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

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Background
Following TCM-06, multiple novel HER2-targeted antibody drug conjugates (ADCs) have been developed with the promise of improved potency and efficacy. The predilection 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 Zymateck™ platforms. ZW49 was generated from the conjugation of our proprietary Zymatik Antibodies to the Asymmetric anti HER2 IgG1, ZW25, via a proprietary 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 Zymatik Antibody 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)

Zymatik Antibody (ZW49) is active and well-tolerated in preclinical studies
• Active in HER2-low to HER2-high patient derived xenograft (PDX) models
• Well-tolerated at 12 mg/kg in repeat dose toxicity 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, pHV6, a highly fluorescent dye at acidic pH (pHv6), was coupled to emericin of a staphylococcal plasmid and ADCs were incubated with HER2-expressing cell lines and fluorescence measured using a high content Cell Insight®.

Toxicology Results Support Clinical Dosing of ZW49 Above Predicted Efficacious Doses

GLP Toxicology Study
<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Days</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0, 6, 12, 18</td>
<td>4</td>
<td>6 week</td>
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ZW49 Successfully Improved Survival Compared to T-Dexatecan Derivative and T-D01 in HER2-High Breast Cancer Brain Metastasis Model

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<tr>
<th>Test Article</th>
<th>Median Survival (days)</th>
<th>10% Increase Value</th>
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<tbody>
<tr>
<td>ZW49, 6 mg/kg</td>
<td>1500</td>
<td>0.00323</td>
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Summary
• ZW49’s biparatopic antibody enhances internalization and lysosomal trafficking compared to a monospecific HER2-targeting ADC
• ZW49 efficacy observed in HER2-high breast cancer brain metastasis model
• ZW49 was well-tolerated in non-human primates (Q2WX6) with an HINDO 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