DRUG of the week Sacituzumab Govitecan-hziy (Trodelvy™)

TRODELVY™ sacituzumab govitecan-hziy

The SARLAH Group

Previously in the Sarlah Group…

Linkers in Antibody-Drug Conjugates

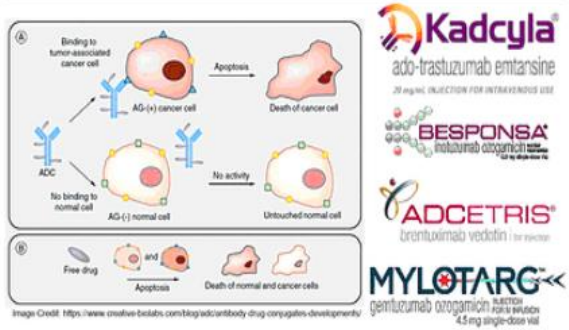


Image Credit: https://www.creative-biolabs.com/blog/adc/antibody-drug-conjugates-development/

Kadcyla® ado-trastuzumab emtansine

BESPONSA® inotuzumab ozogamicin

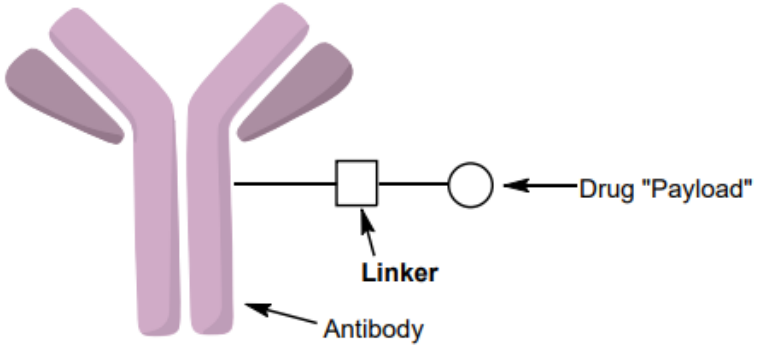
ADCETRIS® brentuximab vedotin

MYLOTARG™ gemtuzumab ozogamicin

Daniel Szczepankiewicz Apr 12, 2019

www.sarlahgroup.com/topic

What is an Antibody-Drug Conjugate?



Antibody-Drug Conjugates (ADCs) are cytotoxic agents bound in an inert form to an antibody through the use of a chemical linker.

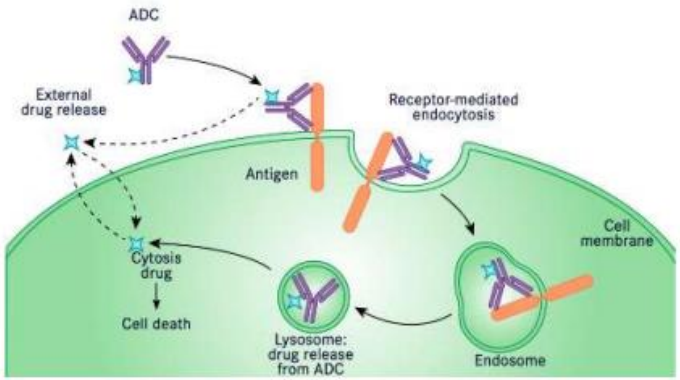


Image Credit: https://www.dilworthip.com/antibody-drug-conjugates-patent-landscape-new-class-cancer-treatment/

Mode of Operation:
The drug binds to an antigen on a cancer cell, and proceeds to release its drug in an active form through a variety of different pathways. When properly designed, this induces highly selective release of a chemotherapeutic drug inside of a cancer cell, or within its immediate vicinity, inducing cancer cell death while leaving healthy cells unharmed.

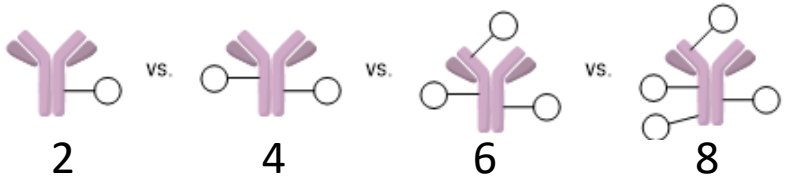
Relevant Refreshers:

Biodistribution:

-Can the ADC be transported across a cell membrane? This requires finely tuned properties of the linker, antibody, and conjugated drug to attain sufficient solubility.

-*The Bystander Effect*: Diffusion of the cytotoxic payload into the surrounding

AMb Heterogeneity issues:
Regulation of polysubstitution on antibodies remains problematic, and the typical distribution on the antibody of linkers is around four linkers/antibody on average. As homogeneity is vital for reproducibility and predictibility of AMb behavior *in vivo*, a current objective in ADC research is increasing the homogeneity of AMb-ADC compounds.



May exhibit different pharmacological properties

"Drug-Antibody Ratio" (DAR)

Sacituzumab Govitecan-hziy (Trodelvy™)

Introduction:

- Sacituzumab Govitecan-hziy is a new antibody-drug conjugate (ADC) for the treatment of adults with triple-negative breast cancer that has spread to other parts of the body, for patients who have received at least two prior therapies for their metastatic disease.

- Approved in late April of 2020, the ADC continues the “second generation” of ADCs:

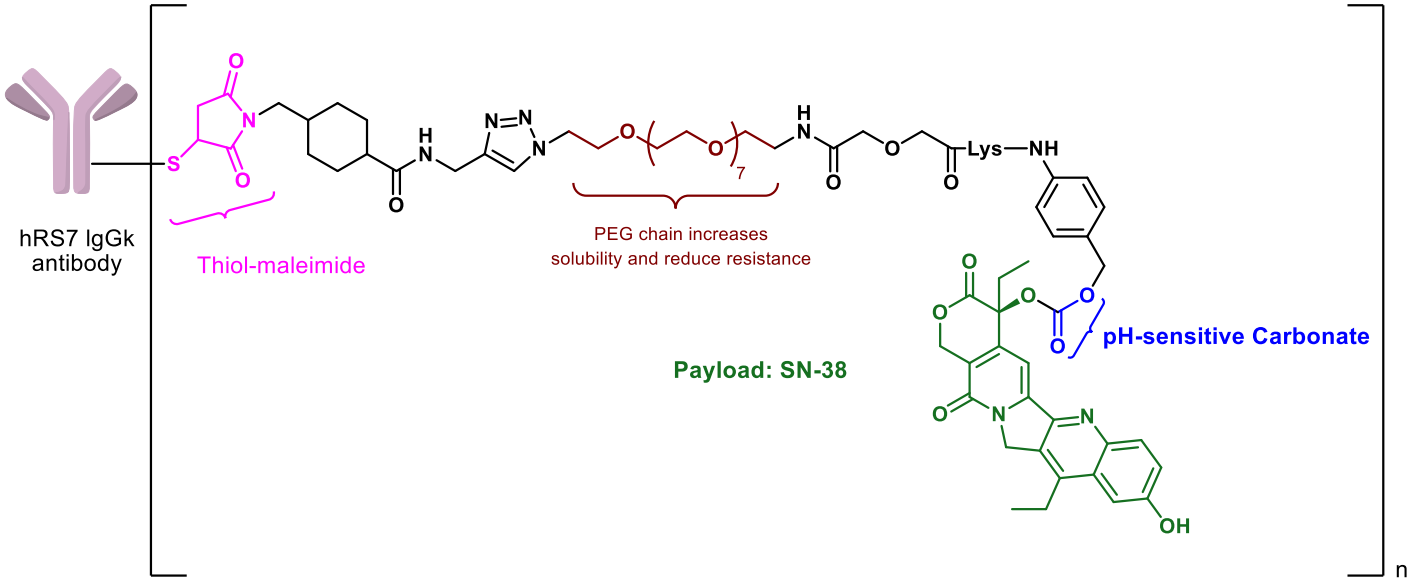
  - Previously, to achieve efficacy an “ultratoxic agent” (e.g. calicheamycin in Mylotarg) would be bound with a relatively low DAR of four or less to regulate dosage. As one may anticipate, this can result in a low therapeutic window and hazards associated with nonspecific release, and highly stable linkers had to be used.
  - More modern ADCS incorporate moderately cytotoxic payloads, but with higher DARs (Trodelvy DAR ~ 7.6) with an intermediately stable linker. This allows for more steady release of moderately potent chemotherapeutics and reduction in off-target effects.

- The antibody component of Trodelvy, Sacituzumab (AKA hRS7 lgGk), targets Trop2, a cell-surface antigen that is expressed in a variety of cancers. The ADC is then internalized to release the payload SN-38, which is the active form of the chemotherapeutic DNA-targeting drug Camptotechin.

- In a phase I/II clinical trial treating patients with a variety of epithelial cancers a 2.8% CR, and 30.6% PR were reported (n = 108).

ClinicalTrials.gov Identifier: NCT01631552

Eur. J. Med. Chem. **2019**, *167*, 583.

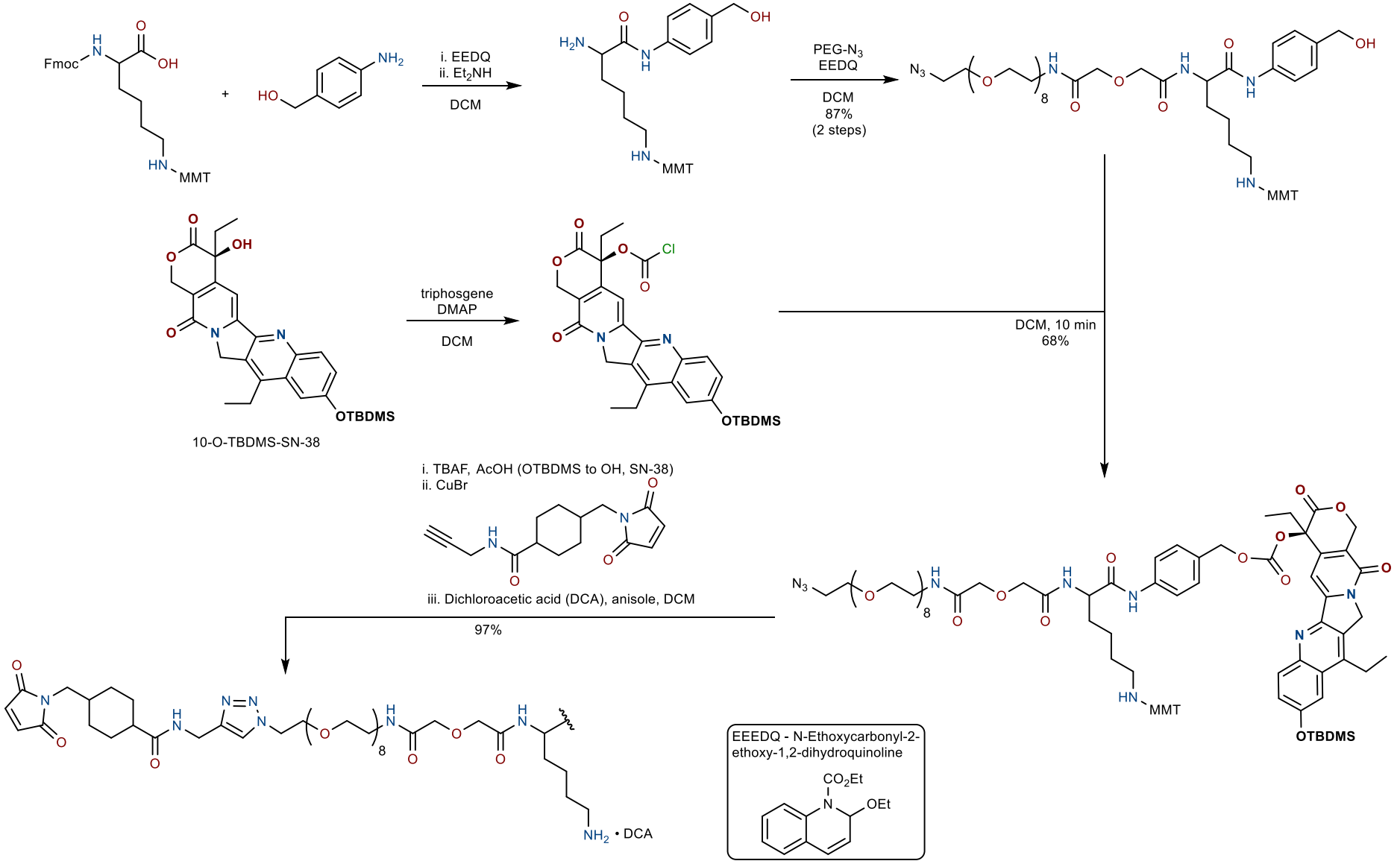


https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trial-snapshot-trodelvy

(n ~ 7.6)

Sacituzumab Govitecan-hziy (Trodelvy™)

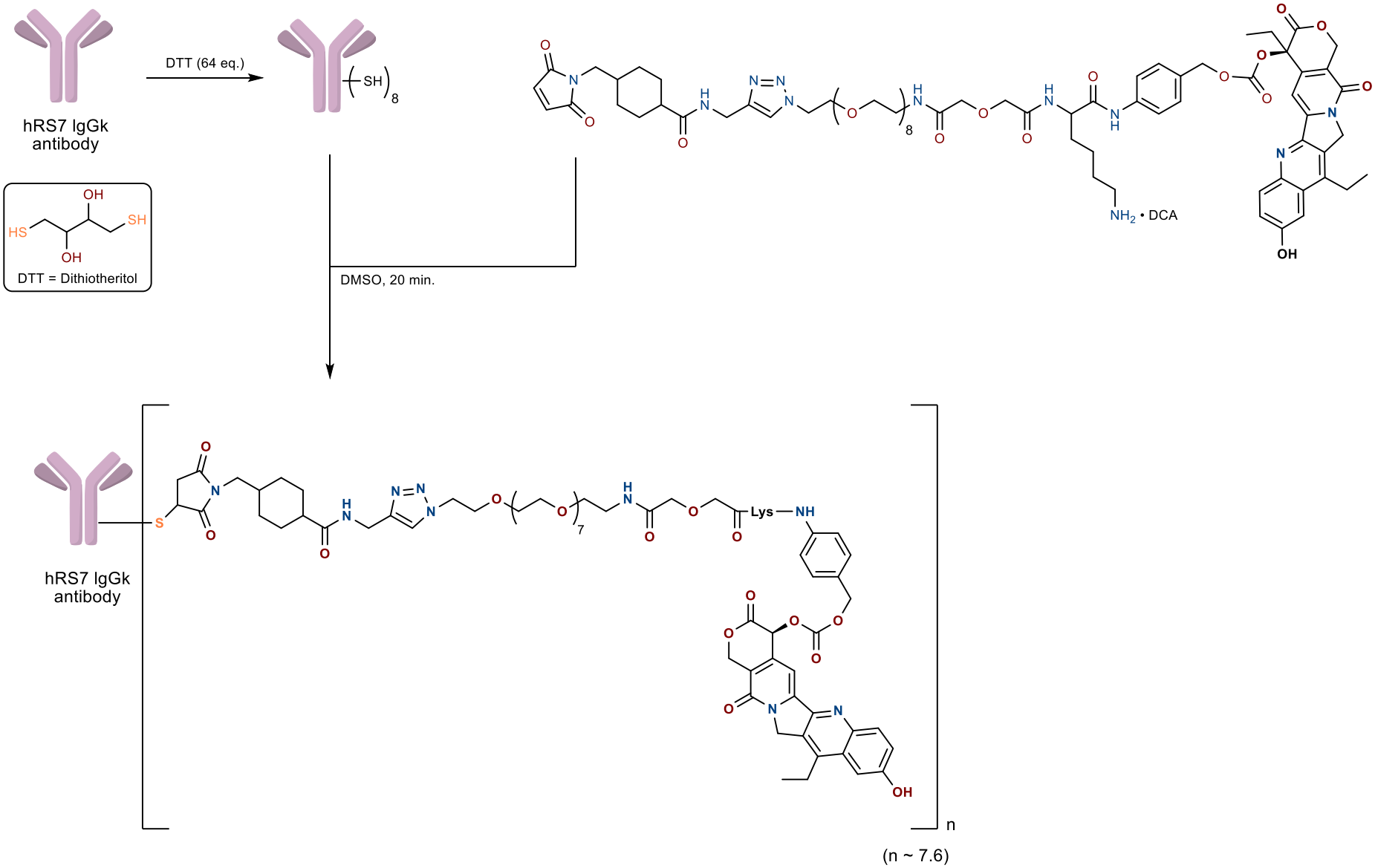
Synthesis:



Clinical Cancer Research **2011,** *17* (10), 3157.

Sacituzumab Govitecan-hziy (Trodelvy™)

Conjugation:



J. Med. Chem. **2008**, 51, 6916.