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 Enrich 1910

1910, Paul Enrich proposed the concept of “Magic bullet”

Several efforts were made but the technology was relatively backward and failed during this period

1957, Matthe firstly tried to conjugated the methotrexate with anti-herapaxa 1210 antigen immunoglobulin for the treatment of leukemia

In 1975, the hybridoma technology was developed to produce monoclonal antibodies by Kohler and Milstein

In 1985, the concept of ADC was firstly presented and the radioimmunotherapy was disclosed

In 1988, the humanized antibodies were developed

In 1993, the HER2-DOX was investigated on xenograft model

In 1995, Cremophor EL was used as the potent payload for preparation of ADC

In 1993, gemcitabine chemotherapy was voluntarily withdrawn as the toxic side effects

In 2000, the first ADC drug, gemcitabine-odesmizumab, was approved by FDA for ALL

In 2001, ontuximab vedotin was approved

In 2010, adetuximab emtansine was approved

In 2013, ade-mustine vedotin was approved

In 2017, inotuzumab ozogamicin was approved

In 2017, tisotuximab vedotin was approved

In 2019, olaratumab vedotin was approved

In 2019, tisotuximab vedotin was approved

In 2020, sintaximab vedotin was approved

In 2020, sintaximab vedotin was approved

In 2021, sintaximab vedotin was approved

In 2021, sintaximab vedotin was approved

In 2021, sintaximab vedotin was approved

Over 100 ADC candidates were in different stages of clinical research

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

Key functions
- Recognition of target cancer cells
- Guidance system for cytotoxic drugs
- Bridge between antibody and drugs and to control the release of drugs inside cancer cells
- Warhead for destroying cancer cells
ADC Design

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

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

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

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

**Drug:**
1. Should have potent efficacy
2. Available linker binding site
• **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
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.
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: \(\sim 8\)
- Stable linker-payload
- Tumor-selectable cleavable linker
- High potency, membrane-permeable payload with short systemic half-life
- Bystander killing effect

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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.

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.

Payload: Monomethyl auristatin E

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

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

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

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

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\(^{a}\) 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 \(\geq\) 80% power to exclude an ORR of up to 11%.

InnovaTV 204: Efficacy

Response Rates by IRC Assessment (N=101)

<table>
<thead>
<tr>
<th>Response Rate by IRC Assessment</th>
<th>(N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR&lt;sup&gt;a&lt;/sup&gt; (95% CI)</td>
<td>24% (16-33)</td>
</tr>
<tr>
<td>CR</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>PR</td>
<td>17 (17%)</td>
</tr>
<tr>
<td>SD</td>
<td>49 (49%)</td>
</tr>
<tr>
<td>PD</td>
<td>24 (24%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>4 (4%)</td>
</tr>
<tr>
<td>Disease control rate&lt;sup&gt;b&lt;/sup&gt; (95% CI)</td>
<td>72% (63-81)</td>
</tr>
<tr>
<td>Median DOR (95% CI), mo</td>
<td>8.3 (4.2-NR)</td>
</tr>
<tr>
<td>Median time to response (IQR), mo</td>
<td>1.4 (1.3-1.5)</td>
</tr>
<tr>
<td>Median PFS (95% CI), mo</td>
<td>4.2 (3.0-4.4)</td>
</tr>
<tr>
<td>Median OS (95% CI), mo</td>
<td>12.1 (9.6-13.9)</td>
</tr>
</tbody>
</table>

Target Lesions Reduced in 79% of Patients with ≥1 Postbaseline Scan<sup>c</sup>

Median follow-up: 10.0 months.

<sup>a</sup> Based on the Clopper-Pearson method. <sup>b</sup> Disease control rate is the proportion of patients with a confirmed CR, PR, or SD.
<sup>c</sup> Percent changes greater than 100% were truncated at 100% (indicated by the + symbol).

InnovaTV 204: Safety

<table>
<thead>
<tr>
<th>TRAEs With $\geq 10%$ Incidence\textsuperscript{a}</th>
<th>Tisotumab Vedotin (N=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
</tr>
<tr>
<td>Any TRAE</td>
<td>65%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>38%</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>30%</td>
</tr>
<tr>
<td>Nausea</td>
<td>27%</td>
</tr>
<tr>
<td>Conjunctivitis</td>
<td>26%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>24%</td>
</tr>
<tr>
<td>Dry eye</td>
<td>23%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>15%</td>
</tr>
<tr>
<td>Anemia</td>
<td>12%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>12%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>12%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>11%</td>
</tr>
<tr>
<td>Keratitis</td>
<td>11%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>10%</td>
</tr>
<tr>
<td>Neuropathy peripheral</td>
<td>8%</td>
</tr>
</tbody>
</table>

- One death due to septic shock was considered by the investigator to be related to therapy\textsuperscript{a}

\textsuperscript{a} 3 deaths unrelated to therapy were reported, including 1 case of ileus and 2 unknown causes.

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

Key eligibility criteria
- Recurrent/metastatic cervical cancer
- Measurable disease per RECIST v1.1

Dose escalation

- Arm A: TV + bev (n = 15)
  - Dose level 1: TV 1.3 mg/kg + bev 7.5 mg/kg
  - Dose level 2: TV 1.3 mg/kg + bev 15 mg/kg
  - Dose level 3: TV 2.0 mg/kg + bev 15 mg/kg

- Arm B: TV + pembrolizumab (n = 13)
  - Dose level 1: TV 1.3 mg/kg + pembrolizumab 200 mg
  - Dose level 2: TV 2.0 mg/kg + pembrolizumab 200 mg

- Arm C: TV + carboplatin (n = 13)
  - Dose level 1: TV 1.3 mg/kg + carboplatin AUC 5
  - Dose level 2: TV 2.0 mg/kg + carboplatin AUC 5

Primary endpoint
- Incidence of DLTs and AE

Secondary endpoints
- ORR, DOR, TTR, PFS, OS, PK

Dose expansion

- Arm D: 1L TV + carboplatin (n = 33)
  - TV 2.0 mg/kg IV (Q3W) + carboplatin AUC 5 IV (Q3W)

- Arm E: 1L TV + pembrolizumab (n = 33)
  - TV 2.0 mg/kg IV (Q3W) + pembrolizumab 200 mg IV (Q3W)

- Arm F: 2L/3L TV + pembrolizumab (n = 33)
  - TV 2.0 mg/kg IV (Q3W) + pembrolizumab 200 mg IV (Q3W)

Primary endpoint
- ORR per RECIST v1.1

Secondary endpoints
- DOR, TTR, PFS, OS, PK

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TV + bev arm followed a 3–3 dose escalation design. TV + pembrolizumab and TV + carboplatin 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; 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 1TV+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.
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
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 tumors1,2

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

Frequency of HER2 mutations across tumor types

**Endometrial cancer**
- ~7%3

**Cervical cancer**
- ~5%4

**Ovarian cancer**
- ~1-2%4

**Bladder cancer**
- 0-13%5

**Other tumors**
- ~10%

**Biliary tract cancer**
- ~1%4

**Pancreatic cancer**
- ~1%

ORR by HER2 status in Cervical Cancer

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

All patients were HER2-positive per local determination

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**DESTINY-PanTumor02**

**PFS by HER2 status in Cervical Cancer**

<table>
<thead>
<tr>
<th>Median PFS in months (95% CI)</th>
<th>Cervical cancer: IH+C 3+ NR (3.3, NR)</th>
<th>Cervical cancer: IH+C 2+G (2.7, 5.7)</th>
<th>Cervical cancer: Total 7.0 (4.2, 11.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Probability of PFS</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**TEAEs**

| All patients (N=267); n (%) | Any drug-related TEAEs 226 (84.6) | Drug-related TEAEs Grade ≥3 100 (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)* |

**Most common TEAEs**

<table>
<thead>
<tr>
<th>Any Grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>55.1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>40.1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>32.6</td>
</tr>
<tr>
<td>Anemia</td>
<td>27.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>24.7</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>17.6</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17.2</td>
</tr>
<tr>
<td>Alopecia</td>
<td>18.9</td>
</tr>
<tr>
<td>Increased transaminases</td>
<td>10.1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10.1</td>
</tr>
</tbody>
</table>

**ILD/pneumonitis adjudicated as T-DXd related, n (%)**

<table>
<thead>
<tr>
<th>All patients (N=267)</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
<th>Grade 5</th>
<th>Any grade</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 (2.6)</td>
<td>17 (6.4)</td>
<td>1 (0.4)</td>
<td>0</td>
<td>3 (1.1)</td>
<td>28 (10.5)</td>
</tr>
</tbody>
</table>

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

*Patients were eligible for either test. All patients were centrally confirmed. *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. 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.

5. Li et al. EBioMedicine. 2020; 62: 103074;
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

Antigen binding:
- Antigen downregulation
- Binding site alterations

Internalization:
- Altered intracellular trafficking
- Altered cell-surface recycling kinetics

Trafficking/ADC degradation:
- Reduced lysosomal processing
- Increased efflux

Payload:
- Alterations to target
- Increased DNA repair
- Apoptotic resistance

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