RINTODESTRANT (G1T48), AN ORAL SELECTIVE ESTROGEN RECEPTOR DEGRADER, IN COMBINATION WITH PALBOCICLIB FOR ER+/HER2– ADVANCED BREAST CANCER: PHASE 1 RESULTS

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BACKGROUND

- Rintodestrant is a potent oral selective estrogen receptor degrader (SERD) that competitively binds to the estrogen receptor (ER) and blocks ER signaling in tumors resistant to other endocrine therapies (ETs)[1,2]
- Study G1T48-01 (NCT03455270) comprises 3 parts: dose escalation of monotherapy rintodestrant (part 1), dose expansion of monotherapy rintodestrant (part 2), and rintodestrant in combination with palbociclib therapy (part 3)
- Results from parts 1 and 2 showed a favorable safety profile and antitumor activity with once-daily (QD) rintodestrant in patients with heavily pretreated ER-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC), including those with tumors harboring pathogenic *ESR1* variants[3–5]
- The optimal dose of rintodestrant was selected to be 800 mg QD
- Here, we present part 3 combining rintodestrant with palbociclib, an oral cyclin-dependent kinase (CDK) 4/6 inhibitor

METHODS

- This phase 1, first-in-human, open-label study is evaluating rintodestrant in women with ER+/HER2– ABC after progression on ET[3,4]
  - **Part 3:** continuous rintodestrant 800 mg QD combined with palbociclib 125 mg QD for 21 days in 28-day cycles (data cut: April 7, 2021)
- Key inclusion criteria:
  - Female patients ≥ 18 years of age
  - Histological/cytological confirmation of ER+/HER2– ABC
  - ≥ 24 months of ET in the adjuvant setting before recurrence or progression OR ≥ 6 months of ET in the advanced/metastatic setting before progression
  - ≤ 1 prior line each of ET or cytotoxic chemotherapy in the metastatic setting
  - Prior CDK4/6 inhibitor therapy, investigational oral SERDs, or selective ER covalent antagonists in any setting were prohibited
  - Prior everolimus therapy was allowed
  - Eastern Cooperative Oncology Group performance status: 0 or 1
- **Primary objectives:** safety and tolerability of rintodestrant with palbociclib
- **Secondary objectives:** antitumor activity per RECIST v1.1, including best overall response, clinical benefit rate in measurable and nonmeasurable disease (as defined by percentage of patients with either confirmed complete or partial response [PR], or stable disease lasting ≥ 24 weeks), progression-free survival (PFS), overall survival, and palbociclib and rintodestrant pharmacokinetics
- **Exploratory objectives:** mutation profiling (cell-free DNA [cfDNA]), change in ER expression from baseline to 6-week on-treatment tumor biopsies (cycle [C] 2 day [D] 15), and assessment of *UGT1A1* genetic polymorphisms

RESULTS

Baseline Characteristics

- Median (range) number of prior lines of therapy in the advanced setting was 1 (0–2), including chemotherapy (48%) and fulvestrant (15%; **Table 1**)
- Median (range) number of prior lines of ET in the advanced setting was 1 (0–1), with 73% of patients having received 1 prior line; 65% of patients received ET in the adjuvant setting and relapsed while on or within 12 months of completing adjuvant therapy
  - Forty-five percent of patients had received both ET and chemotherapy in the advanced setting
- Forty percent of patients had liver metastasis, and 30% had lung metastasis
- All patients had ER+ disease; 90% had tumors defined as high-ER (ER > 10%), 8% as low-ER (ER = 1–10%), and 13% had progesterone receptor-negative ABC

Table 1. Baseline Characteristics

		N = 40
Median age, years (range)		57.5 (35–76)
ECOG PS, n (%)	0 1	28 (70) 12 (30)
Race, n (%)	White	40 (100)
Menopause status, n (%)	Pre/perimenopausal Postmenopausal	5 (12) 35 (88)
Median prior lines of advanced therapy, n (range)		1 (0–2)
Prior treatment in advanced setting,[a] n (%)	None Chemotherapy Endocrine therapy Nonsteroidal AI Steroidal AI Fulvestrant Tamoxifen Targeted therapy CDK4/6 inhibitor mTOR inhibitor	10 (25) 19 (48) 29 (73) 17 (43) 3 (8) 6 (15) 3 (8) 0 0 0
Location of metastases, n (%)	Bone-only Visceral	4 (10) 27 (68)

[a] A patient can be counted in several categories.
AI, aromatase inhibitor; CDK, cyclin-dependent kinase; ECOG PS, Eastern Cooperative Oncology Group performance status; mTOR, mammalian target of rapamycin.

Safety and Tolerability

- Safety data are summarized in **Table 2**; 98% of patients experienced ≥ 1 treatment-emergent adverse event (TEAE)
- Three patients (8%) experienced a rintodestrant-related TEAE; all were grade 2 and included neutropenia (3%), nausea (3%), and vomiting (3%)
  - Hot flashes, diarrhea, and fatigue were the most common rintodestrant-related TEAEs reported in parts 1 and 2 (monotherapy)[4]; in patients treated with combination rintodestrant and palbociclib, 1 case (3%) each of diarrhea and fatigue were reported, but neither were considered related to rintodestrant/palbociclib
- One patient (3%) experienced the serious adverse event (SAE) of grade 2 COVID-19 pneumonia, considered by the investigator to be related to palbociclib
- No rintodestrant-related SAEs or dose reductions were reported
- Palbociclib dose reductions were reported in 9 patients (23%; 8 patients [20%] due to grade 3/4 neutropenia and 1 patient [3%] due to grade 3 febrile neutropenia); palbociclib dose delays were reported in 19 patients (48%)
- No discontinuations or deaths due to TEAEs were reported

Table 2. TEAEs Reported Regardless of Causality

TEAE, n (%)	N = 40	
Grade	**All**	**≥ 3**
Neutropenia	36 (90)	21 (53)
Leukopenia	18 (45)	7 (18)
Anemia	6 (15)	2 (5)
Asymptomatic bacteriuria	4 (10)	0
Thrombocytopenia	4 (10)	0
COVID-19 pneumonia	2 (5)	0
Lymphocytopenia	2 (5)	2 (5)
Nausea	2 (5)	0
Urinary tract infection	2 (5)	0
Vomiting	2 (5)	0

TEAE, treatment-emergent adverse event.

Clinical Activity

- Best overall response and clinical benefit rate are summarized in **Table 3** and **Figure 1**
- Median PFS was 7.4 months (95% CI: 3.7–not reached); data not yet mature
- Median (range) duration of treatment for rintodestrant and palbociclib was 6.2 (1.5–8.5) months (**Figure 1**)
- One patient with confirmed PR had ABC harboring *ESR1* and *PIK3CA* variants at baseline and had received prior treatment with fulvestrant

Table 3. Best Overall Response

	Response Evaluable Set (N = 38)	Full Analysis Set (N = 40)
Best overall response, n (%)		
Confirmed CR	0	0
Confirmed PR	2 (5)	2 (5)
SD	26 (68)	26 (65)
Non-CR/non-PD	NA	1 (3)
PD	9 (24)	10 (25)
Not evaluable	1 (3)	1 (3)
Objective response,[a] n (%)	2 (5)	2 (5)
Clinical benefit,[b] n (%)	23 (61)	24 (60)

[a] Confirmed CR + confirmed PR.
[b] CR + PR + SD or non-CR/non-PD lasting ≥ 24 weeks.
CR, complete response; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.

Pharmacokinetics and Pharmacodynamics

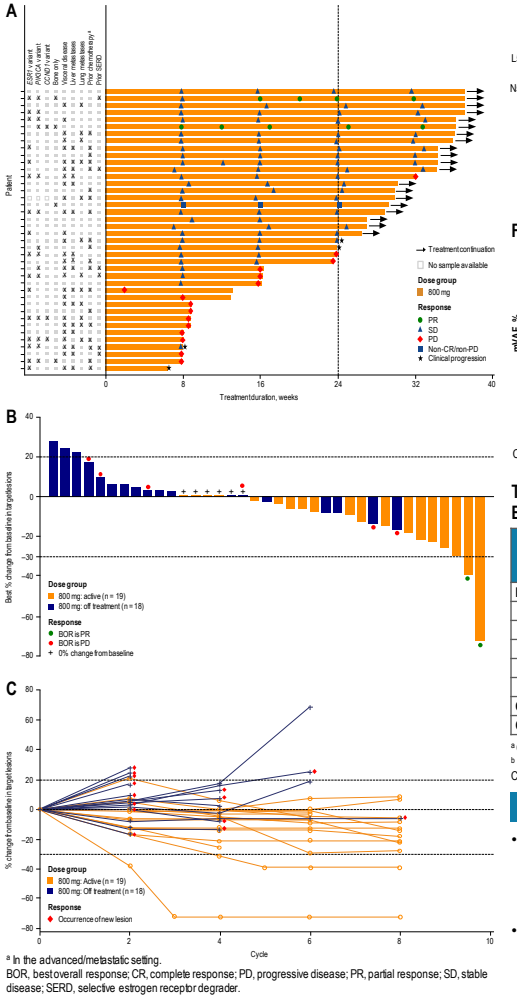
- Rintodestrant exposure levels were as predicted; palbociclib steady-state trough concentrations were similar to historical data[6] (geometric mean 61.7 ng/mL vs 60.8 ng/mL, respectively), indicating that rintodestrant had no impact on palbociclib pharmacokinetics
- Of 39 patients tested for baseline cfDNA, 41% had tumors harboring ≥ 1 *ESR1* variant, 36% ≥ 1 *PIK3CA* variant, and 28% ≥ 1 *ESR1* and ≥ 1 *PIK3CA* variant (**Table 4** and **Figure 2**)
- Of 14 patients with detectable *ESR1* or *PIK3CA* variants at baseline and evaluable samples at C1D15, all patients (100%) whose tumors harbored *ESR1* variants had a decrease in mean variant allele frequency (mVAF), and 10 patients (71%) that harbored *PIK3CA* variants had a decrease in mVAF (**Figure 3**)
- A decrease in mVAF at C1D15 was observed in 29 of 33 patients (88%) with evaluable samples at baseline and C1D15 (**Figure 3**)
- Of the 2 patients who had confirmed PR, 1 patient had 2 *ESR1* variants (*D538G* and *Y537N*) and 1 *PIK3CA* variant (*N345K*), and the other patient had a single *PIK3CA* variant (*E545K*) (**Figure 1** and **Table 5**)

Table 4. *ESR1*, *PIK3CA*, and *CCND1* Variants, and Disease Characteristics

Factor	Prior Lines of Systemic Treatment[a]			Prior Chemotherapy Treatment[a]		Prior Fulvestrant Treatment[a]		Bone-only Disease		Visceral Disease	
Subgroup	**0**	**1**	**2**	**0**	**1**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
n	10	13	16	21	18	6	33	4	35	26	13
***ESR1* variant, n (%)**	1 (10)	7 (54)	8 (50)	8 (38)	8 (44)	3 (50)	13 (40)	2 (50)	14 (40)	13 (50)	3 (23)
***PIK3CA* variant, n (%)**	1 (10)	8 (62)	5 (31)	8 (38)	6 (33)	4 (67)	10 (30)	3 (75)	11 (31)	9 (35)	5 (39)
***CCND1* variant, n (%)**	1 (10)	1 (7)	1 (6)	2 (10)	1 (6)	0	3 (9)	1 (25)	2 (6)	2 (8)	1 (8)

[a] In the advanced setting.

Figure 1. (A) Treatment Duration and Response, and (B, C) Change From Baseline in Tumor Size for Target Lesions



[a] In the advanced/metastatic setting.
BOR, best overall response; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SERD, selective estrogen receptor degrader.

Figure 2. *ESR1* and *PIK3CA* Variants

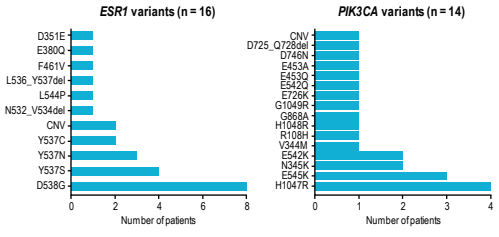
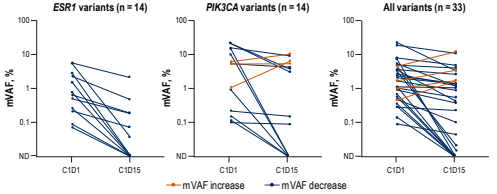


Figure 3. mVAF Changes at C1D1 vs C1D15



C, cycle; D, day; mVAF, mean variant allele frequency; ND, not detectable.

Table 5. *ESR1*, *PIK3CA*, and *CCND1* Variants at Baseline, and Best Overall Response

	ESR1		*PIK3CA*		*CCND1*	
	Wild type (N = 23)	Variant (N = 16)	Wild type (N = 25)	Variant (N = 14)	Wild type (N = 36)	Variant (N = 3)
Best overall response, n (%)						
Confirmed CR	0	0	0	0	0	0
Confirmed PR	1 (4)	1 (6)	0	2 (14)	1 (3)	1 (33)
SD	15 (65)	10 (63)	16 (64)	9 (64)	25 (69)	0
Non-CR/non-PD	1 (4)	0	1 (4)	0	1 (3)	0
PD	6 (26)	4 (25)	7 (28)	3 (21)	8 (22)	2 (67)
Objective response,[a] n (%)	1 (4)	1 (6)	0	2 (14)	1 (3)	1 (33)
Clinical benefit,[b] n (%)	14 (61)	9 (56)	15 (60)	8 (57)	22 (61)	1 (33)

[a] Confirmed CR + confirmed PR.
[b] CR + PR + SD or non-CR/non-PD lasting ≥ 24 weeks.
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

CONCLUSIONS

- Rintodestrant combined with palbociclib was very well tolerated
  - Most common TEAEs of neutropenia and leukopenia are consistent with the known safety profile of palbociclib, as reported in PALOMA-3[6]
  - Addition of rintodestrant to palbociclib did not result in additional or more severe toxicities, in particular, nausea, vomiting, or diarrhea
- Encouraging antitumor activity was observed (data not yet mature)
  - The clinical benefit rate doubled from 30%[4] to 60% when palbociclib was added to rintodestrant, suggesting favorable antitumor activity in patients with ER+/HER2– ABC, including in patients with tumors harboring *ESR1* variants

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ACKNOWLEDGMENTS:
- We thank all the investigators and site staff, with special thanks to the patients and their families
- We thank G1 Therapeutics team members who supported the creation of this poster
- Study sponsored by G1 Therapeutics. Editorial assistance was provided by Alligent Europe (Envision Pharma Group), funded by G1 Therapeutics