

Phase II study of Roche's giredestrant meets primary endpoint in the most frequently diagnosed type of breast cancer

- Giredestrant, an oral selective oestrogen receptor degrader (SERD), showed statistically superior anti-proliferative activity compared to standard-of-care treatment (anastrozole) in neoadjuvant oestrogen receptor (ER)-positive, HER2-negative breast cancer¹
- Giredestrant continues to demonstrate a tolerable safety profile¹
- Enrolment is ongoing in the phase III lidERA Breast Cancer trial for the adjuvant treatment of ER-positive, HER2-negative breast cancer, as part of a comprehensive clinical development programme

Basel, 10 December 2021 – Roche (SIX: RO, ROG; OTCQX: RHHBY) today announced that the phase II coopERA Breast Cancer study met its primary endpoint in the neoadjuvant treatment of early stage ER-positive, HER2-negative breast cancer. Breast cancer is the most frequently diagnosed type of cancer, with major societal impact.² Hormone receptor (HR)-positive breast cancer is the most common subtype, representing ~70% of all diagnoses, or an estimated 1.6 million cases annually across the world.^{2,3}

“The coopERA Breast Cancer results show the potential positive impact giredestrant could bring for people with early, oestrogen receptor-positive breast cancer, and provide a strong rationale for our ongoing phase III lidERA Breast Cancer study in the adjuvant setting,” said Levi Garraway, M.D., Ph.D., Roche’s Chief Medical Officer and Head of Global Product Development. “At Roche, we are striving to develop new treatments that might improve or extend the lives of many people with ER-positive breast cancer.”

The coopERA Breast Cancer trial is evaluating the efficacy and safety of neoadjuvant treatment with giredestrant (formerly known as GDC-9545), an investigational next generation selective oestrogen receptor degrader (SERD) versus standard of care treatment (anastrozole) in postmenopausal women with oestrogen receptor (ER)-positive, HER2-negative, untreated early breast cancer. The primary endpoint of the study, which measured suppression of the tumour proliferation marker Ki67 was met, following two weeks of treatment with giredestrant versus anastrozole:¹

- Giredestrant showed a statistically significant mean Ki67 reduction of 75% (95% CI: -80%, -70%) versus 67% for anastrozole (95% CI: -73%, -59%; p=0.0433).
- The secondary endpoint of complete cell cycle arrest rate was 19.6% with giredestrant versus 12.8% with anastrozole (95% CI: -4.25, 17.97), which suggests that giredestrant was better at stopping tumour cell proliferation than anastrozole.
- Giredestrant was found to be well tolerated and have a safety profile consistent with previous clinical trials.^{4,5}

- Final analysis, including overall response rates and combination data with palbociclib are expected next year.

“A significant unmet need remains in early ER-positive breast cancer with currently around half of people having to stop treatment for reasons such as the toll of side effects,” said Sara Hurvitz, coopERA Breast Cancer Principal Investigator. “The superior, robust anti-tumour activity of giredestrant after just two weeks of treatment in coopERA Breast Cancer provides early insights into its potential as an effective and tolerable alternative treatment in the early-stage setting.”

The coopERA Breast Cancer study is one of several studies to be presented at the San Antonio Breast Cancer Symposium (7-10 December 2021) showing progress in Roche’s comprehensive ER-positive clinical development programme and it provides further evidence of giredestrant’s clinical activity and tolerable safety profile. This includes:

- Abstract #1842 – an analysis of the G039932 study demonstrated encouraging clinical activity of giredestrant as a single agent and in combination with palbociclib, with consistent activity across analysed biomarkers.⁶
- Abstract #1186 – a comprehensive cardiac safety analysis of the G039932 study found no clinically relevant cardiac effects with 100 mg of giredestrant. A lower, standardised once-daily 30 mg dose has been selected for the giredestrant development programme.⁷
- Abstract #2041 – a ‘trial in progress’ update on the phase III lidERA Breast Cancer study, investigating giredestrant in over 4,000 people with early-stage ER-positive, HER2-negative breast cancer. It is the first study to evaluate an oral SERD in the adjuvant setting.⁸

About giredestrant

Giredestrant is a potent, next generation investigational selective oestrogen receptor (SERD) with best-in-class potential. It is designed to fully block oestrogen receptor (ER) signalling with robust receptor occupancy and demonstrates an exceptional preclinical profile. Oestrogen encourages ER-positive breast cancer cells to grow by attaching to the ER. Giredestrant works by blocking this receptor to prevent the action of oestrogen, and in the process causes the receptor to be degraded. This investigational medicine has also shown efficacy regardless of ESR1 mutation status (mutations in the ESR1 gene are important mechanisms of resistance to hormone therapy).^{9,10,11,12,13}

Given orally, giredestrant delivers an encouraging clinical efficacy and safety profile and has shown superior pre-clinical potency over other SERDs in development. The oral administration of giredestrant has the potential to transform the treatment experience for patients, offering greater convenience and a less painful option compared to therapies administered via intramuscular injection.^{4,5,9}

Giredestrant has a comprehensive development programme across a broad range of settings and treatment combinations for patients with ER-positive, HER2-negative breast cancer. Roche have completed recruitment of patients into a phase II study in second/third-line ER-positive, HER2-negative locally advanced or metastatic breast cancer (aceLERA Breast Cancer), and are currently enrolling patients into two phase III studies (persevERA Breast Cancer, lidERA Breast Cancer) evaluating giredestrant across early and metastatic ER-positive, HER2-negative breast

cancer settings, as a monotherapy or in combination with palbociclib. In the phase I/II MORPHEUS study giredestrant is being investigated in combination with multiple treatment partners in pre-treated metastatic ER-positive, HER2-negative breast cancer. We are also planning to investigate giredestrant in ER-positive, HER2-positive breast cancer. A standardised once-daily 30 mg dose has been selected for the giredestrant development programme.^{14, 15, 16, 17}

Giredestrant received U.S. Food and Drug Administration Fast Track Designation (FTD) as a second and third-line treatment for ER-positive, HER2-negative, metastatic breast cancer. FTD is a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need.¹⁸

About coopERA Breast Cancer (NCT04436744)¹⁹

An open-label, two-arm, phase II study to evaluate the efficacy, safety, and pharmacokinetics of giredestrant versus anastrozole (in the window of opportunity phase) and giredestrant plus palbociclib compared with anastrozole plus palbociclib (in the neoadjuvant phase) in postmenopausal women with untreated, ER-positive, HER2-negative early breast cancer. The primary endpoint of the study is the geometric change in Ki67 scores (a measure of how quickly cancer cells are proliferating) from baseline to week 2 during the window of opportunity phase. Secondary endpoints include complete cell cycle arrest rate, safety outcomes and plasma concentration of giredestrant.

About lidERA Breast Cancer²⁰

An open-label, two-arm, randomised, multicentre, phase III study to evaluate efficacy and safety of adjuvant giredestrant compared with endocrine therapy of physician's choice in people with medium- and high-risk stage I-III ER-positive, HER2-negative early breast cancer. The primary endpoint of the study is invasive disease-free survival (iDFS), measured from randomisation to the first occurrence of an iDFS event (up to 10 years). Secondary endpoints include overall survival and disease-free survival. LidERA Breast Cancer is currently the only ongoing early breast cancer trial investigating an oral SERD.

About Roche in breast cancer

Roche has been advancing breast cancer research for more than 30 years with the goal of helping as many people with the disease as possible. Our medicines, along with companion diagnostic tests, have contributed to bringing breakthrough innovations in HER2-positive and triple-negative breast cancers. As our understanding of breast cancer biology rapidly improves, we are working to identify new biomarkers and approaches to treatment for all forms of early and advanced breast cancer, including triple-negative and hormone receptor-positive.

Our targeted medicines Herceptin® (trastuzumab), Perjeta® (pertuzumab), Phesgo®, Kadcyla® (trastuzumab emtansine) and Tecentriq® (atezolizumab) are continuing to transform the treatment of early and advanced HER2-positive and triple-negative breast cancers and, through our clinical programmes, we hope to bring new treatment combinations to people with breast cancer, ultimately improving outcomes.

About Roche

Roche is a global pioneer in pharmaceuticals and diagnostics focused on advancing science to improve people's lives. The combined strengths of pharmaceuticals and diagnostics, as well as growing capabilities in the area of data-driven medical insights help Roche deliver truly personalised healthcare. Roche is working with partners across the healthcare sector to provide the best care for each person.

Roche is the world's largest biotech company, with truly differentiated medicines in oncology, immunology, infectious diseases, ophthalmology and diseases of the central nervous system. Roche is also the world leader in in vitro diagnostics and tissue-based cancer diagnostics, and a frontrunner in diabetes management. In recent years, the company has invested in genomic profiling and real-world data partnerships and has become an industry-leading partner for medical insights.

Founded in 1896, Roche continues to search for better ways to prevent, diagnose and treat diseases and make a sustainable contribution to society. The company also aims to improve patient access to medical innovations by working with all relevant stakeholders. More than thirty medicines developed by Roche are included in the World Health Organization Model Lists of Essential Medicines, among them life-saving antibiotics, antimalarials and cancer medicines. Moreover, for the thirteenth consecutive year, Roche has been recognised as one of the most sustainable companies in the pharmaceutical industry by the Dow Jones Sustainability Indices (DJSI).

The Roche Group, headquartered in Basel, Switzerland, is active in over 100 countries and in 2020 employed more than 100,000 people worldwide. In 2020, Roche invested CHF 12.2 billion in R&D and posted sales of CHF 58.3 billion. Genentech, in the United States, is a wholly owned member of the Roche Group. Roche is the majority shareholder in Chugai Pharmaceutical, Japan. For more information, please visit www.roche.com.

All trademarks used or mentioned in this release are protected by law.

References

1. Hurvitz S, et al. Neoadjuvant giredestrant (GDC-9545) + palbociclib versus anastrozole + palbociclib in postmenopausal women with estrogen receptor-positive, HER2-negative, untreated early breast cancer: primary analysis of the randomized, open-label, phase II coopERA Breast Cancer study. Presented at: San Antonio Breast Cancer Symposium; 2021 December 7-11. Abstract #TBC.
2. Sung H, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;0:1-41.
3. Lim, et al. The natural history of hormone receptor-positive breast cancer. *Oncology (Williston Park).* 2012;8:688-94.
4. Jhaveri KL, et al. Safety and activity of single-agent giredestrant (GDC-9545) from a phase Ia/b study in patients (pts) with estrogen receptor-positive (ER+), HER2-negative locally advanced/metastatic breast cancer (LA/mBC). *Journal of clinical oncology.* 2021;39(15):1017.
5. Lim E, et al. A phase Ib study to evaluate the oral selective estrogen receptor degrader GDC-9545 alone or combined with palbociclib in metastatic ER-positive HER2- negative breast cancer. Presented at: ASCO virtual Meeting; 2020 May 29 - June 30. Abstract #1023.
6. Turner N, et al. Activity and biomarker analyses from a phase Ia/b study of giredestrant (GDC-9545; G) with or without palbociclib (palbo) in patients with estrogen receptor-positive, HER2-negative locally advanced/metastatic breast cancer (ER+/HER2-LA/mBC). Presented at: San Antonio Breast Cancer Symposium; 2021 December 7-10; San Antonio, Texas, USA. Abstract #1842.
7. Neilan T, et al. Heart rate changes, cardiac safety, and exercise tolerance from a phase Ia/b study of giredestrant (GDC-9545) ±palbociclib in patients with estrogen receptor-positive, HER2-negative locally advanced/metastatic breast cancer. Presented at: San Antonio Breast Cancer Symposium; 2021 December 7-10; San Antonio, Texas, USA. Abstract #1186.

8. Bardia J, et al. lidERA Breast Cancer: A phase III adjuvant study of giredestrant (GDC-9545) vs physician's choice of endocrine therapy (ET) in patients (pts) with estrogen receptor-positive, HER2-negative early breast cancer (ER+/HER2-eBC). Presented at: San Antonio Breast Cancer Symposium; 2021 December 7-10; San Antonio, Texas, USA. Abstract #2041.
9. Liang J, et al. GDC-9545 (Giredestrant): A potent and orally bioavailable selective estrogen receptor antagonist and degrader with exceptional preclinical profiles for ER+ breast cancer. *J Med Chem.* 2021;64(16):11841-56.
10. Metcalfe C, et al. GDC-9545: A novel ER antagonist and clinical candidate that combines desirable mechanistic and pre-clinical DMPK attributes. Presented at: San Antonio Breast Cancer Symposium; 2018 December 4-8; San Antonio, Texas, USA. Abstract #P5-04-07.
11. Dustin D, et al. ESR1 mutations in breast cancer. *Cancer.* 2019;125(21):3714-28.
12. Zhao M, Ramaswamy B. Mechanisms and therapeutic advances in the management of endocrine-resistant breast cancer. *World J Clin Oncol.* 2014;5(3):248-62.
13. Jhaveri K, et al. A first-in-human phase I study to evaluate the oral selective estrogen receptor degrader (SERD), GDC-9545, in postmenopausal women with estrogen receptor-positive (ER+) HER2-negative (HER2-) metastatic breast cancer. Presented at: San Antonio Breast Cancer Symposium; 2019 December 10-14; San Antonio, Texas, USA. Abstract #PD7-05.
14. Clinicaltrials.gov. A study evaluating the efficacy and safety of giredestrant compared with physician's choice of endocrine monotherapy in participants with previously treated estrogen receptor-positive, HER2-negative locally advanced or metastatic breast cancer (aceLERA Breast Cancer). [Internet; cited 2021 November]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04576455>.
15. Clinicaltrials.gov. A study evaluating the efficacy and safety of giredestrant combined with palbociclib compared with letrozole combined with palbociclib in participants with estrogen receptor-positive, HER2-negative locally advanced or metastatic breast cancer (persevERA Breast Cancer). [Internet; cited 2021 November]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04546009>.
16. Clinicaltrials.gov. A study evaluating the efficacy and safety of adjuvant giredestrant compared with physician's choice of adjuvant endocrine monotherapy in participants with estrogen receptor-positive, HER2-negative early breast cancer (lidERA Breast Cancer). [Internet; cited 2021 November]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04961996>.
17. Clinicaltrials.gov. A study evaluating the efficacy and safety of multiple treatment combinations in participants with breast cancer. [Internet; cited 2021 November]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04802759>.
18. U.S Food and Drug Administration. Fast Track. [Internet; cited September 2021]. Available from: <https://www.fda.gov/patients/fast-track-breakthrough-therapy-accelerated-approval-priority-review/fast-track>.
19. Clinicaltrials.gov. A study evaluating the efficacy, safety, and pharmacokinetics of giredestrant plus palbociclib compared with anastrozole plus palbociclib for postmenopausal women with estrogen receptor-positive and HER2-negative untreated early breast cancer (coopERA Breast Cancer). [Internet; cited 2021 November]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04436744>.
20. Clinicaltrials.gov. A study evaluating the efficacy and safety of adjuvant giredestrant compared with physician's choice of adjuvant endocrine monotherapy in participants with estrogen receptor-positive, HER2-negative early breast cancer (lidERA breast cancer). [Internet; cited 2021 November]. Available from: <https://clinicaltrials.gov/ct2/show/NCT04961996>.

Roche Investor Relations

Dr. Karl Mahler

Phone: +41 61 68-78503

e-mail: karl.mahler@roche.com

Dr. Sabine Borngräber

Phone: +41 61 68-88027

e-mail: sabine.borngraeber@roche.com

Dr. Bruno Eschli

Phone: +41 61 68-75284

e-mail: bruno.eschli@roche.com

Dr. Birgit Masjost

Phone: +41 61 68-84814

e-mail: birgit.masjost@roche.com

Dr. Gerard Tobin

Phone: +41 61 68-72942

e-mail: gerard.tobin@roche.com

Investor Relations North America

Loren Kalm

Phone: +1 650 225 3217

e-mail: kalm.loren@gene.com