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Trodelvy® (sacituzumab govitecan-hziy) Mechanism of Action

This document is in response to your request for information regarding Trodelvy® (sacituzumab govitecan-hziy [SG]) and its mechanism of action.

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The full indication, important safety information, and boxed warnings for neutropenia and diarrhea are available at: www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

Relevant Product Labeling[1]

Mechanism of Action

SG is a trophoblast cell-surface antigen-2 (Trop-2)-directed antibody-drug conjugate (ADC). Sacituzumab is a humanized antibody that recognizes Trop-2. The small molecule that is the active metabolite of irinotecan (SN-38), is a topoisomerase I (TOP1) inhibitor, which is covalently attached to the antibody by a linker. Pharmacology data suggest that SG binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with TOP1 and prevents re-ligation of TOP1-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.
SG decreased tumor growth in mouse xenograft models of triple-negative breast cancer.

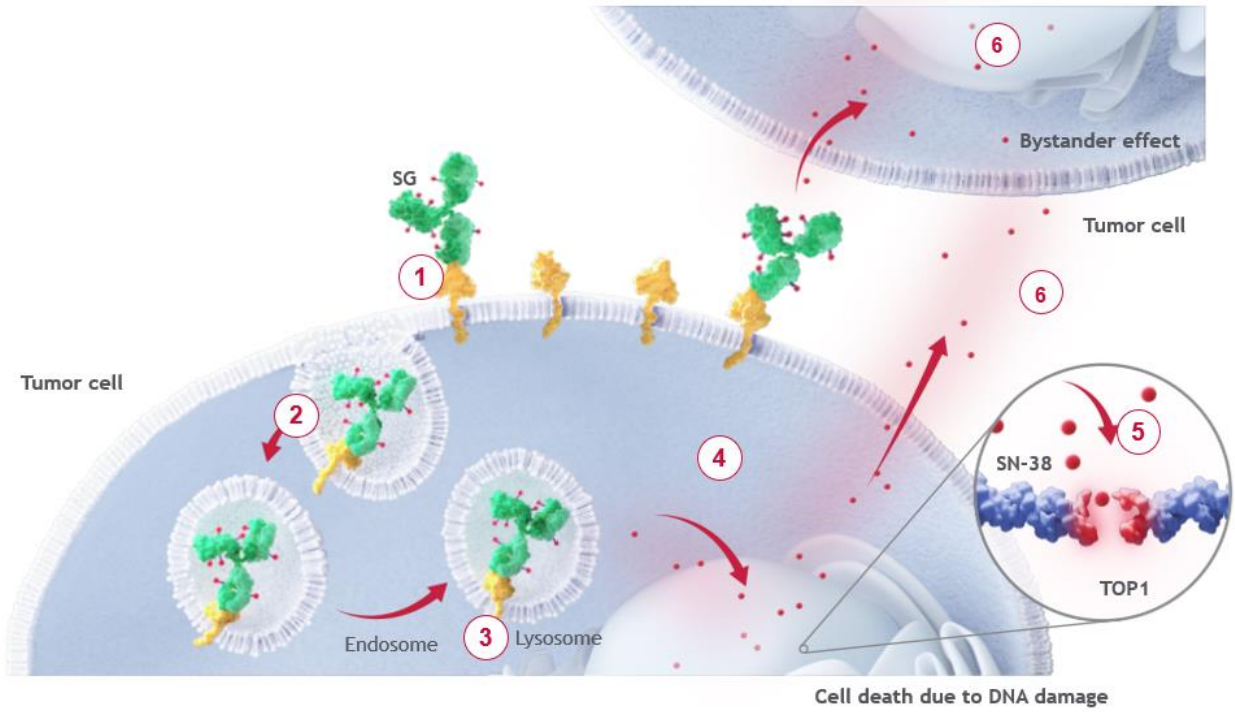
SG Mechanism of Action

SG is an ADC made from a humanized anti-Trop-2 monoclonal antibody (hRS7) conjugated with SN-38 via a hydrolysable linker (CL2A) with a drug-to-antibody ratio of 7.6:1.[2-5] Trop-2 is a transmembrane protein frequently expressed by many cancers.[2-9] The antibody component of SG binds to Trop-2 expressed on the tumor cell surface. The Trop-2-bound antibody complex is internalized, enabling SG to concentrate within the Trop-2 expressing tumor cells.[2-5] The Trop-2-bound antibody complex is then trafficked intracellularly to lysosomes.[4] The linker connecting the antibody to SN-38 is cleaved upon exposure to environments with low pH, followed by hydrolysis of the linker within the lysosome. The free SN-38 is released intracellularly.[4,5] SN-38 is a TOP1 inhibitor that prevents re-ligation of TOP1-induced single strand breaks resulting in DNA damage, apoptosis, and cell death.[2-5]

Bystander Effect

Based on preclinical data, it is hypothesized that given its membrane-permeable nature, free SN-38 can leave the cell once the internalization of the Trop-2-bound antibody complex process has been completed.[4,10] The SN-38 payload was observed in cells distal to blood vessels in the tumor in the absence of detectable levels of the ADC backbone. In addition, after 48 hours, SN-38 was distributed in the tumor in a homogeneous pattern consistent with distribution of SN-38 via the bystander effect to cells lacking expression of Trop-2.[10]
See Figure 1 below.

Figure 1. SG Mechanism of Action[4]



Note: 1=binding; 2=internalization; 3=intracellular trafficking; 4=lysosomal degradation; 5=cell toxicity; 6=bystander effect.

References

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Product Label

For the full indication, important safety information, and boxed warning(s), please refer to the Trodelvy US Prescribing Information available at: www.gilead.com/-/media/files/pdfs/medicines/oncology/trodelvy/trodelvy_pi.

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