OBI 201: A Bispecific TROP2 × HER2 Antibody-Drug Conjugate to Expand Therapeutic Reach Beyond HER2-Low Limitations

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BACKGROUND

- While Enhertu® has delivered meaningful clinical benefits in HER2-positive and HER2-low cancers, many patients still experience suboptimal outcomes, particularly in HER2-low tumors that account for over 50% of the HER2-positive pan cancer population. **Resistance to HER2-targeted therapies remains a critical challenge**, often driven by HER2 downregulation or loss, leading to **reduced antibody binding and limited payload delivery**.
- **OBI Pharma is the first to discover that TROP2 and HER2 form heterodimers** (Data not published) in cancer cells. This TROP2 and HER2 crosstalk provides a strong rationale for dual targeting. OBI-201—a bispecific antibody-drug conjugate (bsADC) engineered to simultaneously engage both TROP2 and HER2, aiming to enhance tumor specificity and overcome resistance.

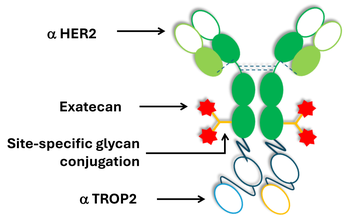
OBJECTIVE

- To evaluate the therapeutic potential of OBI-201, a bispecific ADC targeting both TROP2 and HER2, designed to enhance tumor specificity, improve payload delivery through co-endocytosis, and overcome resistance mechanisms including TROP2-mediated resistance following HER2 targeted therapies.

METHODS

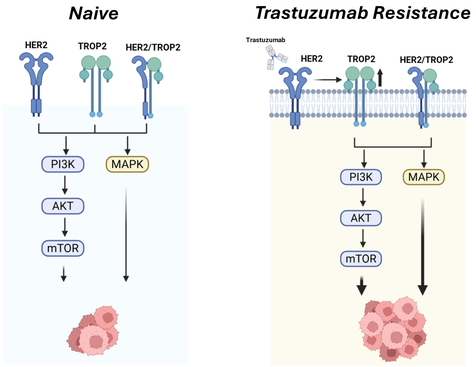
- OBI-201 is a next-generation bsADC that co-targets HER2 and TROP2, leveraging site-specific glycan conjugation and a hydrophilic linker technology to incorporate Exatecan as the payload at a homogeneous drug-to-antibody ratio (DAR) of 4, ensuring precise and consistent payload delivery.
- To assess the efficiency of internalization, pHAb-labeled OBI-201 was applied to HER2/TROP2 co-expressing cells by quantifying fluorescence signals.
- To evaluate its antitumor activity, OBI-201 was tested in both cell line-derived xenograft (CDX) models and patient-derived xenograft (PDX) models

Figure 1. OBI-201, bispecific TROP2 × HER2 ADC



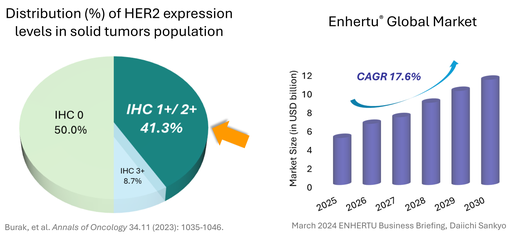
RESULTS

Figure 2. TROP2 and HER2 crosstalk mechanism



HER2/TROP2 heterodimerization provides a potential bypass mechanism for trastuzumab resistance. Upon the acquisition of trastuzumab resistance, the resistant mechanism is potentiated by TROP2 upregulation, leading to a stronger activation of the downstream pro-survival pathways (Data not published).

Figure 3. OBI-201 unlocking multi-billion-dollar market opportunities

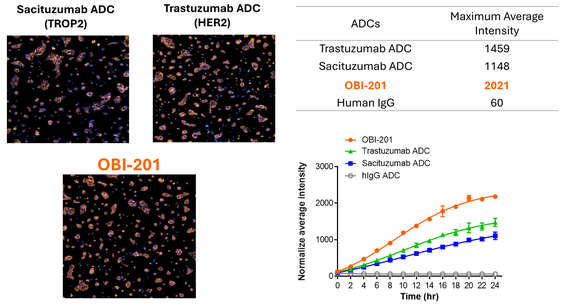


Burak, et al. *Annals of Oncology* 34.11 (2023): 1035-1046.

March 2024 ENHERTU Business Briefing, Daiichi Sankyo

OBI-201 has the potential to address unmet needs in HER2-mid/low and Enhertu®-resistant cancers, supporting its opportunity for broader clinical and commercial development.

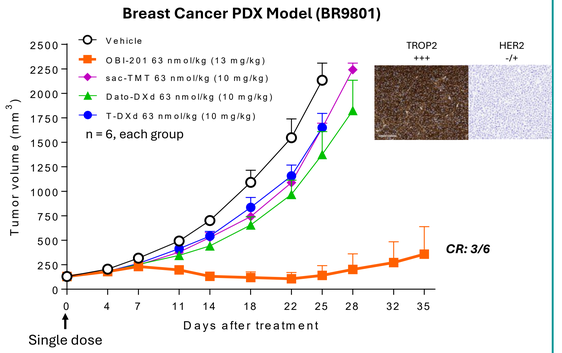
Figure 4. OBI-201 Enhanced Internalization vs Monospecific ADCs



ADCs	Maximum Average Intensity
Trastuzumab ADC	1459
Sacituzumab ADC	1148
OBI-201	**2021**
Human IgG	60

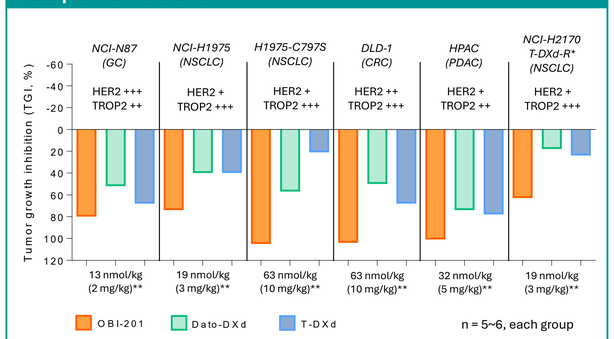
Data represent the signal intensity measured at 24 hours in NCI-N87 gastric cancer cell line.

Figure 5. OBI-201overcomes multidrug resistance in a breast cancer PDX model



PDX , Patient-Derived Xenograft; I/O: immunotherapy, CR: Complete Response
Prior treatments in PDX model including: Multiple lines of Chemotherapies, Kinase inhibitor + I/O, EGFR/MUC1 BsADC, Trodelvy®, and Cell cycle inhibitor (Wee 1)
OBI-201 has a molecular weight of 209 kDa, compared to ≅160 kDa for the monospecific TROP2 or HER2 ADCs. It was administered a single dose of 13 mg/kg, which is equivalent to 10 mg/kg of the monospecific ADCs.

Figure 6. OBI-201 shows superior antitumor activity across multiple CDX models



CDX , Cell-Derived Xenograft. Tumor growth inhibition (TGI), measures antitumor activity by comparing the tumor growth rate in the treated group with that in the untreated control group.
*NCI-H2170 T-DXd-R: A T-DXd–resistant model developed through *in vitro* T-DXd exposure until the IC_{50} exceeded that of the parental cells by more than 10-fold.
**Data represent dose of monospecific ADCs

CONCLUSIONS

- OBI-201, a bsADC enabled by unique linker technology, offers enhanced and highly precise payload delivery, improving efficacy and targeting. These features give it strong potential to outperform Enhertu® in clinical outcomes, particularly in HER2-resistance or HER2 low tumors.

DISCLOSURE

- This study was funded by OBI Pharma, Inc. All authors are employees of OBI Pharma, Inc.

ACKNOWLEDGMENTS

- We are grateful for the support from the National Center for Biomodels (NCB), Taiwan.

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