# RINTODESTRANT (G1T48), AN ORAL SELECTIVE ESTROGEN RECEPTOR DEGRADER, IN ER+/HER2– LOCALLY ADVANCED OR METASTATIC BREAST CANCER: UPDATED PHASE 1 RESULTS AND DOSE SELECTION

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## BACKGROUND

- Rintodestrant is a potent oral selective estrogen receptor (ER) degrader that competitively binds to the ER and blocks ER signaling in tumors resistant to other endocrine therapies[1,2]
- Study G1T48-01 (NCT03455270) is comprised of 3 parts: dose escalation (part 1), dose expansion of monotherapy rintodestrant (part 2), and rintodestrant + palbociclib combination therapy (part 3)
- Preliminary results from part 1 dose escalation showed robust target engagement on [$^{18}$F]-fluoroestradiol positron emission tomography ([$^{18}$F]-FES PET), a favorable safety profile, and encouraging antitumor activity in patients with heavily pretreated ER-positive (ER+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC), including those with *ESR1* variants[3]
- Here, we present updated results from dose escalation and expansion (parts 1 and 2)

## METHODS

- This phase 1, first-in-human, open-label study evaluated rintodestrant monotherapy in women with ER+/HER2– ABC after progression on endocrine therapy
  - **Part 1:** 3 + 3 dose escalation of rintodestrant with a starting dose of 200 mg orally once daily (QD) and escalation to 1000 mg QD (1 cycle = 28 days)
  - **Part 2:** expansion of 600 and 1000 mg QD on the basis of safety profile, pharmacokinetics (PK), and [$^{18}$F]-FES PET data
  - **Part 3:** rintodestrant (800 mg QD) with palbociclib (125 mg QD) in patients who are less heavily pretreated (data not presented)
- Key inclusion criteria (parts 1 and 2):
  - Female patients aged ≥ 18 years (part 1: postmenopausal only)
  - Histological/cytological confirmation of ER+/HER2– ABC
  - ≤ 3 lines of prior chemotherapy in the metastatic setting (part 1 only)
  - ≤ 1 line of prior chemotherapy in the metastatic setting (part 2 only)
  - ≤ 3 prior endocrine therapies, including fulvestrant, aromatase inhibitor, and tamoxifen, in the metastatic setting
  - Eastern Cooperative Oncology Group performance status (ECOG PS): 0 or 1
- Primary objectives: dose-limiting toxicities, maximum tolerated dose, safety, and recommended phase 2 dose
- Secondary objectives: PK; antitumor activity per Response Evaluation Criteria in Solid Tumors v1.1; best overall response, including clinical benefit rate (CBR) in measurable and nonmeasurable disease (as defined by percentage of patients with either confirmed complete or partial response, stable disease, non-complete response, or non-progressive disease lasting ≥ 24 weeks); and progression-free survival (PFS)
- Exploratory objectives: pharmacodynamic inhibition of ER target engagement ([$^{18}$F]-FES PET), mutation profiling (cell-free DNA [cfDNA]), change in ER expression from baseline to 6 weeks on-treatment in tumor biopsies (cycle 2 day 15), and assessment of UGT1A1 genetic polymorphisms

## RESULTS

### Patient Characteristics

- Baseline characteristics are summarized in **Table 1**
- As of September 28, 2020, 67 patients (part 1: n = 26; part 2: n = 41) had been treated, with a median (range) age of 61 (34–83) years and ECOG PS of 0 (49%) or 1 (51%)
- 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%)
- Median (range) number of prior lines of endocrine therapy in the advanced setting was 2 (0–5), with 60% of patients having received ≥ 2 lines
- A total of 64% of patients had visceral disease at baseline and 15% had bone-only disease
- All patients had ER+ disease, of which 85% were defined as high-ER (ER > 10%), 13% as low-ER (ER = 1–10%), and 24% as progesterone receptor–negative by immunohistochemistry

### Table 1. Baseline Characteristics

| | Rintodestrant | | | | | |
|---|---|---|---|---|---|---|
| | 200 mg (N = 3) | 400 mg (N = 6) | 600 mg (N = 29) | 800 mg (N = 7) | 1000 mg (N = 22) | Total (N = 67) |
| **Median age, years (range)** | 59 (51–69) | 61 (56–72) | 60 (34–79) | 66 (43–75) | 60 (37–83) | 61 (34–83) |
| **ECOG PS, n (%)** | | | | | | |
| 0 | 2 (67) | 2 (33) | 15 (52) | 4 (57) | 10 (46) | 33 (49) |
| 1 | 1 (33) | 4 (67) | 14 (48) | 3 (43) | 12 (55) | 34 (51) |
| **Race, n (%)** | | | | | | |
| White | 3 (100) | 6 (100) | 26 (90) | 7 (100) | 21 (96) | 63 (94) |
| Black/African American | 0 | 0 | 2 (7) | 0 | 0 | 2 (3) |
| Other | 0 | 0 | 1 (3) | 0 | 1 (5) | 2 (3) |
| **Menopause status, n (%)** | | | | | | |
| Pre/perimenopausal | 0 | 0 | 5 (17) | 0 | 2 (9) | 7 (10) |
| Postmenopausal | 3 (100) | 6 (100) | 24 (83) | 7 (100) | 20 (91) | 60 (90) |
| **Median number of prior advanced lines of therapy, n (range)** | 2 (1–3) | 2 (1–4) | 2 (0–9) | 4 (2–5) | 2 (1–6) | 2 (0–9) |
| **Prior treatment in advanced setting,[a] n (%)** | | | | | | |
| Chemotherapy | 0 | 2 (33) | 16 (55) | 5 (71) | 8 (36) | 31 (46) |
| Endocrine therapy | 3 (100) | 6 (100) | 28 (97) | 7 (100) | 22 (100) | 66 (99) |
| Nonsteroidal AI | 1 (33) | 4 (67) | 21 (72) | 6 (86) | 14 (64) | 46 (69) |
| Steroidal AI | 0 | 2 (33) | 6 (21) | 2 (29) | 7 (32) | 17 (25) |
| Fulvestrant | 3 (100) | 4 (67) | 18 (62) | 6 (86) | 12 (55) | 43 (64) |
| Tamoxifen | 1 (33) | 2 (33) | 5 (17) | 3 (43) | 2 (9) | 13 (19) |
| Targeted therapy | | | | | | |
| CDK4/6 inhibitor | 3 (100) | 3 (50) | 19 (66) | 6 (86) | 16 (73) | 47 (70) |
| mTOR inhibitor | 0 | 1 (17) | 5 (17) | 2 (29) | 7 (32) | 15 (22) |
| **Location of metastases, n (%)** | | | | | | |
| Bone-only | 0 | 1 (17) | 3 (10) | 1 (14) | 5 (23) | 10 (15) |
| Visceral | 1 (33) | 4 (67) | 20 (69) | 6 (86) | 12 (55) | 43 (64) |

[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/Tolerability

- Safety data are summarized in **Table 2**
- Treatment-related adverse events (TRAEs) were reported in 70% of patients. The most common TRAEs in ≥ 10% of patients included hot flush (24%), fatigue (21%), nausea (19%), diarrhea (18%), and vomiting (10%), of which all were grade 1 or 2
- Serious TRAEs occurred in 2 patients at the 1000 mg dose level: (1) grade 5 cerebral hemorrhage in the setting of low molecular weight heparin (LMWH) administration, and (2) grade 2 upper abdominal pain that resolved after thoracentesis for a worsening pleural effusion
- Dose reduction due to TRAE occurred in 1 patient (1%), with elevated transaminases (grade 3 ALT and grade 2 AST) at the 600 mg dose level
- Treatment discontinuation occurred in 2 patients (3%) due to TRAEs: (1) grade 5 cerebral hemorrhage as noted above, and (2) grade 2 thrombocytopenia in the setting of LMWH administration and positive heparin-induced thrombocytopenia antibodies
- No clinically significant abnormalities were found with electrocardiogram testing
- Overall, the frequency of patients with TRAEs at 800 mg was comparable to that at 600 mg (57% vs 66%) and less than that at 1000 mg (77%)

### Table 2. TRAEs Occurring in ≥ 10% of Patients

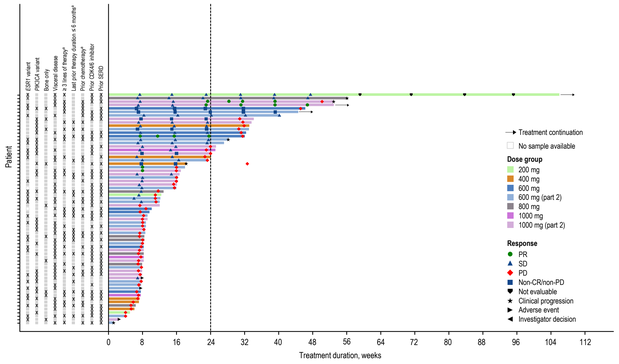
| | Rintodestrant | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 200 mg (N = 3) | | 400 mg (N = 6) | | 600 mg (N = 29) | | 800 mg (N = 7) | | 1000 mg (N = 22) | | Total (N = 67) | |
| **TRAE, n (%)** | | | | | | | | | | | | |
| **Grade** | **All** | **≥ 3** | **All** | **≥ 3** | **All** | **≥ 3** | **All** | **≥ 3** | **All** | **≥ 3** | **All** | **≥ 3** |
| Hot flush | 1 (33) | 0 | 1 (17) | 0 | 8 (28) | 0 | 3 (43) | 0 | 3 (14) | 0 | 16 (24) | 0 |
| Fatigue | 1 (33) | 0 | 3 (50) | 0 | 3 (10) | 0 | 2 (29) | 0 | 5 (23) | 0 | 14 (21) | 0 |
| Nausea | 2 (67) | 0 | 1 (17) | 0 | 5 (17) | 0 | 0 | 0 | 5 (23) | 0 | 13 (19) | 0 |
| Diarrhea | 1 (33) | 0 | 1 (17) | 0 | 5 (17) | 0 | 1 (14) | 0 | 4 (18) | 0 | 12 (18) | 0 |
| Vomiting | 1 (33) | 0 | 0 | 0 | 3 (10) | 0 | 0 | 0 | 3 (14) | 0 | 7 (10) | 0 |

TRAE, treatment-related adverse event.

### Clinical Activity

- Median duration of treatment was 2.3 months, with duration varying from 0.2–24.3 months across the different dose levels (200–1000 mg). Median exposure to treatment was similar between 600 and 1000 mg dose levels (2.3 vs 3.2 months)
- Of 67 patients, 20 were on study treatment for ≥ 24 weeks, including 3 (n = 1 at 600 mg; n = 2 at 1000 mg, including 1 with *ESR1* variant) who had confirmed partial response (CBR: 30%; **Figure 1**). Best overall response is summarized in **Table 3**
- Median PFS at 600 mg was 2.6 months (95% CI: 1.8–5.4) and at 1000 mg was 3.6 months (95% CI: 1.7–5.6)

### Figure 1. Treatment Duration and Response by Dose Group




[a] In the advanced/metastatic setting.
CDK, cyclin-dependent kinase; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease; SERD, selective estrogen receptor degrader.

### Table 3. Best Overall Response by Dose Level (Full Analysis Set)

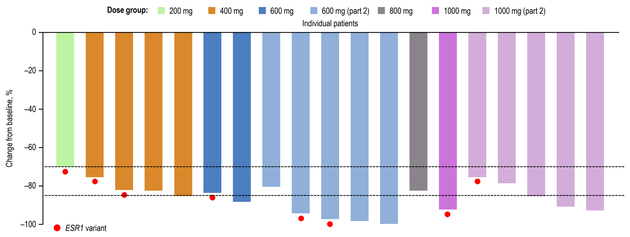
| | Rintodestrant | | | | | |
|---|---|---|---|---|---|---|
| | 200 mg (N = 3) | 400 mg (N = 6) | 600 mg (N = 29) | 800 mg (N = 7) | 1000 mg (N = 22) | Total (N = 67) |
| **Best overall response, n (%)** | | | | | | |
| Confirmed CR | 0 | 0 | 0 | 0 | 0 | 0 |
| Confirmed PR | 0 | 0 | 1 (3) | 0 | 2 (9) | 3 (5) |
| SD | 2 (67) | 2 (33) | 10 (34) | 2 (29) | 8 (36) | 24 (36) |
| Non-CR/non-PD | 0 | 1 (17) | 3 (10) | 0 | 2 (9) | 6 (9) |
| PD | 1 (33) | 3 (50) | 14 (48) | 5 (71) | 9 (41) | 32 (48) |
| Not evaluable | 0 | 0 | 1 (3) | 0 | 1 (5) | 2 (3) |
| **Objective response,[a] n (%)** | 0 | 0 | 1 (3) | 0 | 2 (9) | 3 (5) |
| **Clinical benefit,[b] n (%)** | 1 (33) | 2 (33) | 9 (31) | 1 (14) | 7 (32) | 20 (30) |

[a] Confirmed CR + confirmed PR.
[b] CR + PR + SD or non-CR/non-PD lasting ≥ 24 weeks (including scans within 7 days prior to 24 weeks)
CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

### Pharmacodynamics

- Pharmacodynamic data for rintodestrant are detailed in poster PD8-07[4]; population PK and exposure-response data are shown in poster PS17-08[5] (full PK data previously presented at ESMO 2019)[3]
- [$^{18}$F]-FES PET maximum standard uptake values decreased at week 4, with a mean reduction of 89% (standard deviation ± 8%) at doses ≥ 600 mg (n = 14; **Figure 2**)
- Of 64 patients tested for baseline cfDNA, 45% harbored ≥ 1 *ESR1* variant, 48% harbored ≥ 1 *PIK3CA* variant, and 20% had variants in both *ESR1* and *PIK3CA* (**Figure 3; Tables 4 and 5**)
- Across the 600 and 1000 mg doses, 7 of 9 patients had a decrease in ER immunohistochemistry H-score (median change [range]: –27.8% [–33.8%, –3.4%]), irrespective of *ESR1* variant status, indicating that degradation of the ER was seen at both doses

### Figure 2. [$^{18}$F]-FES PET: Rintodestrant Occupancy of ER by Dose Level

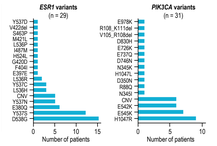



[$^{18}$F]-FES PET, [$^{18}$F]-fluoroestradiol positron emission tomography; ER, estrogen receptor.

### Table 4 and Figure 3. *ESR1* and *PIK3CA* Variant cfDNA Analysis

| Factor | | Prior Chemotherapy[a] | | Prior CDK4/6i Treatment[a] | | Prior Fulvestrant Treatment[a] | | Prior Endocrine Treatment[a] | | Bone-only Disease | | Visceral Disease | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Subgroup** | **Evaluable patients** | **0–2** | **≥ 3** | **N** | **Y** | **N** | **Y** | **0–1** | **≥ 2** | **N** | **Y** | **N** | **Y** |
| **n** | 64 | 62 | 2 | 19 | 45 | 23 | 41 | 26 | 38 | 54 | 10 | 24 | 40 |
| ***ESR1* variant, n (%)** | 29 (45) | 27 (44) | 2 (100) | 9 (47) | 20 (44) | 12 (52) | 17 (41) | 12 (46) | 17 (45) | 25 (46) | 4 (40) | 9 (38) | 20 (50) |
| ***PIK3CA* variant, n (%)** | 31 (48) | 30 (48) | 1 (50) | 11 (58) | 20 (44) | 15 (65) | 16 (39) | 13 (50) | 18 (47) | 26 (48) | 5 (50) | 13 (54) | 18 (45) |

[a] In the advanced setting.
CDKi, cyclin-dependent kinase inhibitor; cfDNA, cell-free DNA; N, no; Y, yes.




### Table 5. Clinical Activity by *ESR1* and *PIK3CA* Variant Status

| | | | mPFS | | | |
|---|---|---|---|---|---|---|
| | | Clinical Benefit,[a] n (%) | Months | HR (95% CI) | *P* Value | Censored, n (%) |
| ***ESR1*** | WT (n = 35) | 11 (31) | 1.9 | 1.2 (0.7–2.06) | 0.506 | 4 (11) |
| | Variant (n = 29) | 9 (31) | 2.6 | | | 5 (17) |
| ***PIK3CA*** | WT (n = 33) | 8 (24) | 1.9 | 0.94 (0.55–1.61) | 0.796 | 6 (18) |
| | Variant (n = 31) | 12 (39) | 2.7 | | | 3 (10) |

[a] CR + PR + SD or non-CR/non-PD lasting ≥ 24 weeks (including scans within 7 days prior to 24 weeks).
CR, complete response; HR, hazard ratio; mPFS, median progression-free survival; PD, progressive disease; PR, partial response; SD, stable disease; WT, wild type.

## CONCLUSIONS

- Rintodestrant continues to demonstrate an excellent safety/tolerability profile across all doses
  - Hot flushes and fatigue were the most common TRAEs
  - TRAEs were mainly grade 1 or 2 in severity
- Promising antitumor activity was observed in this population with heavily pretreated ER+/HER2– ABC, including in patients with tumors harboring *ESR1* variants
- Based on an improved safety profile in patients receiving 600 and 800 mg compared with 1000 mg, as well as comparable efficacy and robust ER degradation across these doses, 800 mg was selected as the optimal dose for further study
- Part 3 of this study, evaluating rintodestrant 800 mg QD with palbociclib in a more endocrine-sensitive population, is ongoing





**Acknowledgments:**
- We thank all the investigators and site staff, with special thanks to the patients and their families
- We thank Jessica A. Sorrentino for pharmacodynamic analysis and Julio Ruiz for programming support
- Study sponsored by G1 Therapeutics. Medical writing assistance was provided by Alligent Europe (Envision Pharma Group), funded by G1 Therapeutics

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