Zynlonta® (loncastuximab tesirine-lpyl) - Mechanism of Action

Summary

- ZYNLONTA is a CD19 targeted antibody drug conjugate (ADC) comprised of a monoclonal antibody (mAb), a protease-cleavable linker, and a highly potent and targeted pyrrolobenzodiazepine (PBD) dimer.[1,5]
- After intravenous (IV) infusion, ZYNLONTA binds specifically to CD19 on the tumor cell surface. The drug conjugate is internalized, the linker is cleaved by lysosomal proteases and the potent PBD dimer is released inside the cell. PBD dimer, SG3199, forms sequence-selective, highly cytotoxic interstrand crosslinks in the minor groove of the DNA, leading to stalled DNA replication fork, interruption in cancer cell division and ultimately cancer cell death.[5]

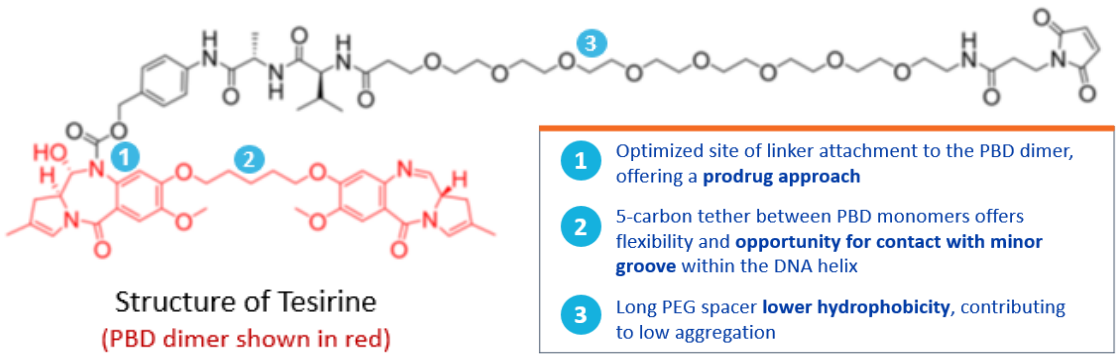
Background

- B-cell lymphomas are a heterogenous group of lymphoid malignancies characterized by proliferation of malignant B-cells. CD19, a transmembrane glycoprotein, is expressed in most B-cell malignancies at normal to high levels including diffuse large B-cell lymphoma (DLBCL), making it a biological target for antitumor drugs.[2]
- Antibody drug conjugates (ADCs) directed against tumor-associated surface antigens permit specific targeting of cancer cells with cytotoxic agents, with the potential to maximize efficacy and exhibit anti-tumor activity with less toxicity. ADCs consist of three key components: an antigen-specific antibody, a stable linker, and a potent cytotoxic agent (also known as a warhead or toxin).[3]

Mechanism of Action

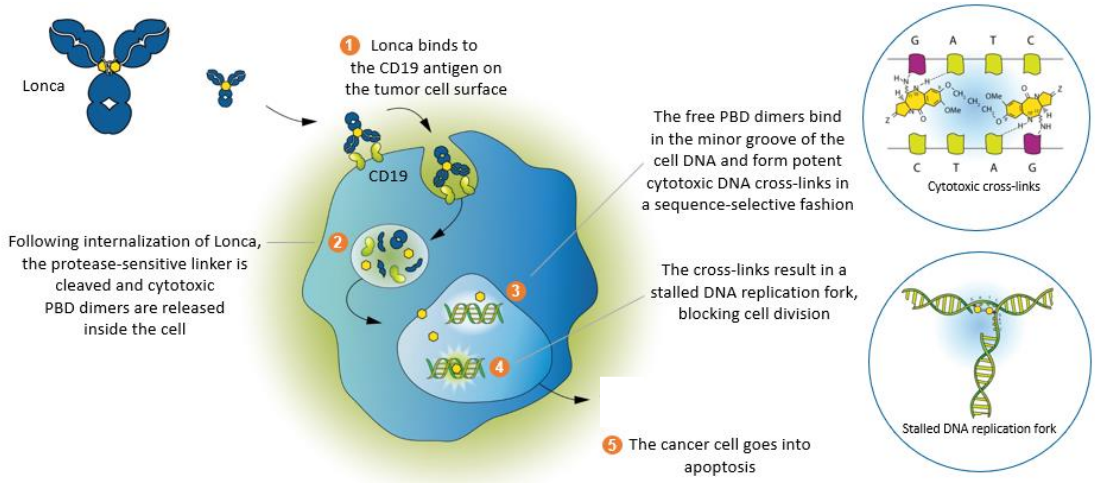
- ZYNLONTA is an antibody-drug conjugate (ADC) composed of an anti-CD19 monoclonal antibody (mAb) conjugated through a valine-alanine linker to a potent PBD dimer.[1] High potency of the PBD dimer allows for a low drug-antibody ratio (DAR); ZYNLONTA has a DAR of approximately 2.3.[5] Tesirine, composed of the PBD dimer SG3199 and all linker components, was designed to combine potent antitumor activity with enhanced physiochemical properties as shown in Figure 1.[3] PBD dimers are sequence-selective DNA cross-linking agents that are distinguished from conventional DNA crosslinking agents in that the interstrand cross-links formed in the minor groove of the DNA are relatively non distorting and may lead to their persistence in cells.[4]

Figure 1. Structure of Tesirine with PBD dimer. Adapted from Tiberghien AC et al. 2016.



- Upon loncastuximab binding to the CD19 antigen on the tumor cell surface, the drug conjugate is then internalized into the cell. Once inside the cell, the PBD dimer is released via cleavage of the linker by specific proteases, such as cathepsin B. The released PBD dimer then forms rapid, sequence-selective interstrand cross-links in the minor groove of the DNA. These cross-links create relatively minimal distortion of the DNA which may contribute to the lack of DNA repair and persistence within the cell, leading to a stalled DNA replication fork and tumor cell death.[5,6]

Figure 2. Mechanism of Action of Loncastuximab Tesirine. Adapted from Kahl 2017 ICML/Lugano



Literature Search

- A PubMed biomedical literature search conducted on April 1st, 2025, yielded no further relevant data regarding the mechanism of action of ZYNLONTA.

Relevant Prescribing Information

Section 12: Clinical Pharmacology

12.1 Mechanism of Action

- Loncastuximab tesirine-lpyl is an antibody-drug conjugate (ADC) targeting CD19. The monoclonal IgG1 kappa antibody component binds to human CD19, a transmembrane protein expressed on the surface of cells of B-lineage origin. The small molecule component is SG3199, a PBD dimer and alkylating agent.
- Upon binding to CD19, loncastuximab tesirine-lpyl is internalized followed by release of SG3199 via proteolytic cleavage. The released SG3199 binds to the DNA minor groove and forms highly cytotoxic DNA interstrand crosslinks, subsequently inducing cell death. Loncastuximab tesirine-lpyl had anticancer activity in animal models of lymphoma.

References

1. ZYNLONTA® (loncastuximab tesirine-lpyl) for injection Prescribing Information, October 2022.
2. Wang K, Wei G, Liu D. CD19: a biomarker for B cell development, lymphoma diagnosis and therapy. *Exp Hematol Oncol*. 2012 Nov 29;1(1):36. DOI: 10.1186/2162-3619-1-36.
3. Tiberghien AC, Levy JN, Masterson LA, et al. Design and synthesis of tesirine, a clinical antibody-drug conjugate pyrrolobenzodiazepine dimer payload. *ACS Med Chem Lett*. 2016;7(11):983-987. DOI: 10.1021/acsmedchemlett.6b00062.
4. Hartley JA, et al. The development of pyrrolobenzodiazepines as antitumor agents. *Expert Opin Investig Drugs*. 2011;20(6):733-44. DOI:10.1517/13543784.2011.573477.
5. Zammarchi F, Corbett S, Adams L, et al. ADCT-402, a PBD dimer-containing antibody drug conjugate targeting CD19-expressing malignancies. *Blood*. 2018;131(10):1094-1105. DOI: 10.1182/blood-2017-10-813493.
6. Kahl 2017 ICML/Lugano oral presentation Slide 7.

ADC Therapeutics encourages all health care professionals to report any adverse events and product quality complaints to medical information at 855-690-0340. Please consult the ZYNLONTA Prescribing Information.