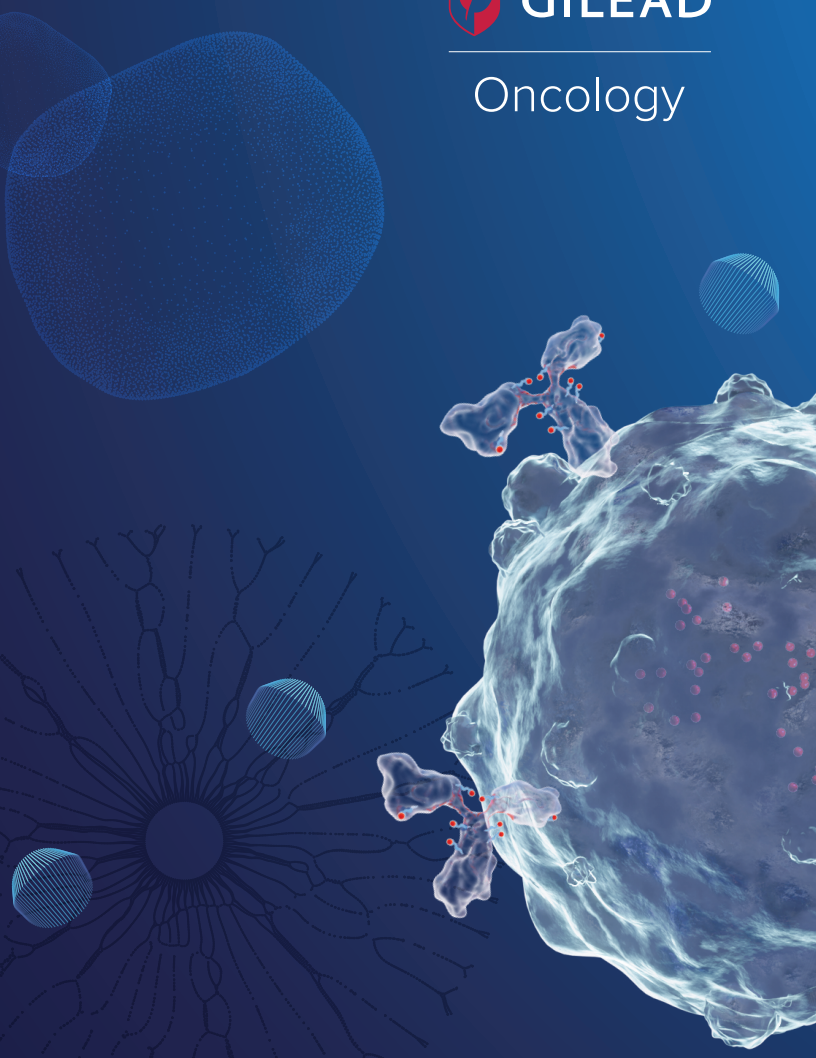
GILEAD

Oncology



Antibody-drug conjugates (ADCs)

Discover the science behind the tumor targeting therapy of antibody-drug conjugates[1]

ADC Anatomy and Components

ADC Mechanism of Action

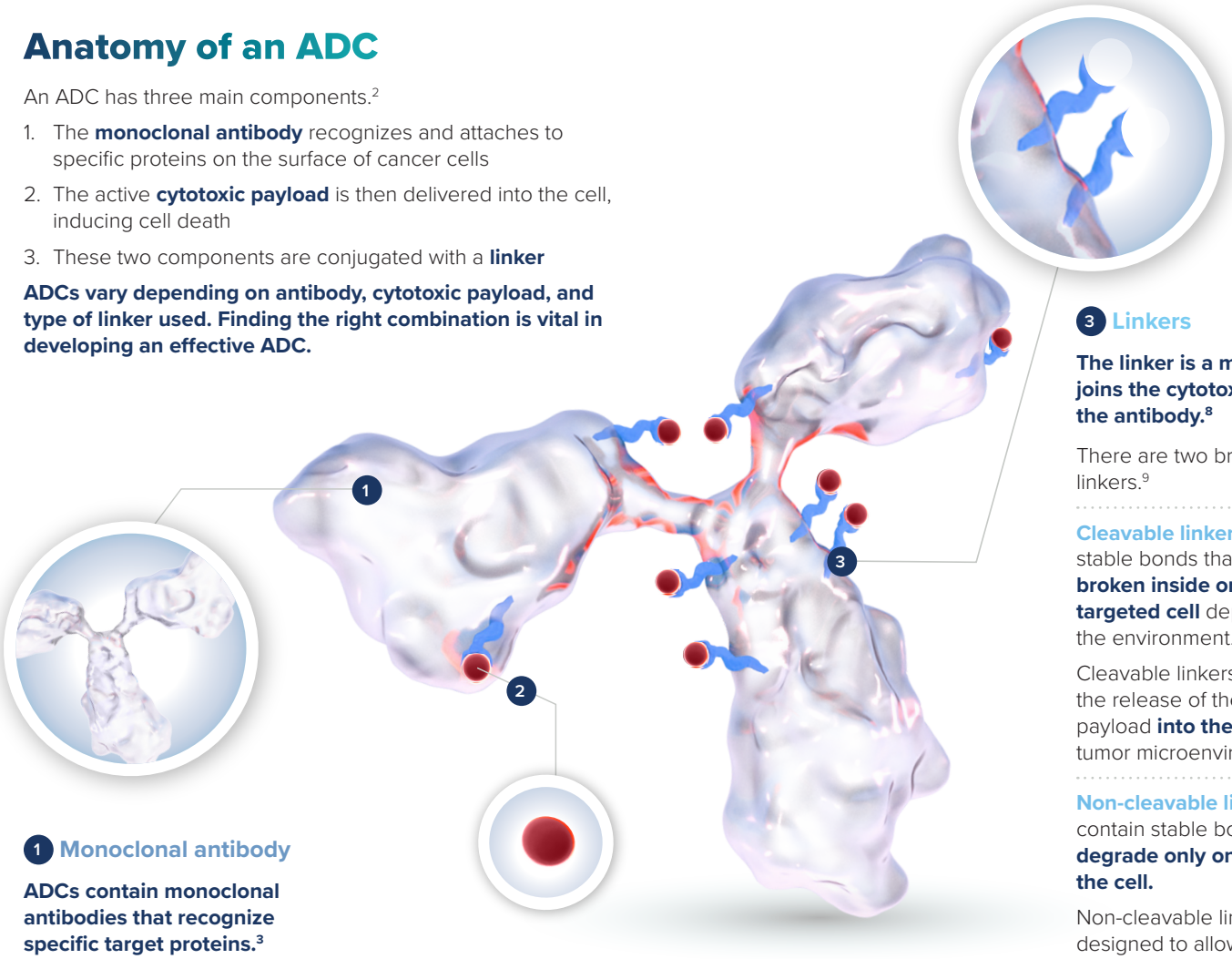
The information contained in this brochure is educational in nature and is intended for U.S. healthcare professionals.

Anatomy of an ADC

An ADC has three main components.[2]

1. The **monoclonal antibody** recognizes and attaches to specific proteins on the surface of cancer cells
2. The active **cytotoxic payload** is then delivered into the cell, inducing cell death
3. These two components are conjugated with a **linker**

ADCs vary depending on antibody, cytotoxic payload, and type of linker used. Finding the right combination is vital in developing an effective ADC.



1 Monoclonal antibody

ADCs contain monoclonal antibodies that recognize specific target proteins.[3]

These specific target proteins are overexpressed on certain tumor cells rather than normal cells, thereby facilitating the site-specific delivery of the drug into the cancer cell.[2]

The goal of the specific antibody-antigen binding is to attach the ADC to the cancer cell and limit impact to healthy cells.

2 Cytotoxic payload

ADCs release the cytotoxic payload into targeted cancer cells.[2]

Delivery of the cytotoxic drug initiates a process that leads to the **cancer cell's death**.

ADCs differ from conventional systemic chemotherapies in that the cytotoxic payload is typically **more potent**[4] and is often released in or near cells that have been targeted by the antibody component.[5-7]

3 Linkers

The linker is a molecule that joins the cytotoxic drug to the antibody.[8]

There are two broad types of linkers.[9]

Cleavable linkers—contain stable bonds that can be **broken inside or outside the targeted cell** depending on the environment.

Cleavable linkers can lead to the release of the cytotoxic payload **into the cells** and the tumor microenvironment.[10]

Non-cleavable linkers—contain stable bonds that **degrade only once inside the cell.**

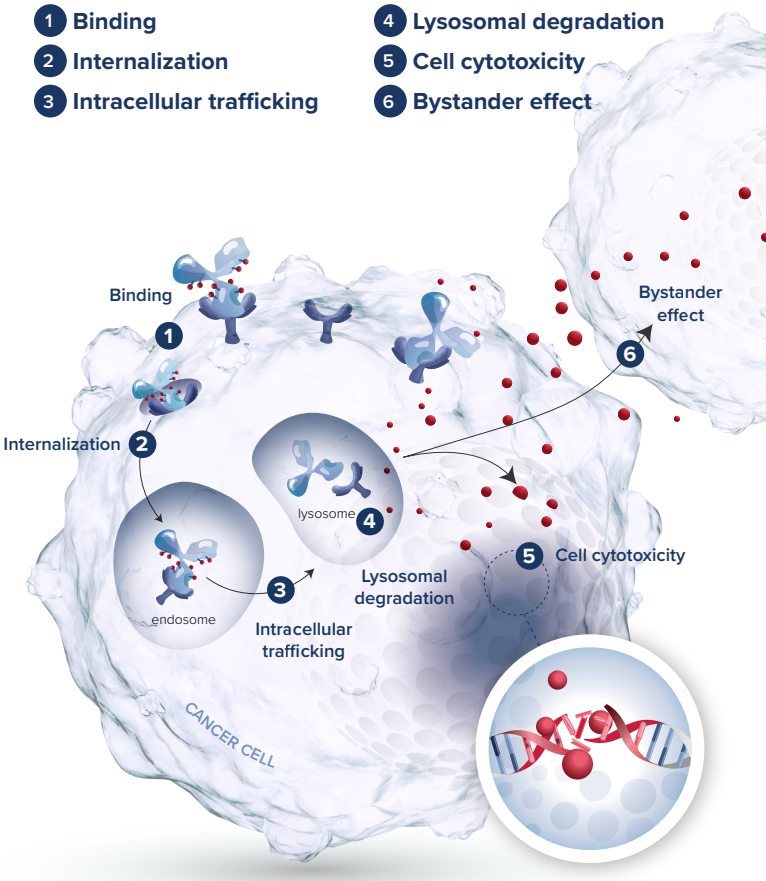
Non-cleavable linkers are designed to allow the cytotoxic drug to remain inactive during circulation and result in the release of the cytotoxic drug once inside the targeted cell.

Release of the cytotoxic agent in the microenvironment results in the **bystander effect**, where nearby cancer cells or stromal cells that do not express the target antigen can still be killed by the cytotoxic drug.[5-7]

1. ADC Review Editorial Team. What are Antibody-drug Conjugates? ADC Review. Published March 2019. Accessed March 24, 2022. www.adcreveiw.com/the-review/antibody-drug-conjugates/what-are-antibody-drug-conjugates.
2. Zhao P, Zhang Y, Li W, et al. Recent advances of antibody drug conjugates for clinical applications. *Acta Pharm Sin B*. 2020;10(9):1589-1600.
3. Hamilton GS. Antibody-drug conjugates for cancer therapy: The technological and regulatory challenges of developing drug-biologic hybrids. *Biologicals*. 2015;43(5):318-32.
4. Peters C, Brown S. Antibody-drug conjugates as novel anti-cancer chemotherapeutics. *Biosci Rep*. 2015;35:e00225.
5. Fu Z, Li S, Han S, et al: Antibody drug conjugate: the "biological missile" for targeted cancer therapy. *Sig Transduct Target Ther.* 2022;7-93.
6. Abdollahpour-Alitappeh M, Lotfinia M, Gharibi T, et al. Antibody-drug conjugates (ADCs) for cancer therapy: Strategies, challenges, and successes. *J Cell Physiol*. 2018;1-15.
7. Staudacher A, Brown M. Antibody drug conjugates and bystander killing: is antigen-dependent internalisation required? *Br J Cancer*. 2017;117, 1736-1742.
8. Panowski S, Bhakta S, Raab H, et al. Site-specific antibody drug conjugates for cancer therapy. *MAbs*. 2014;6(1):34-45.
9. Khongorzul P, Ling CJ, Khan FU, et al. Antibody-drug conjugates: a comprehensive review. *Mol Cancer Res*. 2020;18(1):3-19.
10. Sheyi R, de la Torre BG, Albericio F. Linkers: An Assurance for Controlled Delivery of Antibody-Drug Conjugate. *Pharmaceutics*. 2022;14:396.

ADC Mechanism of Action[1]

1. Binding
2. Internalization
3. Intracellular trafficking
4. Lysosomal degradation
5. Cell cytotoxicity
6. Bystander effect



The antibody component of ADCs may exert antitumor activity via:[2]

- Fab-mediated activity (blocking ligand binding, preventing receptor dimerization, inducing receptor degradation)
- Fc-mediated activity (ADCC, complement-dependent cytotoxicity, antibody-dependent cellular phagocytosis)

The cytotoxic payload may exert antitumor activity via:[3]

- Release from endosomes and/or lysosomes within **tumor** cells resulting in cell death
- Potentially entering and killing **neighboring tumor** cells via the bystander effect (membrane-permeable payloads)

ADC, antibody-drug conjugate; **ADCC**, antibody-dependent cellular cytotoxicity; **Fab**, fragment of antigen binding, variable region that confers antigen specificity; **Fc**, fragment crystallizable, region of antibody that can bind to immune effector cells.

1. Marks S, Naidoo *J Lung Cancer.* 2022;163:59-68.
2. Simpson, A., Caballero, O. Monoclonal antibodies for the therapy of cancer. *BMC Proc*. 2014;8(S4):O6. doi: 10.1186/1753-6561-8-S4-O6.
3. Drago JZ, Modi S, Chandarlapaty S. Unlocking the potential of antibody–drug conjugates for cancer therapy. *Nature Reviews Clinical Oncology*. 2021;18(6):327-344. doi:10.1038/s41571-021-00470-8.