Trial in Progress: Phase II open-label study of ARX788 (anti-HER2 antibody-drug conjugate) for patients with HER2-low locally advanced unresectable or metastatic breast cancer

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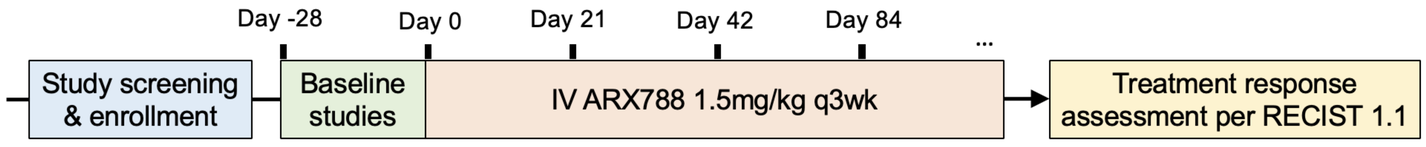
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Background

- ARX788 is a next-generation, site-specific antibody-drug conjugate (ADC) composed of a monoclonal antibody targeting human epidermal growth factor receptor 2 (HER2) conjugated via a non-natural amino acid linker to a potent tubulin inhibitor MMAF payload AS269.
- The phase I ACE-Breast-01 and ACE-Pan Tumor-01(NCT03255070) studies evaluated the safety and efficacy of ARX788 in patients with HER2+ breast cancer and pan tumor types respectively, with promising efficacy
- MMAF payloads have been associated with ocular adverse events including keratitis
- The HER2-targeted ADC T-DXd has demonstrated efficacy for HER2-low breast cancer (HER2 IHC 1+ or 2+ and FISH/ISH negative); novel treatment strategies remain an area of high unmet clinical need, especially agents post-topoisomerase-1 inhibitor ADCs that have novel payloads that lack payload cross-resistance.
- We hypothesize that ARX788 will be safe and efficacious for the treatment of patients with HER2-low locally advanced unresectable or metastatic breast cancer, including patients who have progressed on prior chemotherapies and ADCs.

Study Design

Single-arm, open-label, Phase II clinical trial of ARX788 monotherapy in patients with HER2-low locally advanced unresectable or metastatic breast cancer (NCT06224673). N=30-36



- CT CAP +/- NM bone scan or PET/CT q9 weeks
- Blood draw every cycle
- Eye exam at baseline and then within 7 days after every cycle for C1-4, every other cycle until C12, every third cycle after that or as clinically indicated

Key inclusion criteria:

- HER2-low (IHC 1+ or 2+, ISH neg) locally advanced unresectable or metastatic breast cancer
  - Cohort 1: HR+/HER2-low (n=20-24)
  - Cohort 2: HR-/HER2-low (n=10-12)
- Measurable disease or at least one measurable lytic bone lesion
- At least 1 prior chemo/ADC for MBC (no limit on prior lines of therapy)
- Stable brain metastases allowed
- 14 day washout from prior anti-cancer therapy

Primary Endpoint

- Objective response rate (ORR)

Secondary Endpoints:

- DOR, BOR, DCR, PFS, OS
- Safety
- Efficacy of novel ocular toxicity prevention strategies to prevent grade ≥2 ocular toxicity

NCT06224673

Statistical Design

- The proposed sample will provide ORR estimates with margin of error of 14% and 18% at 90% confidence level with anticipated 25% ORR.

Ocular Toxicity Prevention Substudy

- To evaluate the safety, tolerability, adherence, feasibility, and efficacy of an ocular prophylaxis regimen consisting of:
  - Vasoconstrictor eye drops before infusion
  - Cold compress eye mask during infusion
  - 1:1 randomization to topical amiloride vs vehicle control eye drops
    - 5-(N-ethyl-N-isopropyl)-amiloride reduces ADC corneal toxicity in vitro in human corneal epithelial cells
    - Topical amiloride is safe in both rabbit and human studies
  - Will measure the cornea grade, visual acuity grade, eye symptom grade, corneal topography indices, corneal sensation, and collect tears for subsequent translational analyses

Translational Science

Blood:

- Circulating tumor DNA: Whole exome sequencing, sequential ddPCR on select emerging mutations.
- Circulating tumor cells: Imaging analysis of target/payload protein expression, RNA/DNA analysis.

Tissue:

- Spatial analyses of tissue with multiplex immunofluorescence, RNA/DNA analyses

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