Preclinical development of TJ106, a potent biparatopic dual-payload ADC targeting HER2 for the treatment of Enhertu-resistant tumors

Poster #3298

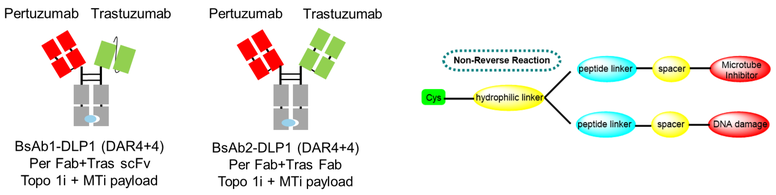
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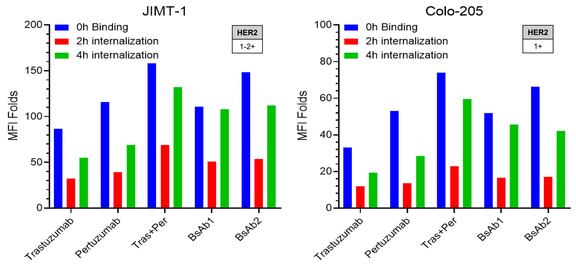
Introduction

- HER2 overexpression has been consistently associated with increased metastatic potential and poor clinical outcome and has been observed across various tumor types, including breast cancer, gastric cancer, gastroesophageal junction adenocarcinoma and lung cancer [1].
- Trastuzumab deruxtecan (Enhertu®, T-DXd or DS-8201), an ADC targeting HER2, has shown impressive efficacy in treating HER2-overexpressing cancers. T-DXd is approved for HER2-positive breast cancer, gastric/GEJ adenocarcinoma, non-small cell lung cancer (NSCLC) and other indications.
- T-DXd is approved as a first-line therapy in combination with pertuzumab for HER2-positive metastatic breast cancer. However, acquired resistance and disease progression eventually develop in many patients.
- Phrontline has developed TJ106, a biparatopic HER2-targeting ADC with dual payloads, Topo I inhibitor + microtubule inhibitor (MTi), and designed to overcome resistance to T-DXd.

Structure design of TJ106 bispecific dual-payload ADCs



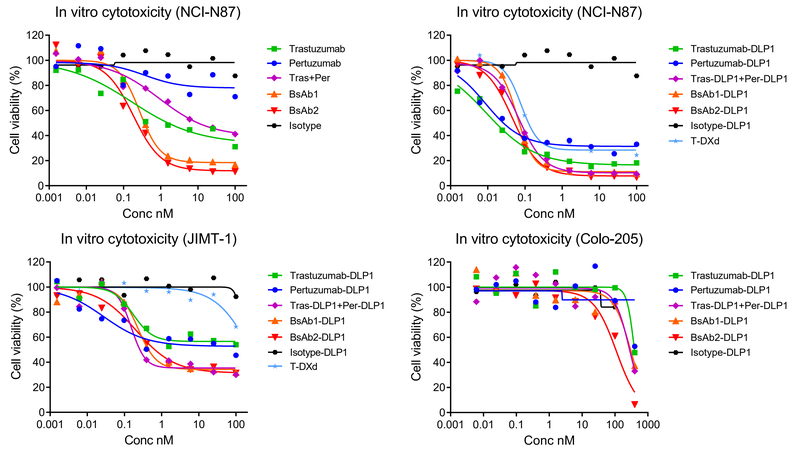
Bispecific antibodies show better internalization than monoclonal antibodies



- The internalization of two candidate BsAbs, Trastuzumab, Pertuzumab and their combination were evaluated using flow cytometry. JIMT-1 (moderate HER2 expression, IHC 2+) and Colo-205 (low HER2 expression, IHC 1+) cells were incubated with fluorescently labeled antibodies for 2 or 4 hours, followed by digestion of surface-bound antibodies prior to flow cytometric analysis.
- BsAbs demonstrated superior internalization compared to Trastuzumab and Pertuzumab monoclonal antibodies, while slightly weaker than their combination.

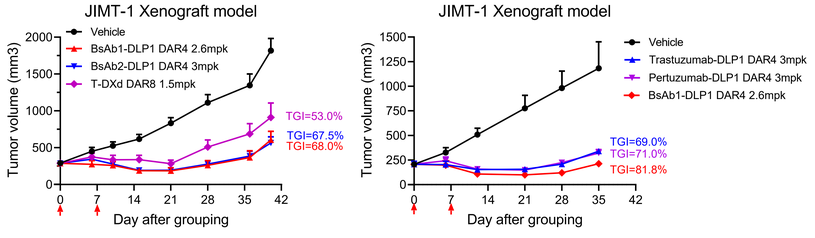
Reference:
[1] Yan M, Schwaederle M, Arguello D, Millis SZ, Gatalica Z and Kurzrock R. HER2 expression status in diverse cancers: review of results from 37,992 patients. Cancer Metastasis Rev 2015; 34: 157-164.

Bispecific dual-payload ADCs show superior in vitro cytotoxicity than monoclonal antibodies and T-DXd



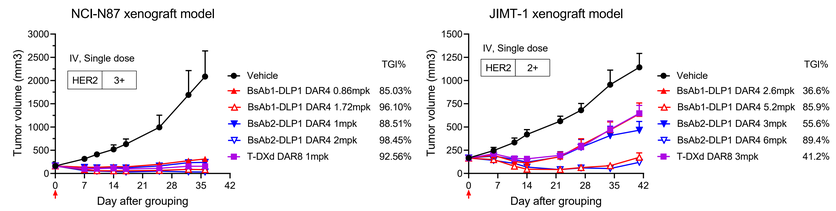
- NCI-N87 (HER2 3+) gastric cancer cells, JIMT-1 and Colo-205 cells were treated with antibodies or ADCs for 144 hours, and cytotoxicity was assessed using CellCounting-Lite 2.0 viability assay.
- BsAbs exhibited better in vitro cytotoxicity compared to Trastuzumab and Pertuzumab monoclonal antibodies or their combination.
- Biparatopic dual-payload ADCs (BsAb1-DLP1, BsAb2-DLP1) demonstrated significantly superior in vitro cytotoxicity compared to Trastuzumab-DLP1, Pertuzumab-DLP1 and T-DXd.

Bispecific dual-payload ADCs show better efficacy in target-moderate expression CDX models



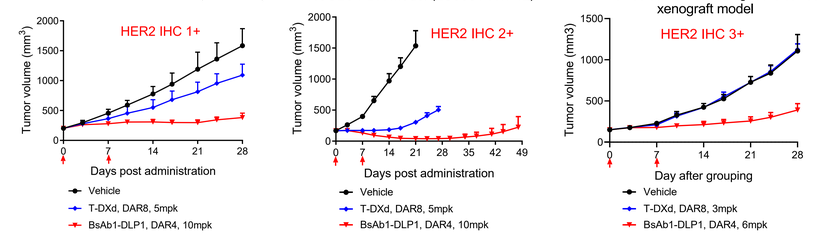
- In vivo efficacy of TJ106 was assessed in JIMT-1 xenograft models established in female CB17-SCID mice (n=5 per group). Tumor volumes are presented as Mean ± SEM.
- Both biparatopic dual-payload ADCs (BsAb1-DLP1, BsAb2-DLP1) showed better anti-tumor activity than T-DXd (at the equivalent dose of Topo 1i payload) in JIMT-1 xenograft model, with TGI% values of 68.0% and 67.5% on day 40 post-dose, respectively.
- BsAb1-DLP1 demonstrated superior anti-tumor activity than two monoclonal antibody dual-payload ADCs (Trastuzumab-DLP1 and Pertuzumab-DLP1) in JIMT-1 xenograft model, with TGI% values of 81.8% on day 35 post-dose.

Bispecific dual-payload ADC shows dose-dependent antitumor activity in CDX models



- Both dual-payload ADCs (BsAb1-DLP1 and BsAb2-DLP1) exhibited significant dose-dependent antitumor efficacy in the NCI-N87 (HER2 3+) gastric cancer xenograft model, with in vivo activity comparable to T-DXd at an equivalent payload dose.
- Both dual-payload ADCs (BsAb1-DLP1 and BsAb2-DLP1) exhibited significant dose-dependent antitumor efficacy in the JIMT-1 (HER2 2+) breast cancer xenograft model, with in vivo activity obviously better than T-DXd at an equivalent payload dose.

Bispecific dual-payload ADC shows good efficacy in T-DXd-resistant PDX or CDX models



- In vivo antitumor efficacy of TJ106 was evaluated in T-DXd-resistant patient-derived xenograft (PDX) or CDX models using female immunodeficient mice (BALB/c Nude or NOD-SCID; n=3 per group).
- TJ106 biparatopic dual-payload ADC (BsAb1-DLP1) showed better efficacy in T-DXd-resistant gastric cancer and NSCLC PDX models, as well as T-DXd-resistant NCI-N87 gastric cancer CDX model.

Conclusion

- TJ106 bispecific dual-payload ADCs are designed to target HER2 high or low expression tumors and overcome T-DXd resistance.
- Biparatopic antibodies with Trastuzumab and Pertuzumab showed better internalization in HER2 expressing cancer cells.
- Biparatopic dual-payload ADCs exhibited in vitro killing advantages than monoclonal ADCs.
- Biparatopic dual-payload ADCs showed better in vivo antitumor efficacy than monoclonal ADCs and T-DXd in CDX models.
- Biparatopic dual-payload ADCs overcame T-DXd resistance in HER2 low expression PDX models.