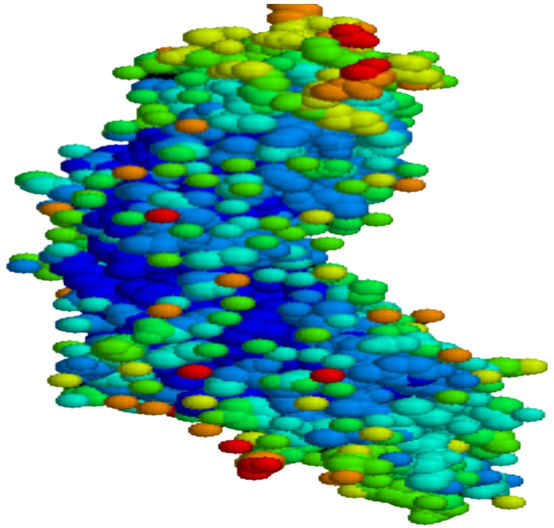
- Tisotumab vedotin is a tissue factor (TF)-directed antibody–drug conjugate covalently linked to the microtubule- disrupting agent MMAE via a protease- cleavable linker
  - TF is a protein highly expressed in cervical cancer and other solid tumors
- Multimodal MOA of tisotumab vedotin
  - Direct cytotoxicity
  - Bystander killing
  - Immunogenic cell death
  - ADCC
  - ADCP

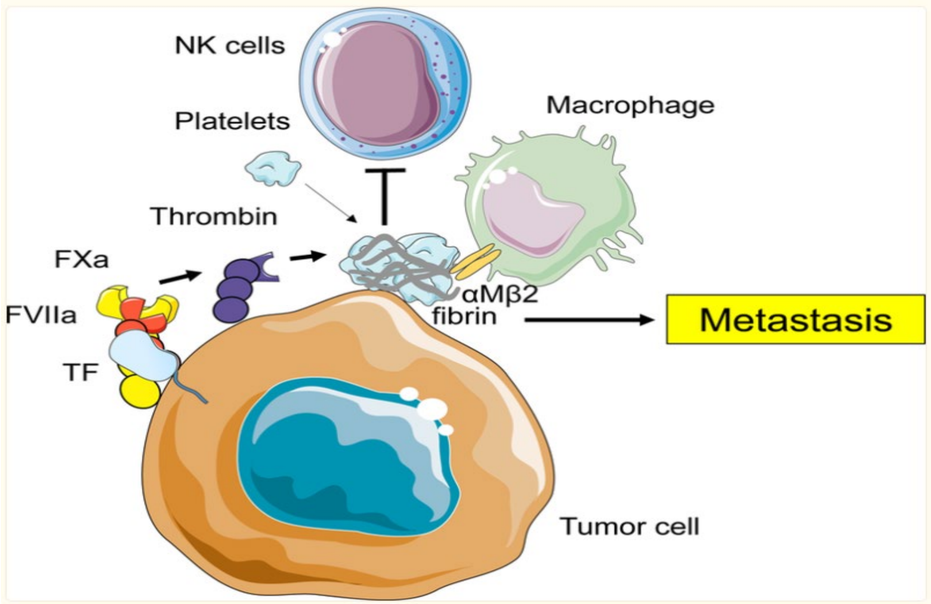


ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; MMAE, monomethyl auristatin E; MOA, mechanism of action.

1. Breij EC et al. *Cancer Res*. 2014;74(4):1214-1226. 2. De Goeij BE et al. *Mol Cancer Ther*. 2015;14(5):1130-1140. 3. Pan L et al. *Mol Med Rep*. 2019;19:2077-2086. 4. Cocco E et al. *BMC Cancer*. 2011;11:263. 5. Zhao X et al. *Exp Ther Med*. 2018;16:4075-4081. 6. Forster Y et al. *Clin ChimActa*. 2006;364:12-21 7. Alley SC et al. American Association for Cancer Research Annual Meeting; March 29-April 3, 2019; Atlanta, GA, USA; Abstract #221.

Biomarker: Tissue Factor





Proposed mechanisms of tumor tissue factor (TF)-dependent metastasis. The full-length TF/factor (F)VIIa/FXa complex generates thrombin that activates platelets and generate fibrin.

These activated platelets and fibrin inhibit the function of natural killer (NK) cells and attract monocytes/macrophage that helps establishment of premetastatic niche and tumor cell survival in metastatic niche.

- **Tissue factor**, also called **platelet tissue factor**, **factor III**, Its role in the clotting process is the initiation of thrombin formation.
- TF is a **transmembrane glycoprotein** found on the surface of various cells, including cancer cells.
- It plays a role in promoting cancer cell **proliferation and survival** through signaling pathways like **PI3K/AKT** and **MAPK**.
- TF is also involved in **metastasis**, **angiogenesis**, and **venous thromboembolism (VTE)**.
- TF is highly expressed in cervical cancer tissues and high expression of TF may enhance the invasion and metastasis of cervical cancer cells.

Hisada Y, Mackman N. Tissue Factor and Cancer: Regulation, Tumor Growth, and Metastasis. Semin Thromb Hemost. 2019 Jun;45(4):385-395;
Zhao X, Cheng C, Gou J, Yi T, Qian Y, Du X and Zhao X: Expression of tissue factor in human cervical carcinoma tissue. Exp Ther Med 16: 4075-4081, 2018

Payload: Monomethyl auristatin E

Monomethyl auristatin E is an antimitotic agent which inhibits cell division by blocking the polymerization of tubulin.

Clinical Data

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InnovaTV 204/GOG-3023/ENGOT-cx6: Phase 2 Trial of Tisotumab Vedotin

Key eligibility criteria

- Recurrent or metastatic cervical cancer
- Progressed during or after doublet chemotherapy[a] plus bevacizumab (if eligible)
- Received ≤2 previous systemic regimens[b]
- ECOG PS 0-1

Tisotumab vedotin
2.0 mg/kg IV q3w
Enrolled: 102[c]
Treated: 101[d]

Until PD or unacceptable toxicity

Tumor responses assessed using CT or MRI at baseline every 6 weeks for the first 30 weeks and every 12 weeks thereafter

- **Primary endpoint:** ORR per RECIST v1.1, assessed by IRC
- Secondary endpoints: ORR (by investigators), DOR, TTR, PFS, OS, safety

FDA approved September 2021 for the treatment of adult patients with recurrent or metastatic cervical cancer **with disease progression on or after chemotherapy**

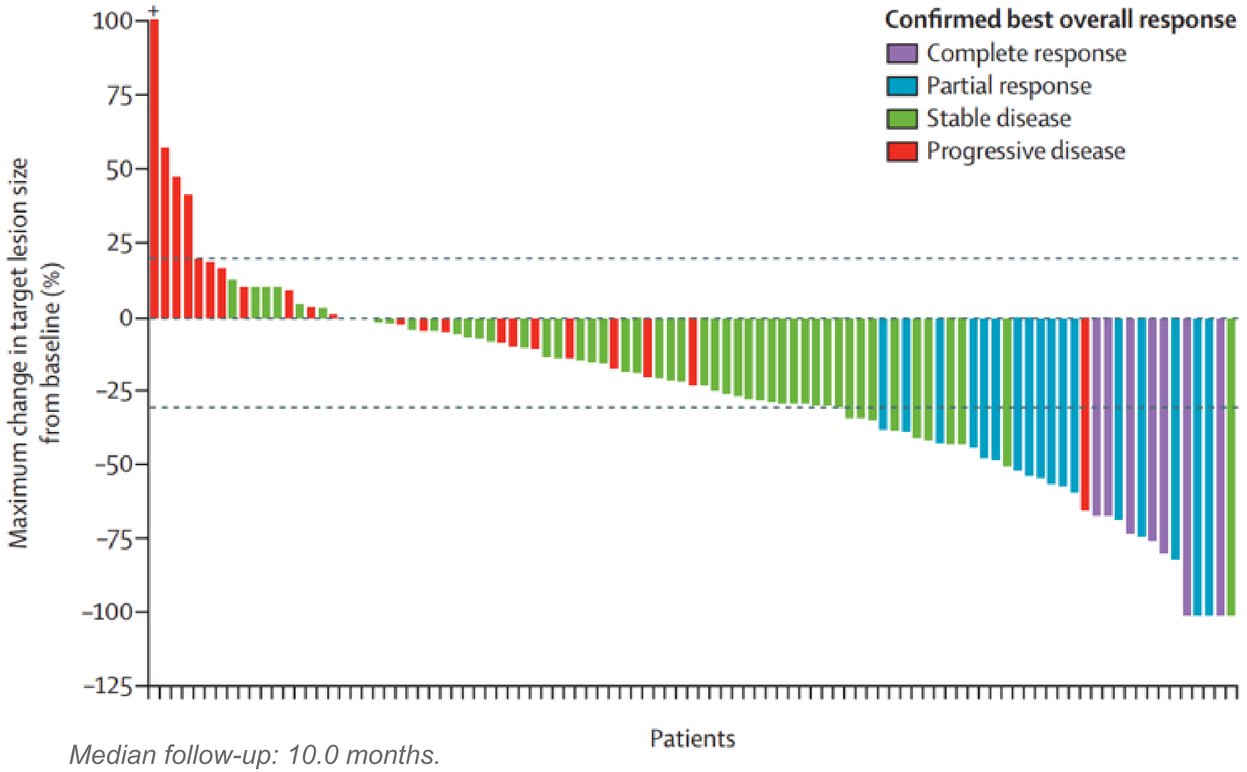
[a] Paclitaxel + platinum (cisplatin or carboplatin) or paclitaxel + topotecan. [b] Adjuvant or neoadjuvant chemotherapy, with or without radiotherapy, was not counted as a previous systemic regimen. [c] June 2018 to April 2019. [d] Study sample size calculated assuming a confirmed ORR of 21% to 25% with tisotumab vedotin, and to provide ≥80% power to exclude an ORR of up to 11%.

Coleman R, et al. Lancet Oncol. 2021;22(5):609-619.

InnovaTV 204: Efficacy

Response Rates by IRC Assessment	(N=101)
ORR[a] (95% CI)	24% (16-33)
CR	7 (7%)
PR	17 (17%)
SD	49 (49%)
PD	24 (24%)
Not evaluable	4 (4%)
Disease control rate[b] (95% CI)	72% (63-81)
Median DOR (95% CI), mo	8.3 (4.2-NR)
Median time to response (IQR), mo	1.4 (1.3-1.5)
Median PFS (95% CI), mo	4.2 (3.0-4.4)
Median OS (95% CI), mo	12.1 (9.6-13.9)

Target Lesions Reduced in 79% of Patients with ≥1 Postbaseline Scan[c]



Median follow-up: 10.0 months.

[a] Based on the Clopper-Pearson method. [b] Disease control rate is the proportion of patients with a confirmed CR, PR, or SD.

[c] Percent changes greater than 100% were truncated at 100% (indicated by the + symbol).

Coleman R, et al. Lancet Oncol. 2021;22(5):609-619.

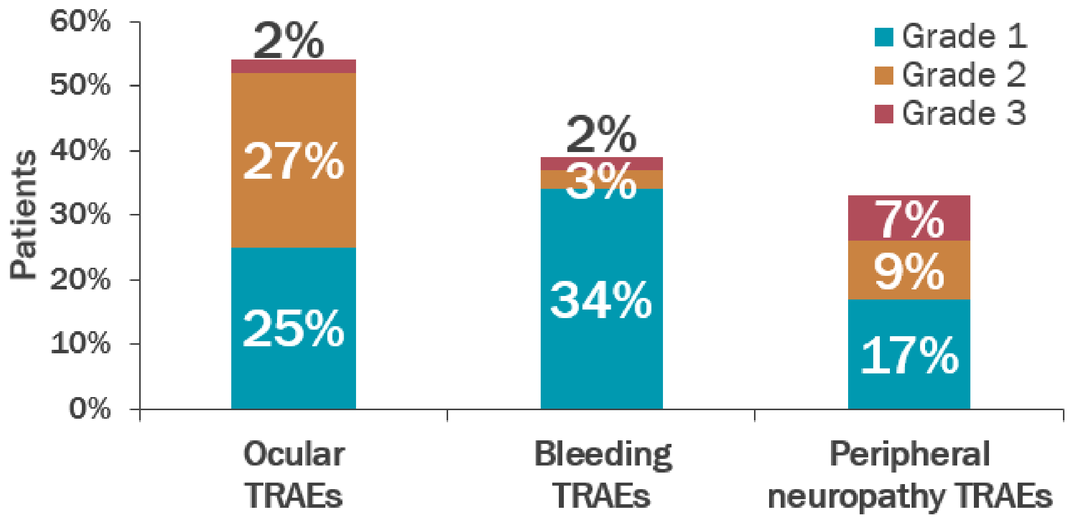
InnovaTV 204: Safety

TRAEs With ≥10% Incidence[a]	Tisotumab Vedotin (N=101)	
	Grade 1-2	Grade ≥3
Any TRAE	65%	28%
Alopecia	38%	0%
Epistaxis	30%	0%
Nausea	27%	0%
Conjunctivitis	26%	0%
Fatigue	24%	2%
Dry eye	23%	0%
Myalgia	15%	0%
Anemia	12%	1%
Asthenia	12%	1%
Arthralgia	12%	0%
Decreased appetite	11%	0%
Keratitis	11%	0%
Pruritus	10%	1%
Neuropathy peripheral	8%	2%

- One death due to septic shock was considered by the investigator to be related to therapy[a]

Prespecified AEs of Interest

Ocular, bleeding, and peripheral neuropathy TRAEs

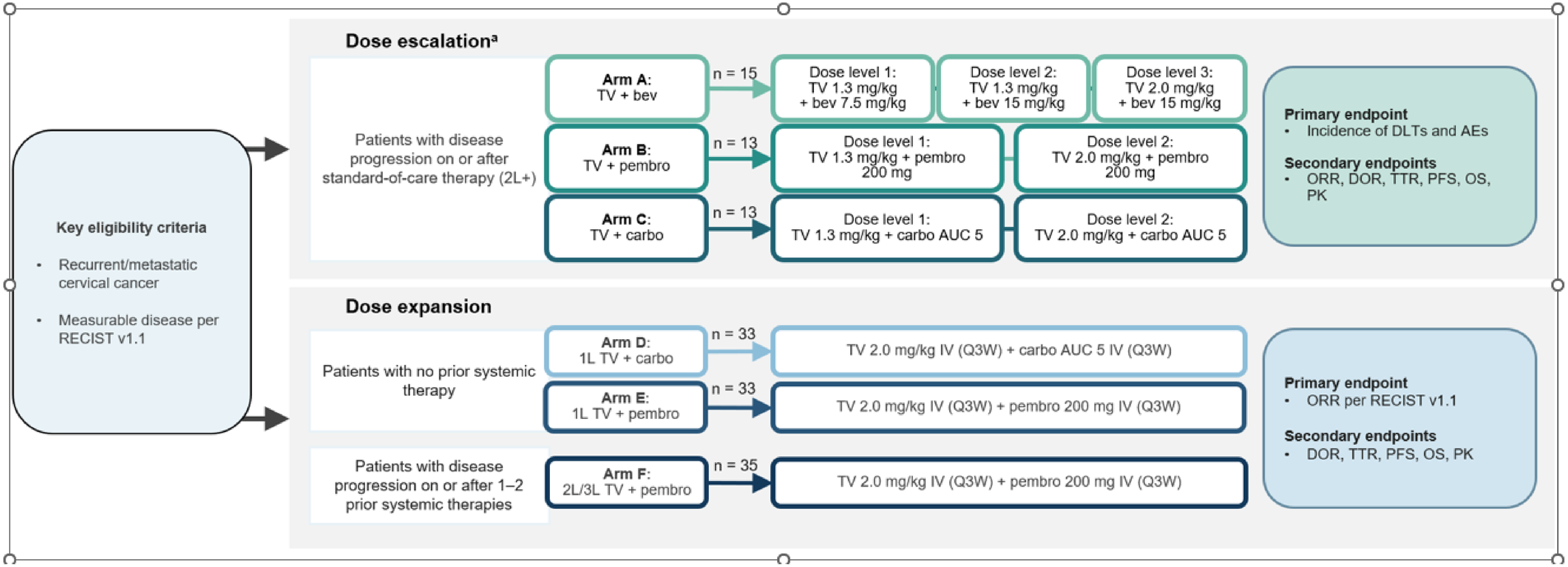


	Ocular	Bleeding	Peripheral Neuropathy
Median time to onset, mo	1.4	0.3	3.1
Events resolved	86%	90%	21%
Median time to resolution,[b] mo	0.7	0.5	0.6

[a] 3 deaths unrelated to therapy were reported, including 1 case of ileus and 2 unknown causes.
[b] Assessment limited by the protocol-defined follow-up period for AE of only 30 days after the last dose.
Coleman R, et al. Lancet Oncol. 2021;22(5):609-619.

InnovaTV 205: Study Design

A phase 1b/2 open-label trial of Tisotumab vedotin monotherapy and in combination with other agents in subjects with recurrent or stage IVB cervical Cancer

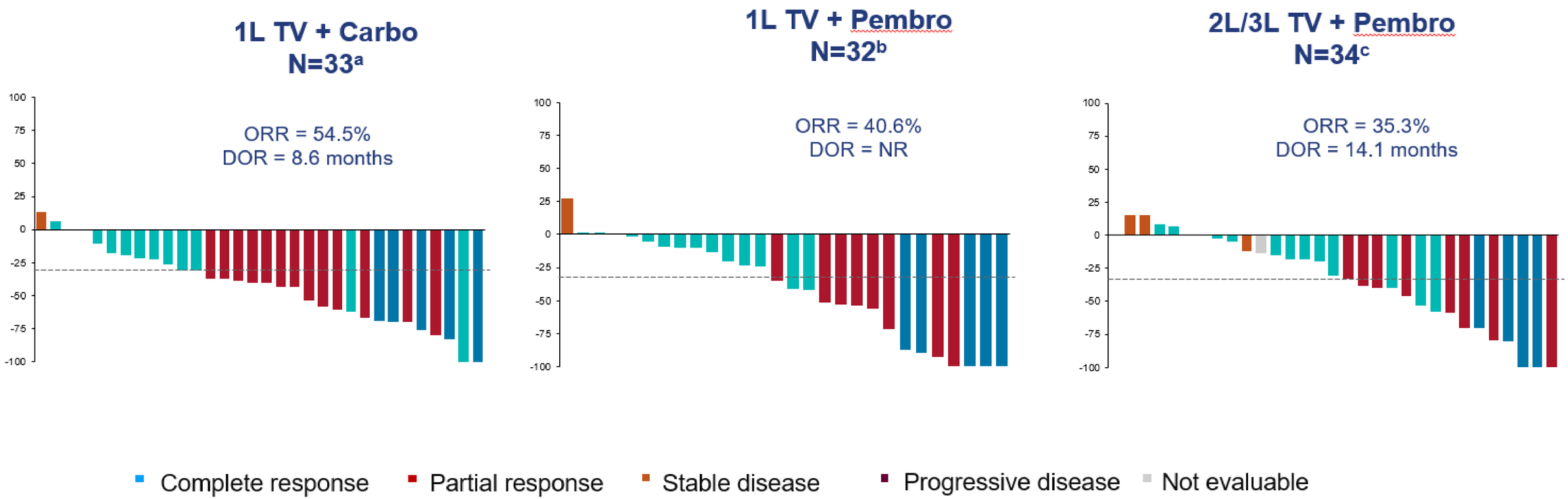


[a]TV + bev arm followed a 3 + 3 dose escalation design. TV + pembro and TV + carbo Arms followed a 6 + 6 dose escalation design. Drugs were administered IV on day 1 of each 21-day cycle. Patients were treated for ≥1 cycle to evaluate DLTs and 2 cycles to evaluate RP2D.

AE, adverse events; AUC, area under the concentration-time curve; bev, bevacizumab; carbo, carboplatin; DLT, dose-limiting toxicity; IV, intravenously; PK, pharmacokinetics; ORR, objective response rate; OS, overall survival; pembro, pembrolizumab; Q3W, every 3 weeks; Progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended phase 2 dose; TTR, time to response; TV, tisotumab vedotin; 1L, first-line; 2L, second-line; 3L, third-line.

Vergote I, et al. *J Clin Oncol*. 2023:JCO2300720.

InnovaTV 205: Best Reduction in Target Lesion Size

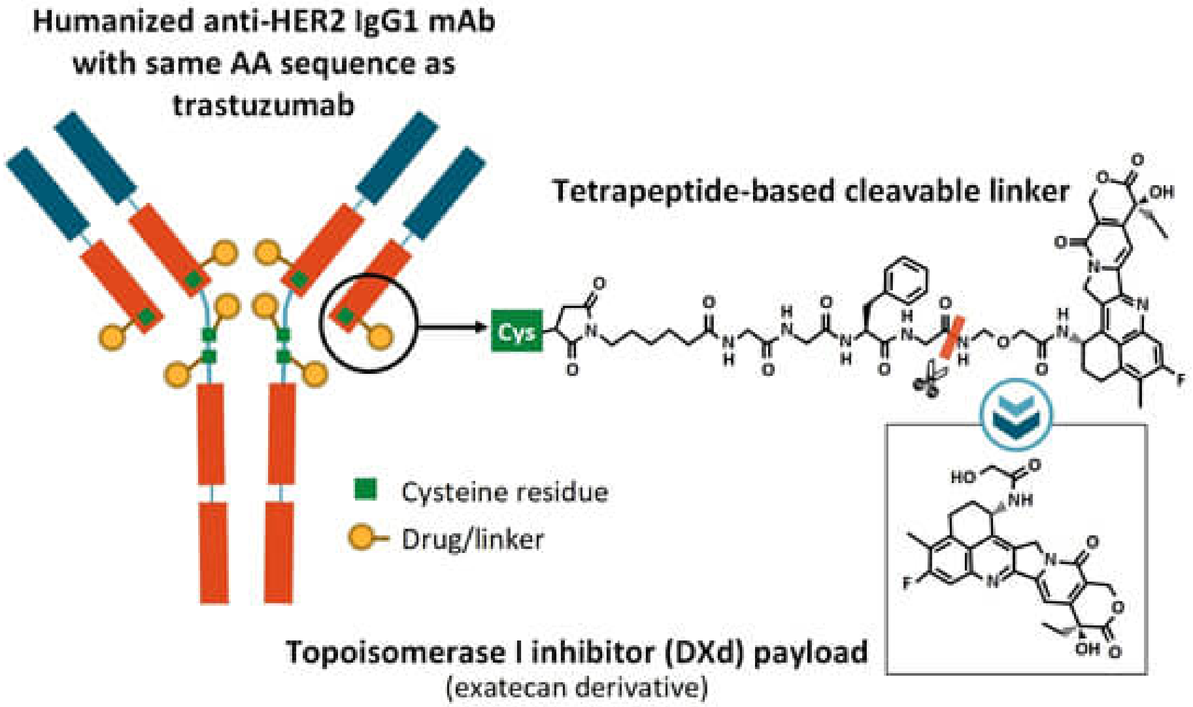


Data cutoff: June 20, 2022.
Median duration of follow-up for 1TV+Carbo: (range):17.8 (1−26) months; for 1 TV+Pembro: 21.7 (1–29) months; for 2L/3L TV + Pembro: 15.0 (1–29) months
The dashed line indicates a 30% reduction from baseline.
Carbo, carboplatin; CBR, clinical benefit rate; CI, confidence interval; DCR, disease control rate; NR, not reached; ORR, objective response rate; pembro, pembrolizumab; TV, tisotumab vedotin; 1L, first-line 2L, second-line; 3L, third-line.
Vergote I, et al. J Clin Oncol. 2023:JCO2300720.

Biomarker: Her 2 neu

Payload: Topoisomerase I inhibitor

HER2-Targeted ADC: Trastuzumab Deruxtecan



- High drug:antibody ratio: ~8
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

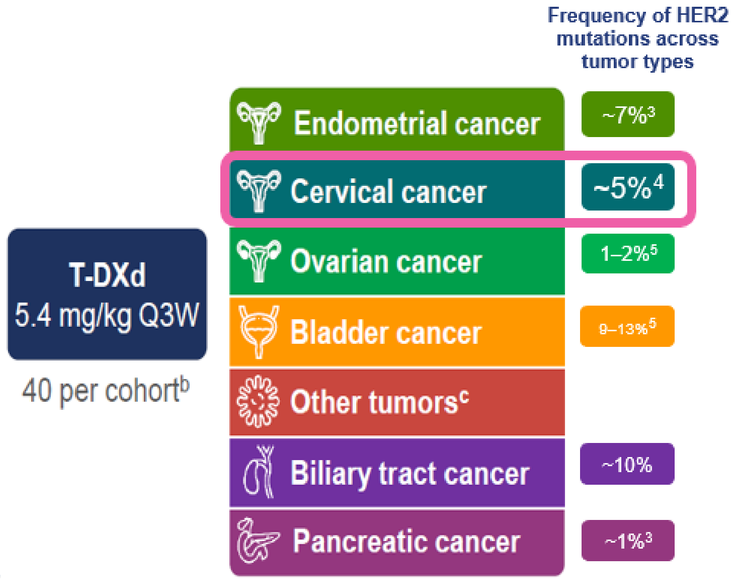
Nakada. Chem Pharm Bull (Tokyo). 2019;67:173, Trail, Pharmacol Ther. 2018:181:156, Ogitani Cancer Sci. 2016 2016;107:1039

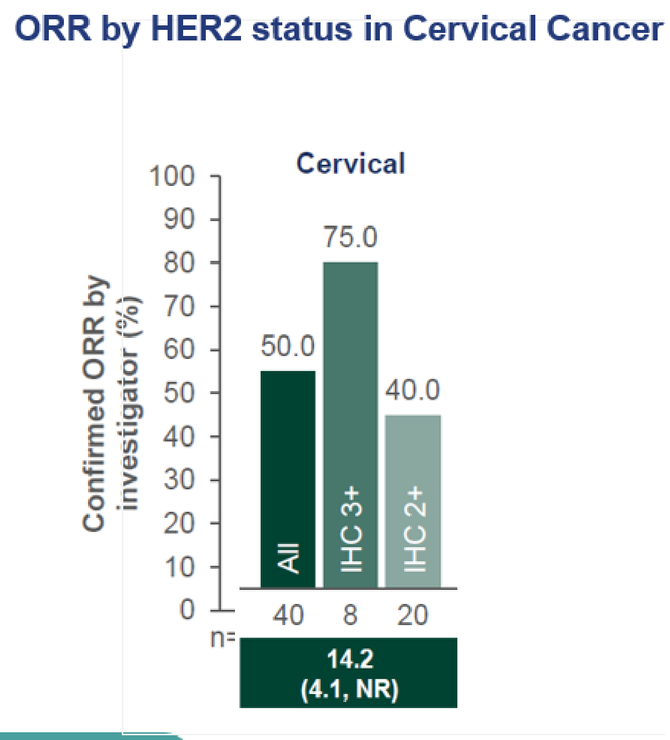
DESTINY-PanTumor02: Study Design

A phase 2, multicenter, open-label study to evaluate the efficacy and safety of trastuzumab deruxtecan for the treatment of selected HER2 expressing tumors[1,2]

Key Eligibility Criteria

- 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 scoring
- Prior HER-targeting therapy allowed
- ECOG/WHO PS ≤1





All patients were HER2-positive per local determination

Data cutoff: June 8, 2023. Medin f/u: 12.75 months

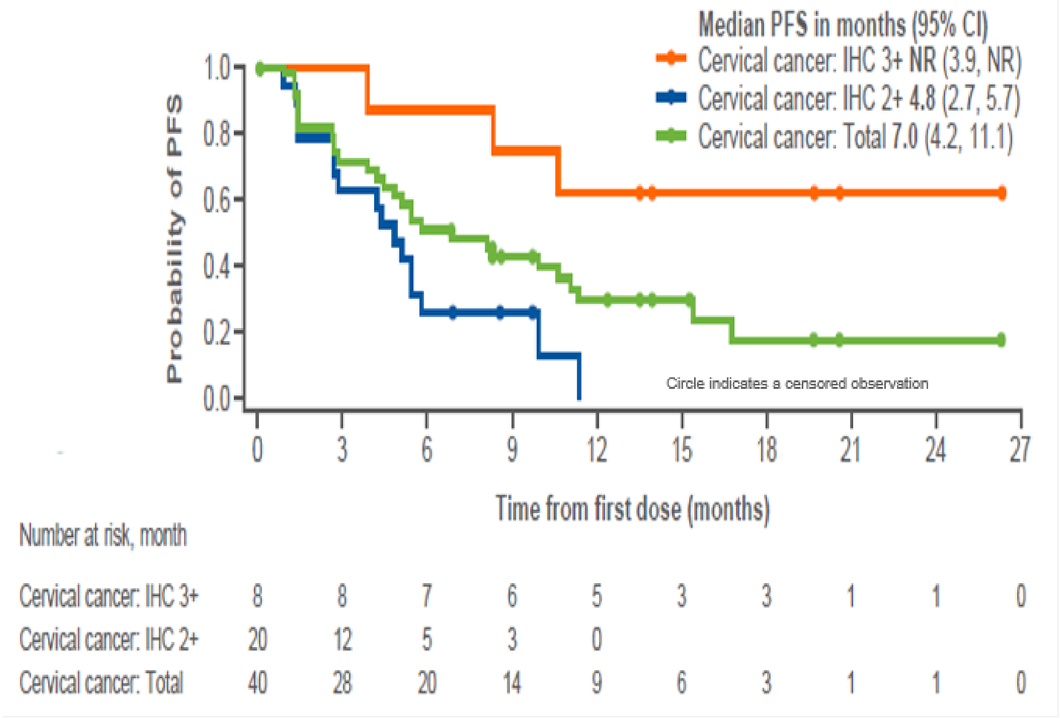
[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. [c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.

ASCO, American Society of Clinical Oncology; CAP, College of American Pathologists; DCR, disease control rate; DOR, duration of response ECOG; Eastern Cooperative Oncology Group; f/u, follow-up; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ORR, objective response rate; OS, overall survival; PFS, progression free survival, PS, performance status; T-Dxd; trastuzumab deruxtecan; Q3W, every 3 weeks; WHO, World Health Organization; 2L, second-line.

1. Clinicaltrials.gov.NCT04482309. Accessed October 03, 2023. 2. Funda Meric-Burnstam. Presented at ***ESMO*** *2023.* ***Presented orally LBA34. 3. Wang et al. Front Immunol. 2022; 13: 799988.4. Oaknin et al. Gynecol Oncol. 2020t;159(1):150-156; 5. Li et al. EBioMedicine. 2020; 62: 103074; 6. Harding JJ et al. Nat Commun. 2023;14(1):630. doi: 10.1038/s41467-023-36399-y.***

DESTINY-PanTumor02

PFS by HER2 status in Cervical Cancer



TEAEs	All patients (N=267); n (%)
Any drug-related TEAEs	226 (84.6)
Drug-related TEAEs Grade ≥3	109 (40.8)
Serious drug-related TEAEs	36 (13.5)
Drug-related TEAEs associated with dose discontinuations	23 (8.6)
Drug-related TEAEs associated with dose interruptions	54 (20.2)
Drug-related TEAEs associated with dose reductions	54 (20.2)
Drug-related TEAEs associated with deaths	4 (1.5)[a]

Most common TEAEs	Any Grade	Grade ≥3
Nausea	55.1	3.7
Fatigue	40.1	7.1
Neutropenia	32.6	19.1
Anemia	27.7	10.9
Diarrhea	25.8	3.7
Vomiting	24.7	1.5
Decreased appetite	17.6	1.5
Thrombocytopenia	17.2	5.6
Alopecia	16.9	
Increased transaminases	10.1	0.4
Leukopenia	10.1	2.6

ILD/pneumonitis adjudicated as T-DXd related, n (%)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any grade
All patients (N=267)	7 (2.6)	17 (6.4)	1 (0.4)	0	3 (1.1)	28 (10.5)

Data cutoff: June 8, 2023. Medin f/u: 12.75 months

[a]Patients were eligible for either test. All patients were centrally confirmed. [b]Patients with tumors that express HER2, excluding tumors in the tumor-specific cohorts, and breast cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer. [c]Investigator-assessed per Response Evaluation Criteria In Solid Tumors version 1.1.

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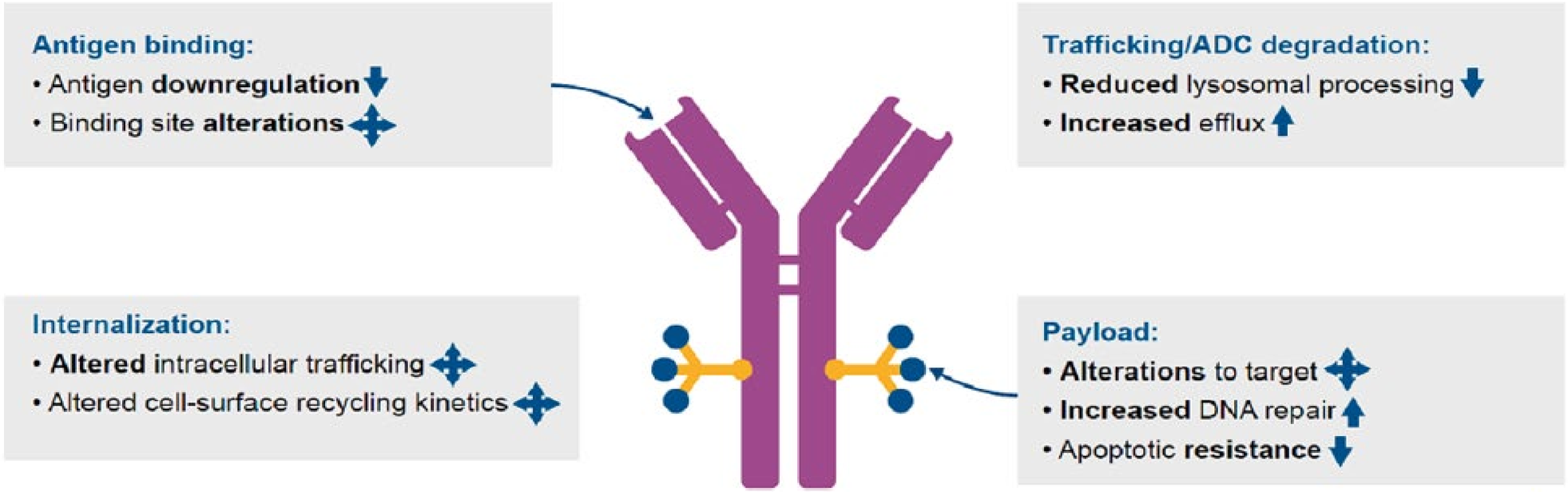
How will ADCs Advance in the Future? Understanding the Mechanisms of Resistance

Mechanisms of ADC Resistance in Tumor Cells at Each Step in the ADC Mechanism of Action



Collins DM, et al. Cancers 2019;Logano F, et al. Mol Cancer Ther 2016; Diaz-Rodriguez E, et al. Cancers 2021

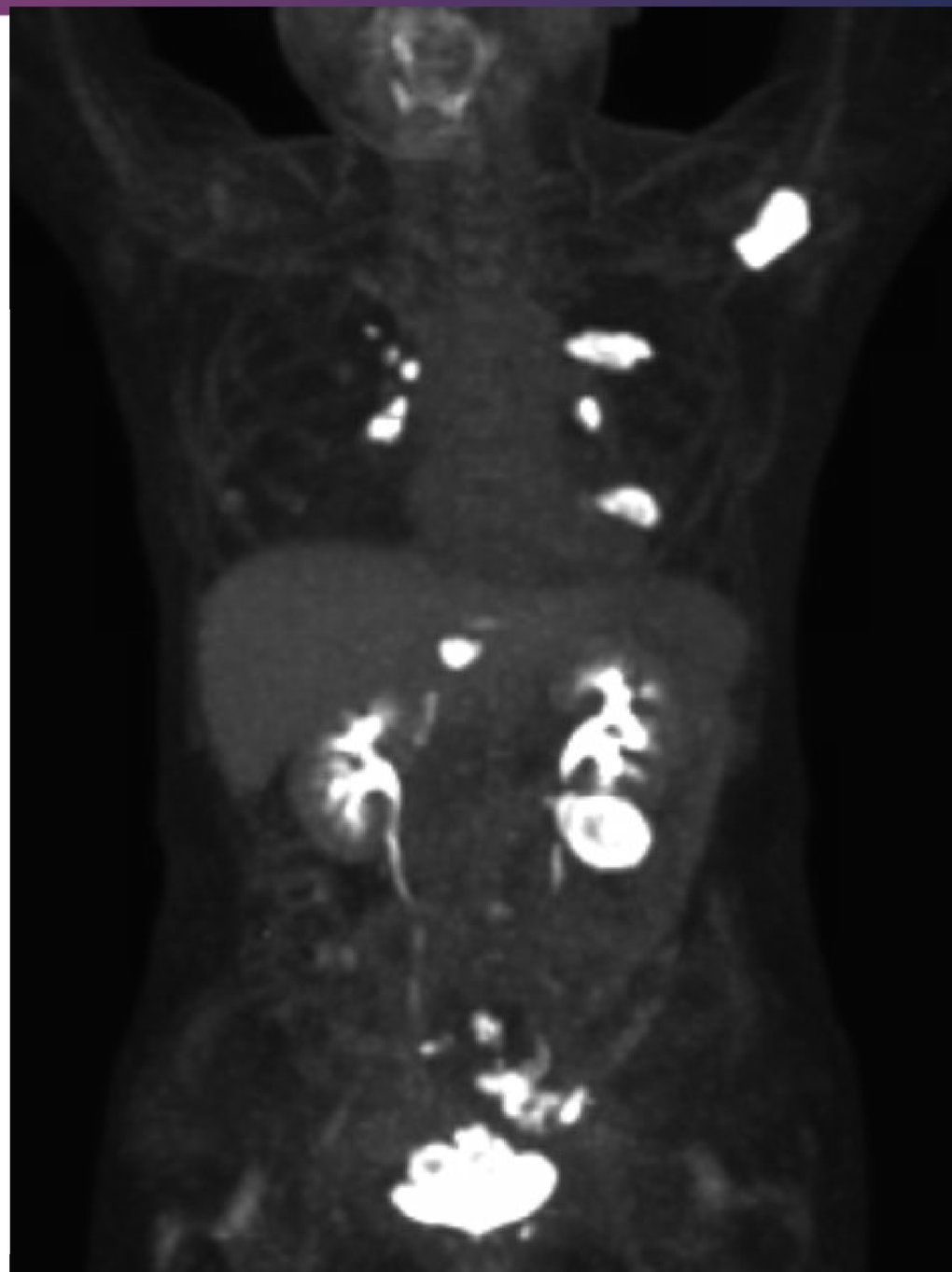
Antibody Drug Conjugates

- ADCs are monoclonal antibodies attached to biologically active agents through chemical linkers
- Increase in the therapeutic window using ADCs compared with chemotherapy
- Tisotumab Vedotin: Innova 204 / Innova 205
- Trastuzumab deruxtecan Destiny Pan Tumor Trial 02

Clinical Case

Clinical History

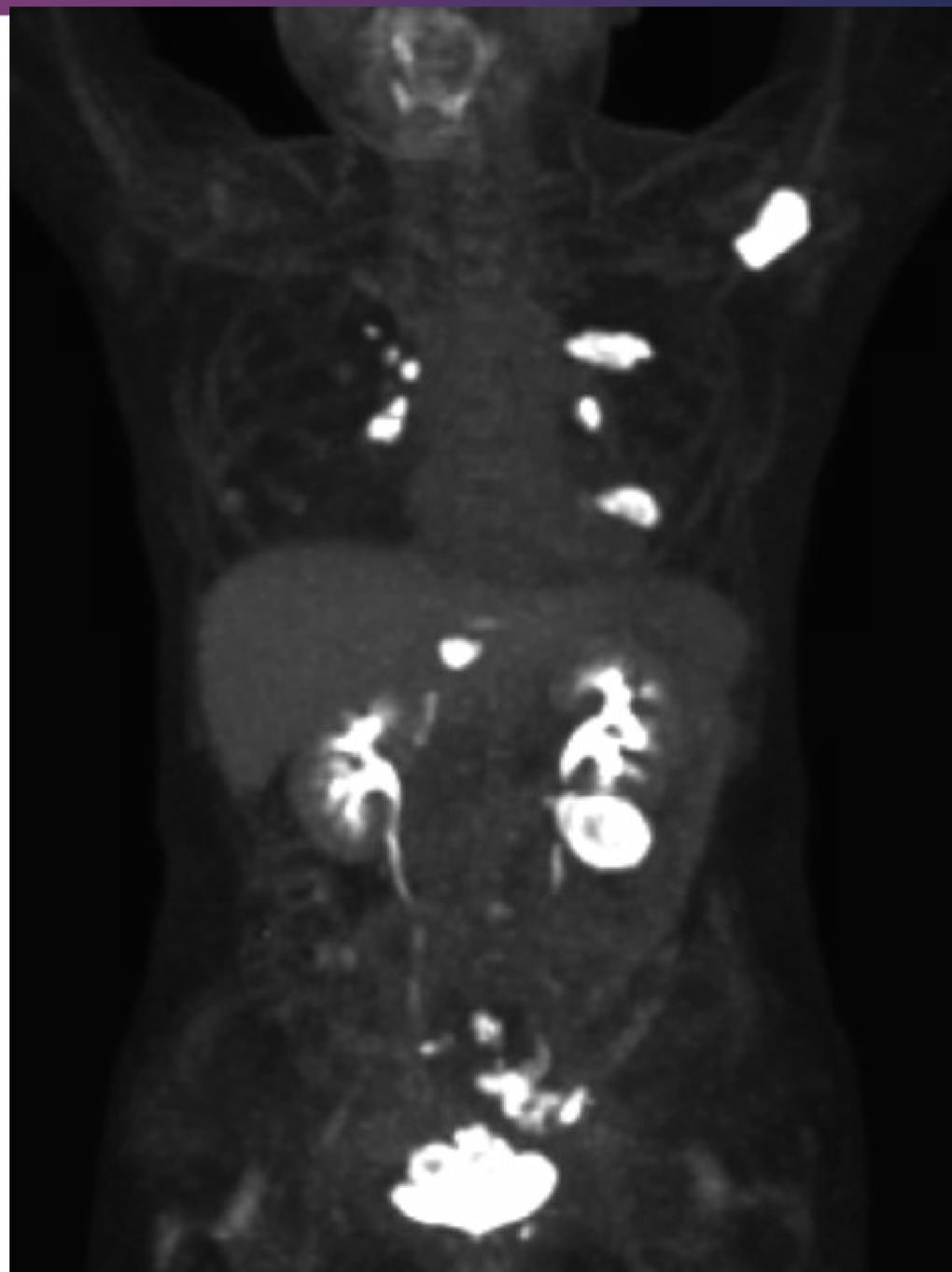
- 36 year from China who presented with advanced cervical cancer (non vaccinated)
- **Symptom:** pelvic pain /vaginal bleeding
- **Pelvic MRI with Contrast:** 3.1 x 1.5 cm mass with ill-defined border to left bladder wall/enlarged lymph nodes adjacent to bilateral iliac vessels, largest one about 1.8 x 1.3 cm in size.
- **Cystoscopy** with space-occupying lesion in bladder
- **Biopsy:** Squamous cell carcinoma, poorly differentiated, non-keratinizing type, involving colonic submucosa. PD-L1 positive , Her 2 neu negative (0)
- **PET Scan:** FDG avid cancer involving lower segment of uterus and bladder, bladder cancer involving adjacent organs was not ruled out; multiple lymph node metastases, abdominal, and pelvic metastases



Clinical Case

Treated Locally

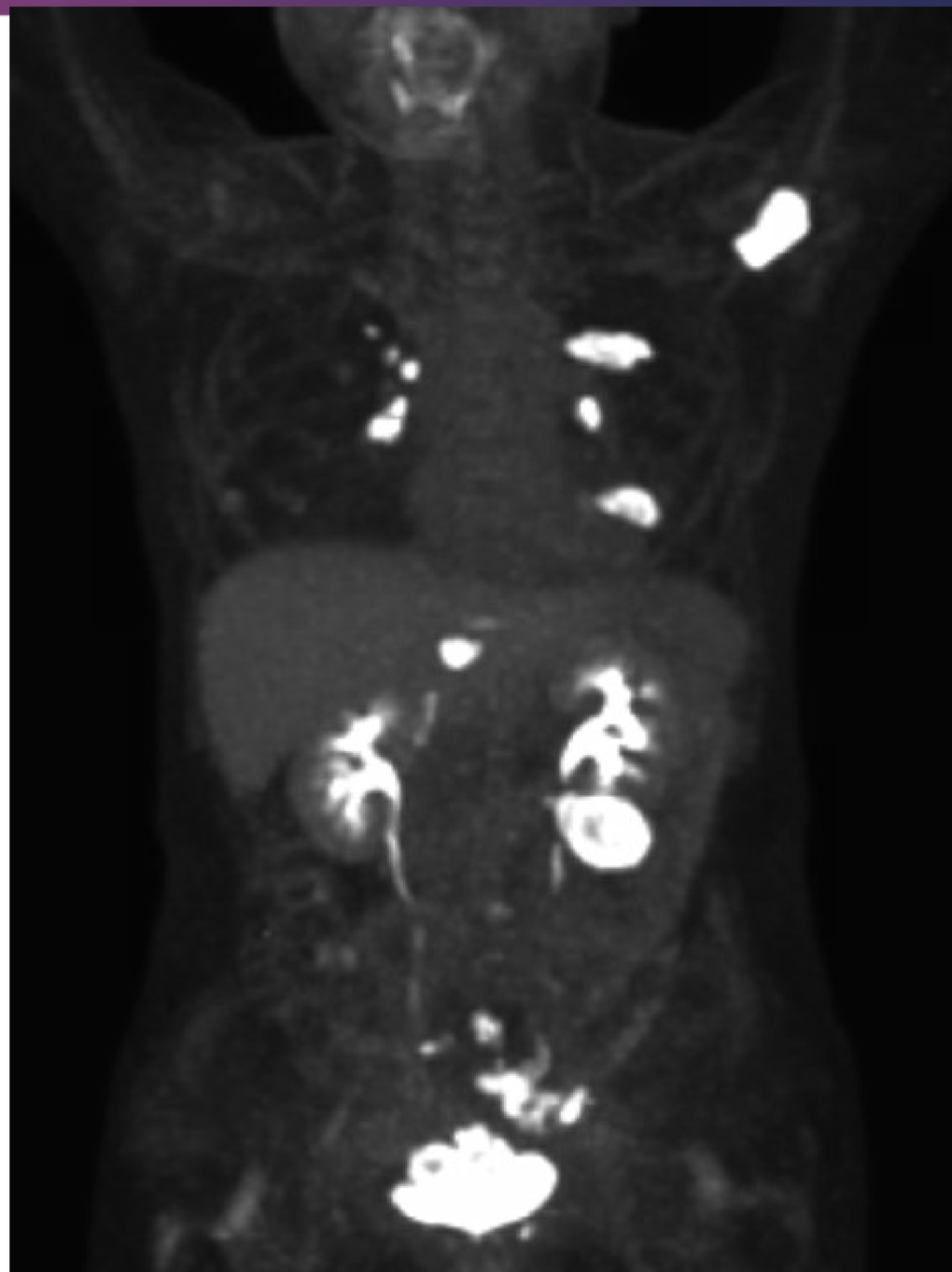
- **Carboplatin and taxol**
- **Radiation Therapy** to the cervical lesion and pelvic NS
- **Pelvic MRI Post Therapy:** Cervical mass involving left bladder wall, s/p radiotherapy, significantly regressed compared with previous scan. Small amount of residual hyperintense signals in local left posterior wall of bladder. Small LNs in bilateral pelvic walls, significantly decreased in size compared with previous scan . Soft tissue edema in pelvic wall.
    - US with multiple solid nodules in subQ fat layer of L perineum. “Multiple heterogeneous masses in peritoneum of left upper abdomen, concerning for malignant tumors
    - Treatment : Paclitaxel + Carboplatin + Pembrolizumab X 6 cycles



Clinical Case

Progression of Disease

- Multifocal areas of FDG avid metastatic disease involving bilateral hilar and right internal mammary lymph nodes, multifocal soft tissue implants in the abdomen and pelvis, and multiple osseous metastases as detailed above.
- FDG avidity along the left rectal wall and along the sigmoid colon although indeterminate raising concern for serosal rather than intramural disease involvement.
- FDG avid subcutaneous nodule in the anterior left lower abdominal wall, concerning for metastatic disease rather than injection site/inflammation.
- Mild avidity along the cervix/vaginal cuff that may reflect residual disease.



Clinical Case

Q: Outside of clinical trials, which treatment would you consider next for this patient?

1. Tisotumab vedotin
2. Cemiplimab
3. Trastuzumab Deruxtecan
4. Nivolumab
5. Chemotherapy
6. Other