Mechanistic and benchmarking studies of ADCT-502, a Pyrrolobenzodiazepine (PBD) Dimer-Containing Antibody Drug Conjugate (ADC) Targeting HER2-Expressing Solid Tumors

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Introduction

1. HER2, a member of the epidermal growth factor family of receptor tyrosine kinases (EGFR-RTKs), including EGFR and ErbB-4, mediates signaling pathways involved in cell proliferation and apoptosis. HER2-overexpressing tumors are sensitive to HER2-targeted therapies, such as trastuzumab (Herceptin®). However, due to the short circulating half-life of trastuzumab and its limited activity in HER2-low expressing cancers, there is a need for new agents that are specifically designed for targeting HER2-low expressing cancers.

2. ADCT-502 is an ADC composed of an engineered version of humanized IgG1 immunoglobulin, directed against human HER2, site-specifically conjugated to the highly cytotoxic PBD-based linker-drug tesirine (1) (drug-antibody ratio [DAR] of 1.7) (Figure 1).

Aim of this study

To further define the mechanism of action of ADCT-502 and benchmark its activity against trastuzumab-resistant (T-DM1) in low HER2-expressing solid tumor models.

Material & Methods

Bystander activity was measured via the conditioned media transfer method and cell viability was determined by CellTiter-Glo® assay (Promega). Bystander activity in breast, gastric and esophageal cancer derived xenografts, but it is inactive against ado-trastuzumab emtansine (T-DM1) in low HER2-expressing solid tumor models.

Results

ADCT-502 shows potent and highly targeted in vitro cytotoxicity in a panel of HER2-expressing solid cancer cell lines (1). In vitro, single low-doses of ADCT-502 demonstrates strong and durable anti-tumor activity in breast, gastric and esophageal cancer derived xenografts, but it is inactive against ado-trastuzumab emtansine (T-DM1) in low HER2-expressing solid tumor models.

Conclusions

1. ADCT-502 specifically bound, internalized and trafficked to the tumors in HER2-positive (HER2+) cells. In contrast, trastuzumab was detected within 2 hours, while by 24 hours no staining for IgG or PBD payload was observed, suggesting complete biochemical degradation of T-DM1. This suggest that the different biodistribution of ADCT-502 may contribute to the difference in anti-tumor activity between these two ADCs.

2. ADCT-502 specifically induced DNA cross-links in HER2+ve NCI-N87 cells, which were maintained even by 24 hours, while by 24 hours no staining for IgG or PBD payload was observed, suggesting complete biochemical degradation of T-DM1. This suggest that the different biodistribution of ADCT-502 may contribute to the difference in anti-tumor activity between these two ADCs.

3. Together, these data further define the mechanism of action of ADCT-502 and showed its superior in vivo anti-tumor activity against T-DM1 in low HER2-expressing solid tumor models.

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References


4. In low HER2-expressing breast, esophageal and gastric PDXs models, a single dose of ADCT-502 demonstrates strong and durable anti-tumor activity against T-DM1 in low HER2-expressing solid tumor models.

5. Together, these data further define the mechanism of action of ADCT-502 and showed its superior in vivo anti-tumor activity against T-DM1 in low HER2-expressing solid tumor models.

Figure 1: HER2 structure.

Figure 2: ADCT-502.

Figure 3: Internalization kinetic.

Figure 4: DNA interstrand cross-linking.

Figure 5: In vivo anti-tumor activity in benchmarking study in HER2+ve breast cancer PDX.

Figure 6: In vivo anti-tumor activity in benchmarking study in HER2+ve esophageal cancer PDX.

Figure 7: In vivo anti-tumor activity in benchmarking study in HER2+ve gastric cancer PDX.