Trastuzumab/Tesirine Antibody-drug Conjugate ADCT-502

National Cancer Institute

Source

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An antibody-drug conjugate (ADC) consisting of an engineered version of the humanized monoclonal anti-human epidermal growth factor receptor 2 (HER2) immunoglobulin G1 (IgG1) trastuzumab that is site-specifically conjugated, via a cleavable linker, to the cytotoxic, DNA cross-linking pyrrolobenzodiazepine (PBD) dimer-based drug tesirine, which targets DNA minor grooves, with potential antineoplastic activity. Upon administration, the trastuzumab moiety of trastuzumab/tesirine ADC ADCT-502 targets the cell surface antigen HER2, which is expressed on various cancer cells. Upon antibody/antigen binding, internalization of the ADC and cleavage of the linker, the cytotoxic PBD moiety is released. The imine groups of tesirine bind to the N2 positions of guanines on opposite strands of DNA. This induces interstrand cross-links in the minor groove of DNA, inhibits DNA replication, leads to G2/M cell cycle arrest, induces cell death and inhibits the proliferation of HER2-overexpressing tumor cells. The tumor-associated antigen (TAA) HER2 is expressed by various solid tumors and is associated with a poor prognosis.