OT1-14-01

Zanidatamab (ZW25) in Combination with Evorpacept (ALX148) in Advanced Human Epidermal Growth Factor Receptor 2 (HER2)-expressing Cancers, Including Breast Cancer: a Phase 1b/2, Multicenter, Open-Label, Dose-Finding and Cohort-Expansion Study (ZWI-ZW25-204)

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BACKGROUND AND RATIONALE

- Breast cancer is the most common malignancy diagnosed in women in the United States and the second leading cause of death from cancer. The HER2-positive subset comprises 15-20% of all breast cancer cases.
- HER2-targeted therapies have markedly improved survival for patients with HER2-positive breast cancer. With the treatment options available today, the median overall survival for patients with metastatic treatment-naïve HER2-positive breast cancer has improved to almost 5 years.
- However, metastatic HER2-positive disease remains incurable with an ongoing need to expand our available anti-HER2 therapies
- Additionally, while historically the HER2-low population has shown a lack of response to trastuzumab therapy[1], there are ongoing efforts to investigate the efficacy of novel anti-HER2 agents in this population
- To address these areas of unmet need, this study is evaluating the novel combination of zanidatamab (zani), a HER2-targeted bispecific antibody, and evorpacept, a CD47-blocker, for the treatment of advanced and/or metastatic HER2-positive and HER2-low breast cancer and other HER2-expressing cancers

Zanidatamab (ZW25)

- Novel HER2-targeted bispecific antibody directed against the juxtamembrane domain (ECD4) and the dimerization domain (ECD2) of HER2[2]
- Multiple mechanisms of action:
  - Receptor clustering, internalization, downregulation
  - Inhibition of growth factor-dependent and -independent tumor cell proliferation
  - Antibody-dependent cellular cytotoxicity (ADCC)
  - Antibody-dependent cellular phagocytosis (ADCP) leading to immune clearance of HER2-expressing tumor cells
  - Complement-dependent cytotoxicity (CDC)
- Bispecific design leads to high affinity HER2 binding including binding to HER2-low breast cancer cell lines
- As monotherapy and in combination with chemotherapy, zanidatamab has demonstrated:
  - antitumor activity across HER2-expressing tumors (including breast cancer) in a Phase 1 study (NCT02892123)
  - encouraging and durable antitumor activity in heavily pretreated patients with HER2-positive breast cancer (refer to 2021 SABCS poster #P2-13-07 for data on zanidatamab in combination with chemotherapy)
  - good tolerability; diarrhea and infusion-related reactions are the most common adverse events (AEs)[3-5]
- Received FDA Breakthrough Therapy Designation for treatment of patients with HER2-amplified biliary tract cancer

Figure 1a: Unique Binding Properties of Zanidatamab

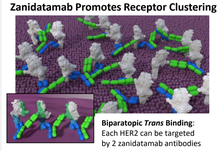


Figure 1b: Zanidatamab

Evorpacept (ALX148)

- High affinity CD47-blocking fusion protein with an inactive human immunoglobulin Fc region
- CD47 is expressed in many cancers, including breast cancer, where it acts as a 'do not eat me' signal and prevents recognition by macrophages, allowing cancer cells to avoid phagocytosis[6]
- Antitumor activity demonstrated in combination with other anticancer therapies, including rituximab, trastuzumab ± chemo, and pembrolizumab ± chemo, with a tolerable and favorable safety profile

Figure 3a: Binding of Evorpacept to CD47

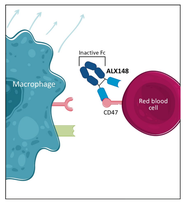
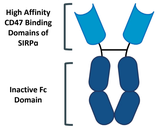
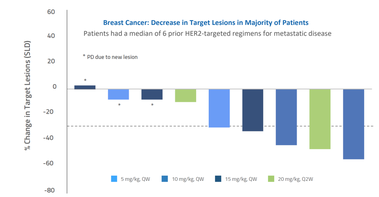


Figure 3b: Evorpacept (ALX148)



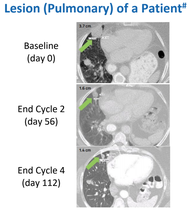
- Hematologic toxicity with evorpacept is limited due to an inactive Fc domain, which prevents phagocytosis of CD47-expressing hematopoietic cells

Figure 2a: Zanidatamab Monotherapy Decreased Target Lesions in Majority of Patients with HER2-positive Breast Cancer



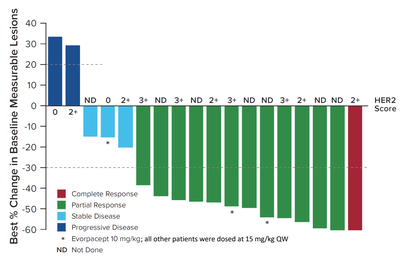
Adapted from: Hamilton E, et al. Presented at: San Antonio Breast Cancer Symposium; December 5-9, 2017. Abstract PS-20-06

Figure 2b: Decrease in Target Lesion (Pulmonary) of a Patient[#]



[#] Third patient (from right) in Figure 2a

Figure 4: Evorpacept + Trastuzumab + Ramucirumab + Paclitaxel in Patients with Gastric Cancer



Adapted from: K-W Lee, et al. Presented at: Society for Immunotherapy of Cancer (SITC) Annual Meeting; November 10-14, 2021. Abstract 498

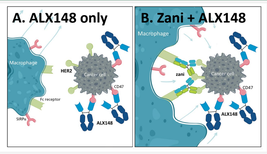
ZANIDATAMAB WITH EVORPACEPT COMBINATION RATIONALE

- Potential development of a novel, chemotherapy-free combination option for patients
  - Zanidatamab is designed with multiple mechanisms of action, including immune clearance of HER2-expressing cancer cells by macrophages through ADCP
  - Cancer cells that express CD47, a "don't eat me" signal, are resistant to immune clearance even when targeted with therapeutic antibodies
  - Treatment with zanidatamab in combination with evorpacept has the potential to augment immune clearance of HER2-expressing cancer cells, by blocking the CD47 signal that inhibits phagocytosis of these cells

Figure 5. Zanidatamab and Evorpacept (ALX148) Proposed Mechanism of Action

A. Evorpacept, with an inactive Fc, binds to CD47 and blocks interaction with signal regulatory protein alpha (SIRPα)

B. Zanidatamab's bispecific and high affinity binding to HER2, together with evorpacept's full blockade of CD47, maximize the ADCP activity of the combination on HER2-expressing cancer cells



ZWI-ZW25-204 STUDY OBJECTIVES AND DESIGN

Objectives

Part 1: Safety Evaluation

- To evaluate the safety and tolerability, and to determine the recommended doses (RDs) of zanidatamab and evorpacept when administered in combination

Part 2: Expansion Cohorts

- To assess the antitumor activity of zanidatamab and evorpacept at their RDs in patients with:
  - HER2-positive breast cancer (Cohort 1)
  - HER2-low breast cancer (Cohort 2)
  - HER2-overexpressing non-breast cancers (Cohort 3)

Endpoints

Part 1

Primary Endpoints

- Incidence of adverse events and serious adverse events
- Incidence of lab abnormalities
- Incidence of dose modifications
- Incidence of dose-limiting toxicities (DLTs)

Part 2

Primary Endpoint

- Confirmed ORR (objective response rate)

Select Secondary Endpoints

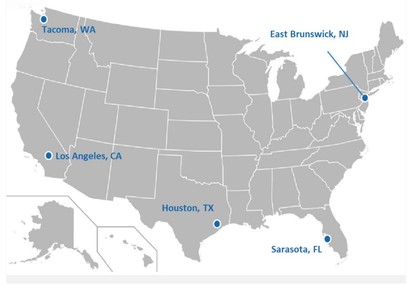
- Disease control rate
- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival
- Safety, pharmacokinetic, and immunogenicity assessments

Exploratory Biomarker Endpoints

Study Status

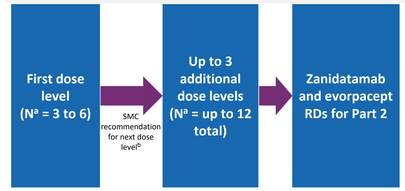
The study is currently open for enrollment at 5 sites in the US
For further information (including updates to active sites):

- Visit www.clinicaltrials.gov (NCT05027139)
- Contact Zymeworks Clinical Trial Resource (206) 237-1030 or medinfo@zymeworks.com



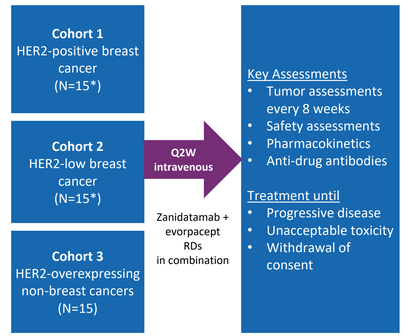
Study Design

Part 1. Safety Evaluation (3+3 Dose Escalation Design) (Cohorts 1 and 2 only)



SMC = safety monitoring committee.
[a] Number of DLT-evaluable patients
[b] SMC will determine next dose cohort based on any DLTs identified

Part 2. Expansion Cohorts

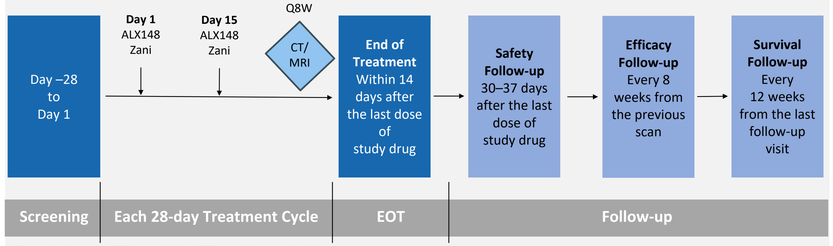


*Patients from Part 1 may be included in the total of 15 patients.

Eligibility

- Locally advanced (inoperable) and/or metastatic HER2-expressing cancer per local and/or central assessment
  - **Cohort 1 (Parts 1 & 2)**: HER2-positive breast cancer as defined per ASCO/CAP guidelines[8]
  - **Cohort 2 (Parts 1 & 2)**: HER2-low breast cancer (defined as IHC 1+ or IHC 2+; AND is not HER2-positive per the ASCO/CAP guidelines[8])
  - **Cohort 3 (Part 2)**: HER2-positive gastroesophageal adenocarcinoma (per ASCO/CAP guidelines[9]) and other HER2-overexpressing non-breast cancers (defined as IHC 3+; or IHC 2+ and ISH+)
- Disease progression on or after most recent systemic therapy
  Required prior therapies
  - **HER2-positive breast cancer**
    - At least 3 prior systemic regimens for advanced disease which must include trastuzumab, pertuzumab, and either ado-trastuzumab emtansine (T-DM1) or tucatinib
  - **HER2-low breast cancer**
    - At least 2 of the following systemic regimens for advanced disease: an anthracycline; a taxane; either capecitabine or eribulin, or both. For hormone receptor (HR)-positive disease, must have had CDK4/6 inhibitor.
  - For **HER2-expressing non-breast cancer patients**, consult the Medical Monitor
- Measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- No prior treatment with any anti-CD47 or anti-signal regulatory protein alpha (SIRPα) agent
- No untreated or symptomatic brain metastases, or radiation for brain metastases within 4 weeks of start of study treatment

Study Schema



CT = computed tomography; EOT = end of treatment; MRI = magnetic resonance imaging.

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