BACKGROUND

- Rintodestrant is an orally bioavailable, potent, and selective estrogen receptor (ER) degrader that inhibits ER gene transcription, degrades the ER, and delays tumor progression in preclinical models.
- Preliminary results from a phase 1 study, overview of study treatment and toxicities in patients with ER-positive (ER+), Human epidermal growth factor receptor-2 negative (HER2-)-advanced breast cancer (ABC; NCT03455270). Rintodestrant has a predictable safety profile and encouraging efficacy.
- Here, we report the results of a pharmacodynamic (PD) analysis from patients who received rintodestrant who received at least one cycle of treatment.

METHODS

Study Design

- This is a phase 1, open-label, 4-arm study of oral rintodestrant in patients aged ≥ 18 years with ER+/HER2- ABC who have progressed on endocrine therapy.
- Part 1: safety, tolerability, maximum tolerated dose, pharmacodynamics (PD), PK, and antitumor activity of rintodestrant were evaluated using a 3+3 dose-escalation design.
- Part 2: an expansion cohort (300 to 350 mg) was intended to further characterize the PD, safety, and tolerability of doses of rintodestrant in patients with ER+/HER2- ABC with confirmed disease progression on previous endocrine therapy.
- Patients were enrolled at study sites across all 4 parts of the study.
- Only data from parts 1 and 2 are presented here.

PD Analysis

- [12] Fluorescent protein expression tomography ([12] FPET) imaging was performed at baseline and cycle 2 day 2 (2-2 days) to determine the impact of rintodestrant on baseline or cycle 2 day 15 on estrogen receptor (ER) occupancy/degradation.
- Tumor biopsies were obtained of baseline and cycle 2 day 15 tissue.
- Variants include amplifications and deletions in the ESR1 gene, which encodes the ER.
- Blood samples were collected at baseline and cycle 2 day 15.
- Gene expression for ER and Ki67 was evaluated using immunohistochemistry.
- Nuclei with Ki67 expression >10% were considered positive.

RESULTS

SAFETY AND Efficacy of Rintodestrant

- Efficacy and toxicity results with rintodestrant treated patients are detailed in poster PS12-64.
- Briefly, of 26 patients (part 1: n = 26, part 2: n = 4), 24 (92%) had been treated before.
- Median (range) number of prior lines of therapy in the advanced setting was 2 (0–20), including prior CDK4/6 inhibitor (14%), fulvestrant (56%), aromatase inhibitors (23%), and/or trastuzumab (23%).
- Treatment-related adverse events were reported in 79% of patients.
- The most common grade 3 or 4 toxicity was fatigue (30%), nausea (23%), diarrhea (18%), and vomiting (17%).
- All of which were grade 1 or 2.
- 20 of 37 patients were evaluable for 3 weeks treatment who had a confirmed partial response for a clinical benefit rate of 32%.

PHARMACODYNAMIC ANALYSIS FROM A PHASE 1 STUDY OF RINTODESTRANT (G148), AN ORAL SELECTIVE ESTROGEN RECEPTOR DEGRADER, IN ER+/HER2- LOCALLY ADVANCED OR METASTATIC BREAST CANCER


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[1] Impact: 100% after 4 weeks of treatment in patients who received rintodestrant 600 mg.

**DISCLOSURES:** Rintodestrant demonstrated robust ER target engagement ([1] FPET) PET, and substantial decreases in ER target expression with Endocrine Therapy (ET) – CTCAE 4.03. CTCAE 3.0 dose escalation showed an increase in VAF with p<0.001 by linear mixed effect model analysis. Rintodestrant has not been approved by the US Food and Drug Administration (FDA) or any other regulatory agency. This presentation is the intellectual property of the author/presenter. Copies of this poster obtained through QR (Quick Response) Code are for personal use only and may not be distributed, shared, or re-used in any manner.

**CONCLUSIONS:**

- A broad range of genes were altered at disconnection, with acquired variants in ESRT, TP53 and PAXCA leading to the most common disconnection (Figure 4A).
- 32 patients had variants that were deleted at disconnection but not at baseline (ESRT: 8/26, TP53: 8/26, and PAXCA: 2/26).
- While VAF was the most common modulator at disconnection at baseline, no new VAF alterations were found at disconnection (Figure 4C).

**Figure 6B:** Changes in ER expression from baseline (Day 1) to cycle 2 day 15 and baseline (Day 1) to cycle 2 day 15 (n = 23).

**Figure 4B:** Changes in ER expression from baseline (Day 1) to cycle 2 day 15 (n = 23).