

**Antibody-drug conjugates (ADCs)** are a class of biopharmaceuticals that specifically target cancer cells by combining a monoclonal antibody, a cytotoxic agent, and a linker. This “targeted chemotherapy” makes it possible to deliver a high dose of anticancer agent directly into the tumor, minimizing damage to healthy cells and reducing side effects.

### **Antibody-drug conjugates: mechanisms of action and presentation of different molecules**

ADCs are composed of an antibody directed against a tumor antigen, an antitumor agent (payload), and a linker, which connects the antitumor agent to the antibody. To induce cytotoxicity, the ADC binds to its target on the surface of cancer cells, is internalized, and transported to the lysosome, where the cytotoxic molecule is released.

The antibody target should ideally be overexpressed or selectively and uniformly expressed on the surface of cancer cells.

## **How do ADCs work?**

In simple terms, there are 3 main steps:

1. **Specific targeting**

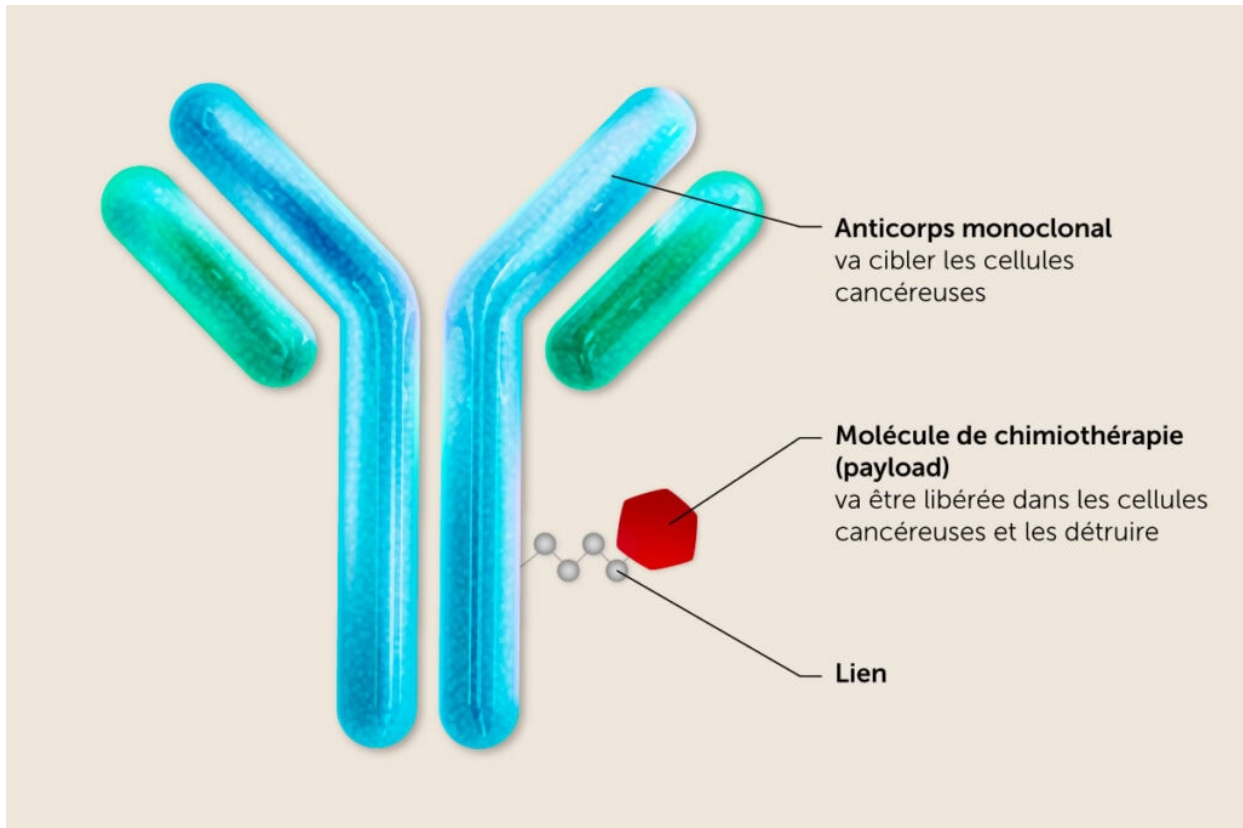
The antibody recognizes and binds to a protein on the surface of cancer cells. Ideally, this target exists only on cancer cells to avoid harming healthy cells.

2. **Drug release**

Once the antibody binds to the target cell, the cytotoxic molecule is released inside the cell, destroying it while minimizing damage to healthy cells.

3. **Targeted action**

Thanks to this precision, ADCs reduce side effects compared to traditional chemotherapy, which affects all rapidly dividing cells without distinction.



## Advantages of ADCs

- **More precise targeting** → less damage to healthy cells
  - **Greater effectiveness** → highly potent drugs can be used safely when linked to antibodies
  - **Improved patient outcomes** → effective even in difficult-to-treat or relapsed cancers
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## Disadvantages of ADCs

- **Complex manufacturing** → requires high precision
- **Side effects** → immune reactions or unintended damage may still occur
- **High cost** → due to complex development

## Examples of ADC Treatments

# ADCs associated with Herceptin™ (trastuzumab)

## KADCYLA™

T-DM1 (trastuzumab emtansine) is a hybrid compound consisting of a microtubule inhibitor, emtansine, conjugated to the antibody ado-trastuzumab (Herceptin™), designed to specifically target HER2-positive cells and deliver a cytotoxic agent.

### Approved indications (breast cancer):

- **Early HER2+ breast cancer:**  
Used as monotherapy in the adjuvant setting for patients with residual invasive disease in the breast and/or lymph nodes after neoadjuvant treatment with a taxane and anti-HER2 therapy.  
Treatment is given for a total of 14 cycles, unless disease recurrence or unacceptable toxicity occurs.
- **Metastatic HER2+ or unresectable locally advanced breast cancer:**  
In patients previously treated with trastuzumab and a taxane (separately or in combination).  
Treatment continues until disease progression or unacceptable toxicity.

**Dose:** 3.6 mg/kg intravenously every 3 weeks (21-day cycle).

**Side effects:** thrombocytopenia and elevated liver enzymes.

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## ENHERTU™

Trastuzumab deruxtecan is a humanized monoclonal antibody conjugated with deruxtecan, a topoisomerase I inhibitor.

In the Phase III DESTINY-BREAST04 trial, it demonstrated efficacy in locally advanced breast cancer with low HER2 expression, improving progression-free survival (PFS) and overall survival (OS).

**Indication:** HER2-positive unresectable or metastatic breast cancer after at least two prior anti-HER2 treatments.

**Dose:** 5.4 mg/kg IV every 3 weeks until progression or toxicity.

**Side effects:** nausea, vomiting, moderate hair loss, and lung toxicity.

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## ELAHERE™

Mirvetuximab soravtansine is an ADC linked to DM4, a microtubule inhibitor.

**Indication:** High-grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer expressing folate receptor alpha (FR $\alpha$ ), resistant to platinum-based therapy, after 1–3 prior treatments.

**Dose:** 6 mg/kg (adjusted ideal body weight) every 3 weeks IV.

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## ADCs targeting TROP2

### **TROP2 (Trophoblast cell-surface antigen 2):**

A transmembrane glycoprotein (323 amino acids), initially identified on trophoblast cells, later found overexpressed in many cancers.

It regulates tumor growth, invasion, metastasis, and plays a role in stem cell biology.

Encoded by the TACSTD2 gene, it is involved in calcium signaling.

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### **TRODELVY™**

Sacituzumab govitecan consists of an anti-Trop-2 antibody linked to SN-38 (active metabolite of irinotecan, a topoisomerase I inhibitor).

**Indication:** Metastatic or unresectable triple-negative breast cancer after at least two prior treatments.

**Dose:** 10 mg/kg IV on days 1 and 8 of a 21-day cycle.

**Side effects:** neutropenia, diarrhea, nausea, hair loss, fatigue, anemia.

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### **DATROWAY™**

Datopotamab deruxtecan targets TROP2. After binding, deruxtecan enters the cancer cell and inhibits topoisomerase I.

**Indication:** Advanced/metastatic hormone receptor–positive (HR+) and HER2-negative breast cancer after hormone therapy and chemotherapy.

**Administration:** IV every 3 weeks.

**Side effects:** stomatitis, nausea/vomiting, fatigue, hair loss, constipation, dry eyes, keratitis, anemia, loss of appetite.

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## Other approved ADCs

## ADCETRIS™

Brentuximab vedotin targets CD30 and is linked to auristatin.

### Indications:

- Hodgkin lymphoma
- Anaplastic large cell lymphoma
- Cutaneous T-cell lymphoma

**Dose:** 1.8 mg/kg IV every 3 weeks.

**Side effects:** infections, peripheral neuropathy, nausea, fatigue, diarrhea, neutropenia.

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## ZYNLONTA™

Loncastuximab tesirine is an ADC targeting CD19 with a pyrrolobenzodiazepine (PBD) cytotoxic agent.

**Indication:** Relapsed/refractory diffuse large B-cell lymphoma (DLBCL) after  $\geq 2$  treatments.

### Dose:

- 0.15 mg/kg every 3 weeks (first 2 cycles)
- Then 0.075 mg/kg every 3 weeks

Premedication with dexamethasone is required.

**Side effects:** febrile neutropenia, thrombocytopenia, fever, abdominal pain, pleural effusion.

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## BESPONSA™

Inotuzumab ozogamicin targets CD22 and induces DNA double-strand breaks.

**Indication:** Relapsed/refractory B-cell acute lymphoblastic leukemia (ALL).

**Administration:** Fractionated doses over 3–4 week cycles.

Premedication is recommended.

**Side effects:** thrombocytopenia, neutropenia, infections, anemia, fatigue, nausea, headache.

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## PADCEV™

Enfortumab vedotin targets nectin-4 and is linked to MMAE.

**Indication:** Advanced or metastatic urothelial carcinoma after platinum chemotherapy and PD-1/PD-L1 inhibitors.

**Dose:** 1.25 mg/kg IV on days 1, 8, and 15 of a 28-day cycle.

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## Summary of approved ADCs

### Hematologic malignancies

- Gemtuzumab ozogamicin → CD33+ acute myeloid leukemia
- Brentuximab vedotin → CD30+ lymphomas
- Inotuzumab ozogamicin → B-cell ALL
- Polatuzumab vedotin → B-cell lymphoma
- Loncastuximab tesirine → B-cell lymphoma

### Solid tumors

- Trastuzumab emtansine → HER2+ breast cancer
  - Enfortumab vedotin → urothelial cancer
  - Trastuzumab deruxtecan → HER2+ breast & gastric cancer
  - Sacituzumab govitecan → triple-negative breast cancer
  - Tisotumab vedotin → cervical cancer
  - Mirvetuximab soravtansine → ovarian cancer
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## Future of ADCs

As with the development of new cancer therapies, once an agent proves effective in improving survival in advanced-stage disease, the next step is to **move its use earlier in treatment lines**, with the goal of increasing the chances of cure.

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## Conclusion

ADCs represent a **major breakthrough in cancer treatment**, enabling more targeted and often less toxic therapies.

By delivering powerful drugs directly to cancer cells, they offer a promising and already widely used treatment option.