A Single-Arm, Phase 2 Study of Evorpacept in Combination with Trastuzumab and Chemotherapy in Participants with HER2-Positive Metastatic Breast Cancer (mBC) (ASPEN-09-03)

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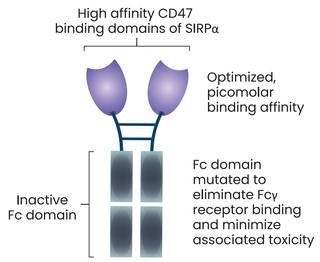
Background

- CD47, a marker of self, engages SIRPα and signals macrophages to ignore the cell on which CD47 is expressed. Tumors upregulate CD47 to evade the innate immune response[1]
- Evorpacept is designed to bind to CD47 and block the antiphagocytic signal[2]
- Evorpacept also has an inactive Fc domain, which requires a second prophagocytic signal provided by anticancer antibodies that contain an active Fc domain for effective antibody-dependent cellular phagocytosis (ADCP)[2]
- The inactive Fc avoids targeting healthy cells and minimizes toxicity, which allows it to be safely combined with standard anticancer antibodies (**Figure 1** and **Figure 2**)[2–4]
- By separating the 2 signals, it is possible to selectively direct macrophages to cancer cells and spare normal cells, thus avoiding cytopenias associated with traditional approaches to targeting CD47 blockade
- Augmentation of antitumor activity of targeted anticancer antibodies has been observed in various clinical trials
  - In a Phase 1b study, evorpacept plus zanidatamab (HER2-bispecific antibody) showed promising activity in heavily pretreated patients with centrally confirmed HER2+ mBC (n=9; ORR 55.6%, PFS 7.4 months). All patients had previously received T-DXd. The combination was well tolerated, with a manageable safety profile.[3]
  - In patients receiving 2L+ treatment for gastric cancer that was HER2+ in a fresh biopsy (where available) or HER2 (*ERBB2*) amplified in baseline ctDNA (n=96), the addition of evorpacept to trastuzumab–ramucirumab–paclitaxel (TRP) demonstrated an ORR of 48.9% and DoR of 15.7 months compared with the TRP control (ORR 24.5% and DoR 9.1 months) per INV assessment.[4] Patients with CD47 overexpression (n=43) were observed to have an ORR of 65% vs 26%. Safety data confirmed that evorpacept can be safely combined with TRP.[4]
- To date, evorpacept's inactive Fc has enabled it to be safely combined with multiple antibody and chemotherapy regimens in more than 700 patients

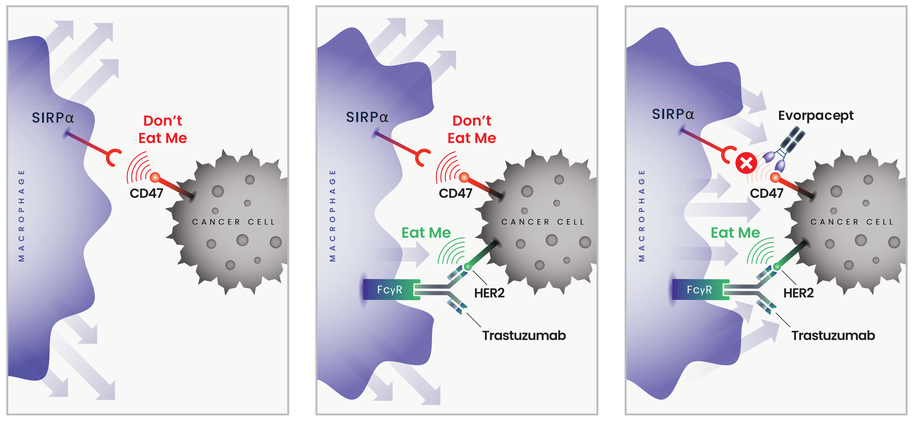
Figure 1. Evorpacept Selectively and Potently Binds CD47 to Block Interaction with SIRPα



Evorpacept
A differentiated CD47 blocker

- Fc domain enables antibody-like PK, which allows less frequent dosing and matching regimen with combinations

Figure 2. Evorpacept Plus Trastuzumab Mechanism of Action



Cancer cells overexpress CD47 in order to evade immune detection

ADCP of trastuzumab is inhibited by CD47

Evorpacept blocks the "don't eat me" signal and maximizes trastuzumab activity

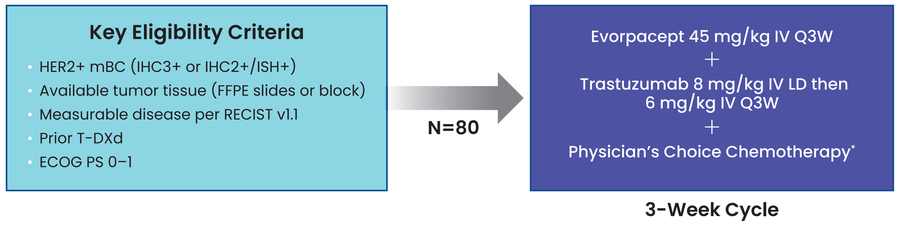
Evorpacept and Trastuzumab Have Complementary Mechanisms of Action

- Trastuzumab, a humanized monoclonal antibody, exerts antitumor effects in part by stimulating ADCC and ADCP of HER2+ cells[5]
- Current standard of care for 1L treatment of HER2+ mBC includes trastuzumab, pertuzumab, and a taxane[6]
- T-DXd is a HER2-targeted antibody–drug conjugate that is approved in 2L+ HER2+ breast cancer
- Trastuzumab is commonly combined with single-agent chemotherapy in the later-line treatment of these patients[6]
- However, HER2 loss following treatment with T-DXd has been observed, highlighting a potential need to verify HER2 expression after T-DXd treatment.[7] ctDNA offers a noninvasive option in lieu of a repeat biopsy
- CD47 is higher in HER2+ vs HER2- breast cancer patients, and has been observed to be upregulated in response to T-DXd treatment in HER2+ breast cancer cell lines[8,9]
- The addition of evorpacept to trastuzumab and single-agent chemotherapy has the potential to augment innate antitumor immune responses through ADCP (**Figure 2**)
- This study will also evaluate HER2 amplification by ctDNA after T-DXd therapy and the correlation of CD47 expression with efficacy

Study Methods

- **ASPEN-09 Breast** (Figure 3) is an ongoing, single-arm, open-label, Phase 2 global study of evorpacept + trastuzumab + physician's choice chemotherapy in patients with metastatic HER2+ mBC who have received prior treatment with T-DXd
- The study will enroll ~80 patients to receive evorpacept + trastuzumab + physician's choice chemotherapy
- Patients will receive evorpacept 45 mg/kg IV, trastuzumab 8 mg/kg loading dose followed by 6 mg/kg IV, and physician's choice chemotherapy of capecitabine, eribulin, gemcitabine, paclitaxel, or vinorelbine, all on a Q3W cycle
- Chemotherapy may be discontinued, and evorpacept and/or trastuzumab therapy continued after 6 cycles if participants have a response of stable disease or better

Figure 3. ASPEN-09-03 Breast Trial Design



*Capecitabine 1000 mg/m² PO BID for 14 days, eribulin 1.4 mg/m² IV D1 and D8, gemcitabine 1000 mg/m² IV D1 and D8, paclitaxel 175 mg/m² IV D1, or vinorelbine 25–30 mg/m² IV D1 and D8.

Study Objectives

Primary Objective

- ORR in HER2+ breast cancer with *ERBB2* amplification in ctDNA (ctDNA+)

Key Secondary Objectives

- Secondary measures of efficacy (DoR, CBR, PFS, and OS) in ctDNA+ subpopulation
- ORR in ctDNA+ by CD47 expression
- Safety

Key Exploratory Objectives

- ORR by HER2 ctDNA status (positive vs negative) and by levels of CD47 expression

Eligibility Criteria

Key Inclusion Criteria

- **Histologically confirmed invasive HER2+ breast cancer** using the ASCO/CAP Clinical Practice Guideline,[10] from the most recent evaluable biopsy performed and **post T-DXd treatment** if possible
- **Most recent tissue FFPE slides or block (fresh or archival)** for analysis of HER2 status, CD47, and other tumor markers
- **Received ≥1 prior line of therapy including T-DXd** for locally advanced/metastatic HER2+ (IHC3+ or IHC2+/ISH+) breast cancer
- Measurable disease per RECIST v1.1
- ECOG PS 0–1
- Adequate cardiac function: LVEF ≥50%
- Adequate renal, bone marrow, and liver function

Key Exclusion Criteria

- Known, untreated **CNS metastases** or leptomeningeal disease
- **Any condition that would contraindicate receiving trastuzumab** as described in the approved local label
- **Prior treatment with any CD47 or SIRPα–targeting agents**
- Anticancer therapy with insufficient washout before C1D1
  - **Chemotherapy, hormonal therapy, radiation therapy, or small-molecule anticancer therapy within 14 days or 5 half-lives** (whichever is shorter) of C1D1
  - **Immune therapy or other biologic therapy** (e.g., monoclonal antibodies, antibody–drug conjugates) for the treatment of cancer within 28 days or 5 half-lives (whichever is shorter) of C1D1
- History of autoimmune hemolytic anemia, autoimmune thrombocytopenia, or hemolytic transfusion reaction

References: **1.** Weiskopf K. *Eur J Cancer.* 2017;76:100–109; **2.** Kauder SE, et al. *PLoS One.* 2018;13:e0201832; **3.** Montero AJ, et al. *Clin Cancer Res.* 2025;31(suppl 12):Abstract PS8-09; **4.** Shitara K, et al. *J Clin Oncol.* 2025;43(suppl 4):Abstract 332; **5.** Valabrega G, et al. *Ann Oncol.* 2007;18:977–984; **6.** National Comprehensive Cancer Network®. NCCN Guidelines: Breast Cancer. Version 4.2025; **7.** Gouda MA, et al. *Clin Cancer Res.* 2025;31:1268–1274; **8.** Candas-Green D, et al. *Nat Commun.* 2020;11:4591; **9.** Tsao LC, et al. *Nat Commun.* 2025;16:3167; **10.** Wolff AC, et al. *J Clin Oncol* 2023;41(22):3867–3872.

Abbreviations: **ADCC** – Antibody-dependent cell-mediated cytotoxicity; **ADCP** – Antibody-dependent cellular phagocytosis; **ASCO** – American Society of Clinical Oncology; **BID** – Twice daily; **C** – Cycle; **CAP** – College of American Pathologists; **CBR** – Clinical benefit rate; **CNS** – Central nervous system; **D** – Day; **DoR** – Duration of response; **ECOG PS** – Eastern Cooperative Oncology Group performance status; **FcγR** – Fc-gamma receptor; **FFPE** – Formalin-fixed paraffin-embedded; **HER2** – Human epidermal growth factor receptor 2; **IHC** – Immunohistochemistry; **INV** – Investigator; **ISH** – *In situ* hybridization; **IV** – Intravenous; **LD** – Loading dose; **LVEF** – Left ventricular ejection fraction; **mBC** – Metastatic breast cancer; **ORR** – Objective response rate; **OS** – Overall survival; **PFS** – Progression-free survival; **PK** – Pharmacokinetics; **PO** – Orally; **Q3W** – Every 3 weeks; **RECIST** – Response Evaluation Criteria in Solid Tumors; **SIRPα** – Signal regulatory protein alpha; **T-DXd** – Trastuzumab-deruxtecan; **1L** - First line; **2L+** – Second or later line.

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