TPS1100

acelERA Breast Cancer (BC): Phase II study evaluating efficacy and safety of giredestrant (GDC-9545) vs. physician's choice of endocrine monotherapy in patients (pts) with estrogen receptor-positive, HER2-negative (ER+/HER2–) locally advanced or metastatic breast cancer (LA/mBC)

Miguel Martín,[1] Elgene Lim,[2] Mariana Chavez-MacGregor,[3] Mahesh Shivhare,[4] Graham Ross,[5] Monika Patre,[6] Laura Roncoroni,[6] Maria Louka,[6] Joohyuk Sohn[7]

[1]Hospital General Universitario Gregorio Marañón, Madrid, Spain; [2]St Vincent's Hospital and Garvan Institute of Medical Research, Sydney, Australia; [3]MD Anderson Cancer Center, Houston, TX; [4]Roche Products Limited, Welwyn Garden City, UK; [5]Graham Ross Oncology Consulting Services Ltd; [6]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [7]Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Korea

Study overview

- acelERA BC is a randomized, open-label, multicenter phase II study evaluating the efficacy and safety of giredestrant compared with physician's choice of endocrine monotherapy in postmenopausal or pre/perimenopausal females, and in men with ER+/HER2– LA/mBC whose disease progressed after treatment with one or two lines of systemic therapy (but not more than one prior targeted therapy) in the LA (recurrent or progressed) or metastatic setting (Figure 1).
- Recruitment for the global enrollment phase is ongoing, the first pt was enrolled on November 27, 2020.
- After completion of global enrollment, additional pts may be enrolled in China.

Enrollment

- The acelERA BC study is currently open for enrollment.

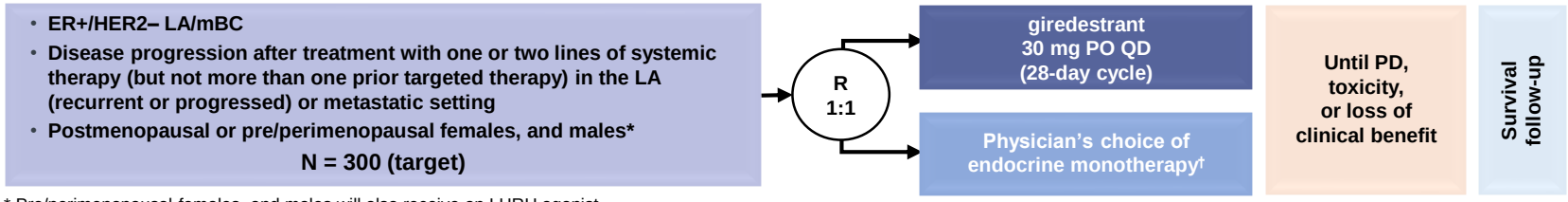
Contact information

- Email: global-roche-genentech-trials@gene.com
- Phone: 1-888-662-6728 (USA Only)
- ClinicalTrials.gov: https://www.clinicaltrials.gov/ct2/show/NCT04576455

Background

- The standard-of-care therapy for ER+ BC typically involves modulation of estrogen synthesis and/or ER activity.[1]
- Despite disease progression with standard treatments, growth and survival of the majority of tumors are thought to remain dependent on ER signaling; therefore, pts with ER+ BC can still respond to second- or third-line ET after progression on prior therapy.[2,3]
- *ESR1* mutations may drive estrogen-independent transcription and proliferation leading to resistance.[1]
- The highly potent, non-steroidal oral SERD, giredestrant, achieves robust ER occupancy and is active regardless of *ESR1* mutation status.[1]
- Phase I data have shown that giredestrant is well tolerated and active, both as a single agent and in combination with the CDK4/6i, palbociclib.[4]
- Single-agent giredestrant has also shown encouraging antitumor activity in pts previously treated with fulvestrant and/or a CDK4/6i.[1,4]

Figure 1: Study design



* Pre/perimenopausal females, and males will also receive an LHRH agonist.
† Endocrine monotherapy options: fulvestrant, letrozole, anastrozole, exemestane, formestane, aminoglutethimide, and testolactone.
Stratification factors: Site of disease, assessed locally (visceral vs. non-visceral), prior treatment with CDK4/6i (yes vs. no); prior treatment with fulvestrant (yes vs. no).

Eligibility criteria | **Statistical analysis** | **Key assessments** — ***Click the buttons to view more information***

Table 1: Endpoints

Primary endpoint	Secondary endpoints	

• Investigator-assessed progression-free survival (according to RECIST v1.1)	• Overall survival
	• Objective response rate
	• Duration of response
	• Clinical benefit rate
	• Investigator-assessed progression-free survival in subgroups categorized by baseline *ESR1* mutation status
	• Safety
		• Time to deterioration in:
		  • Pain level
		  • Pain presence and interference
		  • Physical functioning
		  • Role functioning
		  • Global health status and QoL
		• Pharmacokinetics

Biomarkers and health status utility will also be assessed.

References

1. Jhaveri KL, *et al*. SABCS 2019; PD7-05; 2. Di Leo A, *et al*. *J Clin Oncol* 2010; 28: 4594–600; 3. Baselga J, *et al. N Engl J Med* 2012; 366: 520–9; 4. Lim E, *et al.* 2020 ASCO Virtual Congress; 1023.

Abbreviations

AI, aromatase inhibitor; BC, breast cancer; CDK4/6i, cyclin-dependent kinase 4/6 inhibitor; ER+/HER2–, estrogen receptor-positive, HER2-negative; ET, endocrine therapy; LA, locally advanced; mBC, metastatic breast cancer; LHRH, luteinizing hormone-releasing hormone; PO, orally; pts, patients; QD, once daily; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; SERD, selective ER degrader.

Acknowledgments

We would like to thank the patients, their families, the nurses, and the investigators who are participating in this study. Support for third-party writing assistance for this ePoster, furnished by Bonnie Jordan, BSc of Health Interactions, was provided by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Conflicts of interest

MM: Honoraria: Roche-Genentech, Novartis, Eli Lilly, Pfizer, Pierre Fabre. Consulting or advisory role: AstraZeneca, Taiho Oncology, Roche-Genentech, Novartis, Pfizer, PharmaMar, Eli Lilly. Speakers' bureau: Lilly/ImClone, Roche-Genentech, Pierre Fabre. Research funding (institution): Roche, PUMA, Novartis. Research (medical writing support): F. Hoffmann-La Roche Ltd. Please refer to the abstract for all author conflicts of interest. This study is sponsored by F. Hoffmann-La Roche Ltd.

Presented at the 2021 American Society of Clinical Oncology (ASCO) Virtual Congress, June 4–8, 2021.

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Supplementary: Eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Confirmed diagnosis of LA (recurrent or progressed) or metastatic adenocarcinoma of the breast, not amenable to treatment with curative intent • Documented ER+/HER2– tumors (locally assessed) • For women of premenopausal or perimenopausal status or men: treatment with approved LHRH agonist therapy for the duration of study treatment on Day 1 of each 28-day cycle • Disease progression after treatment with one or two lines of systemic therapy (but not more than one prior targeted therapy) in the LA (recurrent or progressed) or metastatic setting • Measurable disease (RECIST v1.1) • ECOG PS 0–1 • Adequate organ function	• Prior treatment with a SERD, with the exception of fulvestrant • Treatment with any investigational therapy within 28 days prior to randomization. • Advanced, symptomatic, visceral spread that is at risk of life-threatening complications. • Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease • Active cardiac disease or history of cardiac dysfunction • Pregnant or breastfeeding

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Abbreviations
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; ER+/HER2–, estrogen receptor-positive, HER2-negative; LA, locally advanced; LHRH, luteinizing hormone-releasing hormone; RECIST, Response Evaluation Criteria in Solid Tumors; SERD, selective estrogen receptor degrader.

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Supplementary: Statistical analysis

- The primary analysis will assess investigator-assessed progression-free survival:
  - Progression-free survival will be compared between treatment arms using the stratified log-rank test. The hazard ratio will be estimated using a stratified Cox proportional hazards model. The 95% CI for the hazard ratio will be provided
  - Median progression-free survival will be estimated using the Kaplan–Meier method in both arms, and the Brookmeyer–Crowley method will be used to construct the 95% CI. Kaplan–Meier curves will also be produced
- Determination of sample size:
  - Approximately 300 patients will be enrolled and randomized in a 1:1 ratio to receive either giredestrant or physician's choice of endocrine monotherapy
  - The sample size is determined by the primary endpoint, investigator-assessed progression-free survival, comparing the two treatment arms

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Abbreviation
CI, confidence interval.

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Supplementary: Key assessments

- Tumor response will be assessed by the investigator on the basis of physical examinations, computed tomography scans, magnetic resonance imaging scans, and bone scans, per Response Evaluation Criteria in Solid Tumours v1.1
- Baseline tumor assessment should be performed at screening within 28 days of randomization (unless otherwise specified)
- Post-baseline tumor assessments will be performed every 8 weeks (± 7 days) from randomization for the first 18 months, then every 12 weeks (± 7 days) thereafter, with the exception of bone scans, which will be performed every 24 weeks or as clinically indicated
- The following samples will be collected for biomarker analyses:
    - Tumor tissue: at baseline (days –28 to –1) and within 8 weeks of disease progression (optional)
    - Plasma: Day 1 Cycle 1, Day 1 Cycle 2, Day 1 Cycle 3, and Day 1 of every two cycles thereafter (Cycle 5, 7, 9, etc.), treatment discontinuation visit
    - Blood: Day 1 Cycle 1
- Safety assessments will include physical examinations, vital signs, and laboratory evaluations
- Single electrocardiogram recordings will be obtained at specified timepoints, and may be obtained at unscheduled timepoints as indicated
- Blood samples will be collected for pharmacokinetic and biomarker analyses

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