PHARMACODYNAMIC ANALYSIS FROM A PHASE 1 STUDY OF RINTODESTRANT (G1T48), AN ORAL SELECTIVE ESTROGEN RECEPTOR DEGRADER, IN ER+/HER2– LOCALLY ADVANCED OR METASTATIC BREAST CANCER

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BACKGROUND

- Rintodestrant is an orally bioavailable, potent, and selective estrogen receptor (ER) degrader that inhibits ER gene transcription, degrades the ER, and delays tumor proliferation in preclinical models[1]
- Preliminary data from a first-in-human, open-label study of rintodestrant in patients with ER-positive (ER+) /human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC; NCT03455270) demonstrated that rintodestrant has a favorable safety profile and encouraging antitumor activity[2,3]
- Here, we report the results of a pharmacodynamic (PD) analysis from patients who received rintodestrant once daily (QD) in part 1 (200–1000 mg dose escalation) and part 2 (600 and 1000 mg dose expansion) to molecularly characterize the patient population and mechanisms of response

METHODS

Study Design

- This is a phase 1, open-label, first-in-human study of oral rintodestrant in women aged ≥ 18 years with ER+/HER2– ABC who have progressed on endocrine therapy
  - **Part 1:** safety, tolerability, maximum tolerated dose, pharmacokinetics (PK), PD, and antitumor activity of rintodestrant were evaluated using a 3 + 3 dose-escalation design
  - **Part 2:** an expansion cohort (600 and 1000 mg) was included to further characterize the PK, safety, and preliminary antitumor activity of rintodestrant
  - **Part 3:** patients will receive rintodestrant (800 mg QD continuously on days 1–28) in combination with palbociclib (125 mg QD on days 1–21 of each 28-day cycle)
- Only data from parts 1 and 2 are presented here

PD Analysis

- [^{18}F]-fluoroestradiol positron emission tomography ([^{18}F]-FES PET) imaging was performed at baseline and cycle 2 day 2 (± 2 days) to determine the impact of rintodestrant at steady state on ER occupancy/degradation
- To assess mutational changes in cell-free DNA (cfDNA), peripheral blood samples were evaluated at baseline, cycle 1 day 15, and treatment discontinuation
  - Samples were processed and analyzed using the Guardant360 panel at Guardant Health, Inc.
- To evaluate circulating tumor cells (CTCs), peripheral blood mononuclear cells were collected and analyzed at baseline and cycle 3 day 1
  - Antibodies to cytokeratin and CD45, and 4',6-diamidino-2-phenylindole (DAPI) were used for phenotypic identification of CTCs
  - Samples were processed and analyzed at Precision Medicine Group, LLC
- Tumor biopsies were obtained at baseline and 6 weeks on treatment
  - Proliferation (Ki67) and ER degradation were assessed using immunohistochemistry
  - Samples were processed and analyzed at Epistem Ltd.

RESULTS

Safety and Efficacy of Rintodestrant

- Safety and efficacy data with rintodestrant are detailed in poster PS12-04[3]
- Briefly:
  - As of September 28, 2020, 67 patients (part 1: n = 26; part 2: n = 41) had been treated
  - The median (range) number of prior lines of therapy in the advanced setting was 2 (0–9), including prior CDK4/6 inhibitor (70%), fulvestrant (64%), chemotherapy (46%), and/or mTOR inhibitor (22%)
  - Treatment-related adverse events were reported in 70% of patients
    - The most common (reported in ≥ 10% of patients) were hot flush (24%), fatigue (21%), nausea (19%), diarrhea (18%), and vomiting (10%), all of which were grade 1 or 2
  - 20 of 67 patients were on study treatment for ≥ 24 weeks including 3 who had a confirmed partial response for a clinical benefit rate of 30%

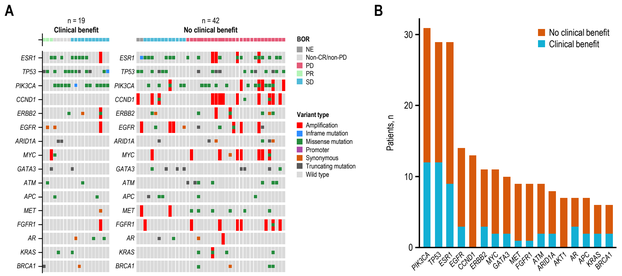
[^{18}F]-FES PET

- [^{18}F]-FES PET data were obtained from 19 patients
- Maximum standard uptake values (SUVmax) decreased in all patients, with mean reduction in SUVmax ranging from 70–100% after 4 weeks of rintodestrant therapy across all doses
  - At doses ≥ 600 mg (n = 14), mean reduction in SUVmax was 89% (± 8%)

cfDNA Analysis

- Of 64 patients tested for baseline cfDNA, 61 (95%) harbored ≥ 1 somatic variant (median 4 variants per patient; **Figure 1A**)
- Among the 64 patients tested (**Figure 1B**):
  - 29 (45%) had *ESR1* variants, with *D538G* being the most common (52%)
  - 31 (48%) had *PIK3CA* variants, with *H1047R* being the most common (29%)
  - 13 (20%) had variants in both *ESR1* and *PIK3CA*
  - 29 (45%) had *TP53* variants
- Alterations in *ESR1*, *PIK3CA*, and *TP53* were not correlated with rintodestrant efficacy (data not shown)

Figure 1. cfDNA Results: Variants at Baseline Associated With Clinical Response



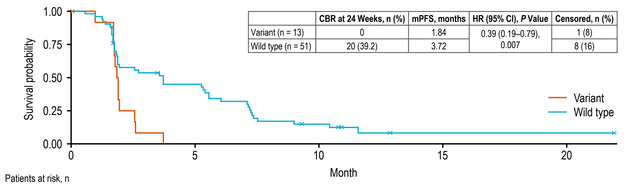
Variants include amplifications and inframe, missense, promoter, and truncating mutations. Graphs include variants in ≥ 6 patients.
BOR, best overall response; cfDNA, cell-free DNA; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

- Among patients with *CCND1* variants, a higher percentage had visceral disease and had received prior CDK4/6 inhibitor therapy in the advanced setting (**Table 1**)
- The presence of ≥ 1 *CCND1* variant was significantly associated with shorter progression-free survival (PFS) (hazard ratio [HR] [95% CI] = 0.39 [0.19–0.79]; *P* = 0.007; **Figure 2**)
  - No clinical benefit was observed
  - 10 patients (77%) had progressive disease, 2 patients (15%) had stable disease, 1 patient (8%) was not evaluable; no patients had partial response
- *CCND1* variants included focal amplifications (12 patients [92%]) and missense mutations (4 patients [31%])
- Of 59 patients with evaluable samples at baseline and cycle 1 day 15, 35 patients (59%) had a decrease in mean variant allele frequency (mVAF) at cycle 1 day 15 (**Figure 3A**)
- Patients with a decrease in mVAF had a longer PFS than patients with an increase in mVAF at cycle 1 day 15 (HR [95% CI] = 0.56 [0.33–0.98]; *P* = 0.038; **Figure 3B**)
- Of 28 patients with detectable *ESR1* variants at baseline and evaluable samples at cycle 1 day 15, 22 (79%) had a decrease in *ESR1* mVAF, including 6 patients (21%) who cleared all *ESR1* variants by cycle 1 day 15 (**Figure 3C**)

Table 1 and Figure 2. Baseline cfDNA Analysis of *CCND1* and Clinical Correlation

	Evaluable Patients	Prior Chemotherapy[a]		Prior CDK4/6i Treatment[a]		Prior Fulvestrant Treatment[a]		Prior Endocrine Treatment[a]		Bone-only Disease		Visceral Disease	
		0–2	≥ 3	No	Yes	No	Yes	0–1	≥ 2	No	Yes	No	Yes
n	64	62	2	19	45	23	41	26	38	54	10	24	40
CCND1 variants, n (%)	13 (20)	13 (21)	0	3 (16)	10 (22)	6 (26)	7 (17)	7 (27)	6 (16)	12 (22)	1 (10)	2 (8)	11 (28)

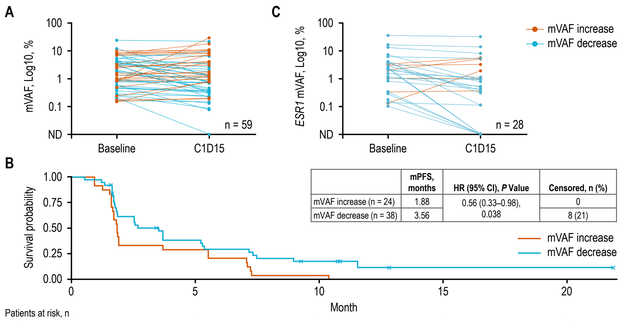
[a] In the advanced setting.



	CBR at 24 Weeks, n (%)	mPFS, months	HR (95% CI), *P* Value	Censored, n (%)
Variant (n = 13)	0	1.84	0.39 (0.19–0.79), 0.007	1 (8)
Wild type (n = 51)	20 (39.2)	3.72		8 (16)

CBR, clinical benefit rate; CDKi, cyclin-dependent kinase inhibitor; cfDNA, cell-free DNA; HR, hazard ratio; mPFS, median progression-free survival.

Figure 3. mVAF at Cycle 1 Day 15 (A and C) and PFS by mVAF (B)

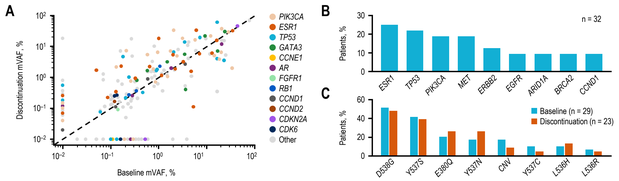


	mPFS, months	HR (95% CI), *P* Value	Censored, n (%)
mVAF increase (n = 24)	1.88	0.56 (0.33–0.98), 0.038	0
mVAF decrease (n = 38)	3.56		8 (21)

C, cycle; D, day; HR, hazard ratio; mPFS, median progression-free survival; mVAF, mean variant allele frequency; ND, not detectable; PFS, progression-free survival.

- A broad range of genes were altered at discontinuation, with acquired variants in *ESR1*, *TP53*, and *PIK3CA* being the most common (**Figure 4A**)
- 32 patients had variants that were detected at discontinuation but not at baseline
  - *ESR1* (8 patients [25%]) and *TP53* (7 patients [22%]) were the most common variants detected at discontinuation that were not detected at baseline (**Figure 4B**)
- While *D538G* was the most common mutation in *ESR1* at baseline, no new *ESR1* alterations were found at discontinuation (**Figure 4C**)

Figure 4. Potential Mechanisms of Acquired Resistance

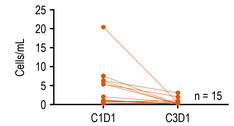


Scatter plot, n = 32, view of variants (where ≥ 2 patients had a variant). All patients in this analysis discontinued treatment due to progression except for 2 patients (1 discontinued due to investigator's discretion and 1 discontinued due to adverse event).
mVAF, mean variant allele frequency.

CTC Enumeration

- 11/15 patients (73%) showed a decrease in Epi+CD45– CTCs after 8 weeks of treatment
- Mean value of Epi+CD45– CTCs decreased from 3.9 cells/mL at baseline to 0.6 cells/mL (84% decrease; **Figure 5**)
- 4/7 patients (57%) with detectable Epi+CD45– CTCs at baseline and cycle 3 day 1 showed a decrease in ER levels

Figure 5. CTC Enumeration

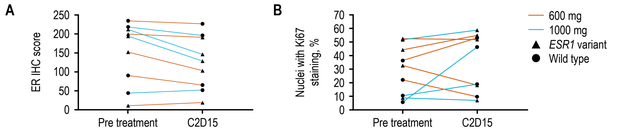


C, cycle; CTC, circulating tumor cell; D, day.

Tumor Biopsies

- Tumor biopsies were collected from 9 patients (5 who received rintodestrant 600 mg and 4 who received rintodestrant 1000 mg) at baseline and after 6 weeks on treatment
- Of 7 patients who had a decrease in the ER H-score (median change [range]: –27.8% [–33.8%, –3.4%]), 4 patients had ≥ 1 variant in *ESR1* at baseline (**Figure 6A**)
- 4 patients had a decrease in Ki67, with reductions mostly observed in patients who received rintodestrant 600 mg (**Figure 6B**)
- ER degradation did not correlate with Ki67 expression

Figure 6. IHC Analysis of A) ER Degradation and B) Tumor Cell Proliferation (Ki67)



C, cycle; D, day; ER, estrogen receptor; IHC, immunohistochemistry.

CONCLUSIONS

- Rintodestrant demonstrated robust ER target engagement on [^{18}F]-FES PET, and substantial decreases in ER H-score and Epi+CD45– CTCs
- *CCND1* variants and an increase in mVAF were associated with worse PFS, but there was no association between *ESR1*, *PIK3CA*, and *TP53* variants and efficacy
- These data, along with promising clinical benefit in patients with heavily pretreated ER+/HER2– ABC, regardless of *ESR1* or *PIK3CA* variant status, warrant additional investigation of rintodestrant
- Part 3 of this study, evaluating rintodestrant 800 mg QD with palbociclib in a more endocrine-sensitive population, is ongoing

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