# ZW49, A HER2-Targeted Biparatopic Antibody Drug Conjugate for the Treatment of HER2-Expressing Cancers

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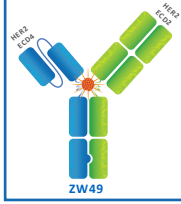
## Background

Following T-DM1, multiple novel HER2-targeted antibody drug conjugates (ADCs) have been developed with the promise of improved potency and efficacy. The preclinical characterization of a new anti-HER2 biparatopic ADC, ZW49, combines the potential for improved potency and greater tolerability due to the unique properties of Zymeworks' Azymetric™ and ZymeLink™ platforms. ZW49 was generated from the conjugation of our proprietary ZymeLink Auristatin to the Azymetric anti-HER2 IgG1, ZW25, via a protease cleavable linker. The Azymetric biparatopic antibody of ZW49 demonstrates lysosomal trafficking and superior internalization relative to a HER2-targeted monospecific ADC. The unique properties of the ZymeLink Auristatin of ZW49 enable greater tolerability and exposure. These properties enable ZW49 to generate complete responses in HER2 low to high-expressing PDX models at exposures tolerated in non-human primates.

## ZW49 – Anti-HER2 Biparatopic Antibody-Drug Conjugate




**Biparatopic antibody (ZW25) targets two distinct HER2 epitopes**

- Same domains as trastuzumab (ECD4) and pertuzumab (ECD2)

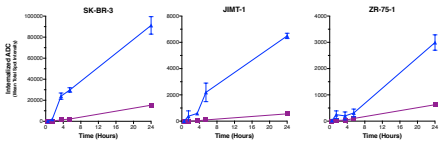
**ZymeLink Auristatin ADC enhanced therapeutic index**

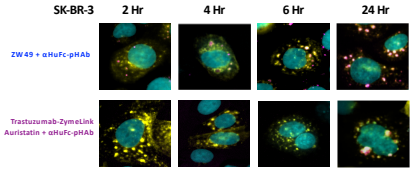
- Proprietary linker-drug conjugated via disulfides containing a cleavable linker and novel auristatin payload

**ZW49 is active and well-tolerated in preclinical studies**

- Active in HER2-low to HER2-high patient derived xenograft (PDX) models
- Well tolerated at 18 mg/kg in repeat dose toxicology studies in non-human primates

## ZW49 Internalizes and Traffics to Lysosomes in HER2 Expressing Cells to Greater Levels and More Rapidly Than Monospecific ADC



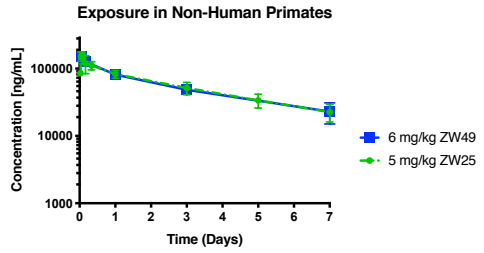

To determine internalization, pHAb, a highly fluorescent dye at acidic pH (pink), was coupled to amines of a αHuFc. αHuFc-pHAb and ADCs were incubated with HER2-expressing cell lines and fluorescence measured using a high content CellInsight™.

## Toxicology Results Support Clinical Dosing of ZW49 Above Predicted Efficacious Doses

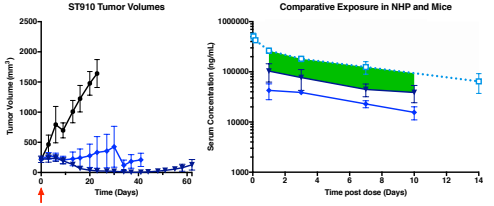
| | |
|---|---|
| **GLP Toxicology Study** | 0, 6, 12, 18 mg/kg<br>4 doses at 2 week intervals<br>6 week recovery |
| **Highest Non-Severely Toxic Dose (HNSTD)** | 18 mg/kg |

- ZW49 is well tolerated in non-human primates
- No clinical observations were considered adverse
- No mortality on study
- No significant change in body weight
- No clinical pathology findings were considered adverse

## ZW49 Exhibits Similar Pharmacokinetics to Naked Antibody ZW25 in Non-Human Primates

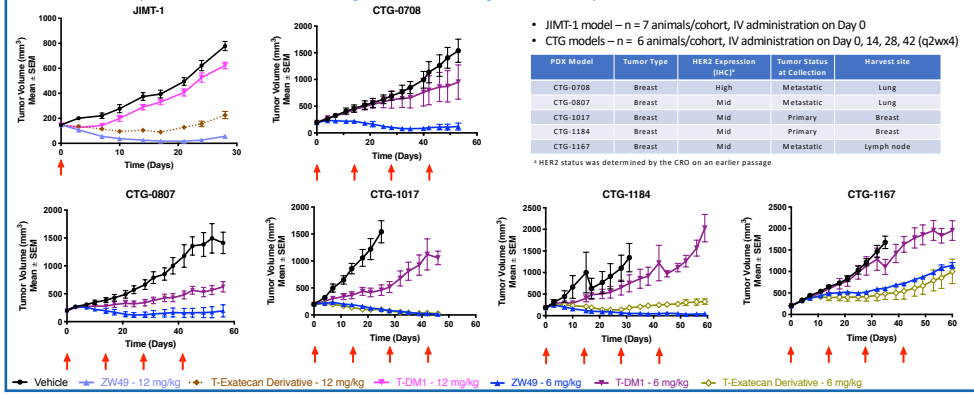



## Predicted Therapeutic Window of ZW49 Allows Doses Resulting in Regressions of HER2 Low Tumors




N = 6 animals/cohort, IV administration on Day 0
HER2 status was determined with an earlier passage by IHC using SP3 Ab

## ZW49 Exhibits Efficacy in Panel of HER2-Mid and HER2-High Breast Cancer Xenograft Models Compared to T-Exatecan Derivative and T-DM1

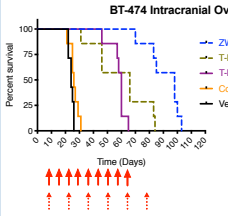



- JIMT-1 model – n = 7 animals/cohort, IV administration on Day 0
- CTG models – n = 6 animals/cohort, IV administration on Day 0, 14, 28, 42 (q2wx4)

| PDX Model | Tumor Type | HER2 Expression (IHC)[a] | Tumor Status at Collection | Harvest site |
|---|---|---|---|---|
| CTG-0708 | Breast | High | Metastatic | Lung |
| CTG-0807 | Breast | Mid | Metastatic | Lung |
| CTG-1017 | Breast | Mid | Primary | Breast |
| CTG-1184 | Breast | Mid | Primary | Breast |
| CTG-1167 | Breast | Mid | Metastatic | Lymph node |

[a] HER2 status was determined by the CRO on an earlier passage

## ZW49 Significantly Improved Survival Compared to T-Exatecan Derivative and T-DM1 in HER2-High Breast Cancer Brain Metastasis Model




- BT-474 HER2 positive ductal breast carcinoma
- Animals intracranially implanted on Day 0
- IV dosing commenced on Day 8
- IV dosing once weekly (qw) for T-DM1, Control conjugate, and Vehicle or once every two weeks for 6 weeks (q2wx6) for ZW49 and T-Exatecan Derivative
- N=7/cohort
- Body weight measured twice a week until D18 and daily thereafter

| Test Article | Dose (mg/kg) | Schedule | Median Survival (days) | Median Survival p-value compared to T-DM1 | Median Survival p-value compared to T-Exatecan Derivative |
|---|---|---|---|---|---|
| ZW49 | 6 | q2wx6 | 98 | 0.00323 | 0.0224 |
| T-Exatecan Derivative | 6 | q2wx6 | 66 | 0.396 | N/A |
| T-DM1 | 6 | qw | 60 | N/A | 0.396 |

P-values were calculated using the log-rank test. P-values were corrected for multiple tests using the Holm-Bonferonni procedure.

## Summary

- ZW49's biparatopic antibody enhances internalization and lysosomal trafficking compared to a monospecific HER2-targeting ADC
- Complete tumor regressions observed in Low to High HER2-expressing models
- ZW49 efficacy observed in HER2-high breast cancer brain metastasis model
- ZW49 was well tolerated in non-human primates (Q2W dosing for 4 doses) with an HNSTD of 18 mg/kg
- Toxicology results support clinical dosing well above predicted efficacy levels
- Expanded therapeutic window of ZW49 may enable higher doses and greater exposures leading to improved anti-tumor activity in patients with High and Low HER2-expressing cancers
- Investigational New Drug (IND) application filed in 2018, Phase 1 clinical trial planned to initiate in early 2019

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## Acknowledgements

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