

LBA16
Giredestrant (GIRE), an oral selective oestrogen receptor (ER) antagonist and degrader, + everolimus (E) in patients (pts) with ER-positive, HER2-negative advanced breast cancer (ER+, HER2– aBC) previously treated with a CDK4/6 inhibitor (i): Primary results of the phase III evERA BC trial

E. Mayer¹, S. Tolaney¹, M. Martin², G. Vidal³, L. Moscetti⁴, K. Jhaveri⁵, A. Brufsky⁶, W. Gradishar⁷, A. Schneeweiss⁸, N. Niikura⁹, A. Favret¹⁰, M. Alfie¹¹, K.S. Lee¹², S. Khan¹³, M. Feldman¹⁴, B.-M. Day¹⁴, L. Lam¹⁵, W. Darbonne¹⁴, P.D. Perez Moreno¹⁵, H. Rugo¹⁶

¹ Breast Oncology Center, Dana-Farber Cancer Institute, Boston, MA, United States of America, ² Hospital Gregorio Marañón, Universidad Complutense, GEICAM, CIBERONC, Madrid, Spain, ³ Department of Medical Oncology, The West Cancer Center, Germantown, TN, United States of America, ⁴ Department of Medical Oncology, Universitaria Policlinico Modena, Modena, Italy, ⁵ Breast Center, Memorial Sloan-Kettering Cancer Centre, New York, NY, United States of America, ⁶ Department of Hematology-Oncology, University of Pittsburgh Cancer Institution, Pittsburgh, PA, United States of America, ⁷ Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL, United States of America, ⁸ Department of Gynaecological Oncology, Heidelberg University Hospital and German Cancer Research Center, Heidelberg, Germany, ⁹ Department of Breast Oncology, Tokai University School of Medicine, Kanagawa, Japan, ¹⁰ Department of Medical Oncology, Virginia Cancer Specialists, PC, Fairfax, VA, United States of America, ¹¹ Department of Medical Oncology, Organizacion Medica de Investigacion, Buenos Aires, Argentina, ¹² Center for Breast Cancer, National Cancer Center, Goyang, Republic of Korea, ¹³ Department of Oncology, Nottingham University Hospital, Nottingham, United Kingdom, ¹⁴ Medical Affairs, Genentech, Inc., South San Francisco, CA, United States of America, ¹⁵ Product Development, Genentech, Inc., South San Francisco, CA, United States of America¹⁶ Department of Medical Oncology & Therapeutics Research, City of Hope Comprehensive Cancer Center, Duarte, CA, United States of America

Background

CDK4/6i + endocrine therapy (ET) is first-line standard of care (SOC) for pts with ER+, HER2– aBC but effective post-CDK4/6i options are limited. GIRE and E target the ER and PI3K/AKT/mTOR pathways, which are implicated in ET resistance. evERA BC (NCT05306340) is a global, randomised, open-label trial.

Methods

Pts had ER+, HER2– aBC with disease progression (PD) or relapse during/post-CDK4/6i + ET. Randomisation was 1:1 to once-daily oral 30 mg GIRE + 10 mg E or SOC ET (exemestane/fulvestrant/tamoxifen) + E until PD or unacceptable toxicity. Co-primary endpoints: Investigator-assessed progression-free survival (INV-PFS; RECIST v1.1) in pts with detectable ESR1 mutation (m) and the intent-to-treat (ITT) population. Overall survival (OS) was a secondary endpoint.

Results

373 pts were randomised; 183 to GIRE + E and 190 to SOC ET + E. Data cutoff was 16 July 2025; median follow-up was 18.6 months. 55% of pts had an ESR1m. Efficacy is shown in the Table. The most common adverse events (AEs) were stomatitis (47.3% in the GIRE + E arm [n = 182] vs 48.9% in the SOC ET + E arm [n = 186]), diarrhoea (26.9% vs 22.6%) and anaemia (23.6% vs 21.0%). The most common grade 3/4 AEs were anaemia (6.0% vs 8.6%), hypokalaemia (3.8% vs 2.7%), pneumonia (1.6% vs 4.3%) and stomatitis (2.7% vs 3.2%). Grade 1 bradycardia was reported (3.8% vs 0.5%) with no treatment interruptions/discontinuations. 8.2% and 6.5% of pts withdrew from GIRE and SOC ET, respectively, due to AEs. Table: LBA16

	ESR1m GIRE + E	SOC ET + E	ITT GIRE + E	SOC ET + E
INV-PFS				
Median (95% CI), months	9.99 (8.08, 12.94)	5.45 (3.75, 5.62)	8.77 (6.60, 9.59)	5.49 (4.01, 5.59)
HR [†] (95% CI)	0.38 (0.27, 0.54) <i>P</i> < 0.0001		0.56 (0.44, 0.71) <i>P</i> < 0.0001	
Interim OS [‡]				
Median (95% CI), months	NE (20.17, NE)	21.03 (14.78, 26.87)	NE (NE, NE)	26.87 (22.21, NE)
HR [†] (95% CI)	0.62 (0.38, 1.02) <i>P</i> = 0.0566		0.69 (0.47, 1.00) <i>P</i> = 0.0473	

CI, confidence interval; HR, hazard ratio; NE, not evaluable.[†]Stratified by prior fulvestrant (yes vs no), ESR1m (yes vs no/indeterminate) and visceral disease (yes vs no).[‡]Centrally tested via circulating tumour DNA.[‡]Stratified by prior fulvestrant (yes vs no), ESR1m (yes vs

no/indeterminate) and visceral disease (yes vs no).‡At data cutoff, OS maturity was 59% in the *ESR1*m population and 67% in the ITT population.

Conclusions

GIRE + E showed statistically significant and clinically meaningful improvements in INV-PFS in ER+, HER2– aBC post-CDK4/6i, for both the *ESR1*m and ITT pt populations. The safety profile of GIRE + E was manageable with no unexpected findings. GIRE + E may represent a new effective treatment option in the post-CDK4/6i setting.

Clinical trial identification

NCT05306340, first posted 1 April 2022.

Editorial acknowledgement

Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland.

Legal entity responsible for the study

F. Hoffmann-La Roche Ltd.

Funding

F. Hoffmann-La Roche Ltd.

Disclosure

E. Mayer: Financial Interests, Personal, Advisory Role: AstraZeneca, Lilly, Novartis; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. S.M. Tolaney: Financial Interests, Personal, Advisory Role: 4D Pharma, AstraZeneca, Athenex, BeyondSpring Pharmaceuticals, Blueprint Medicines, Bristol-Myers Squibb, Certara Inc, Chugai Pharma, CytomX Therapeutics, Daiichi Sankyo, Eisai, Ellipses Pharma, G1 Therapeutics, Genentech, Inc, Immunomedics/Gilead, Infinity Pharmaceuticals, Kyowa Hakko Kirin, Lilly, Merck, Mersana, NanoString Technologies, Nektar, Novartis, Odonate Therapeutics, OncoPep, OncoSec, OncXerna Therapeutics, Paxman, Pfizer, Puma Biotechnology, Reveal Genomics, Samsung Bioepis, Sanofi, Seagen, Zentalis, Zymeworks; Financial Interests, Institutional, Research Funding: AstraZeneca, Bristol-Myers Squibb, Cyclacel, Eisai, Exelixis, F. Hoffmann-La Roche Ltd, Genentech, Inc, Immunomedics, Lilly, Merck, NanoString Technologies, Nektar, Novartis, Odonate Therapeutics, Pfizer, Sanofi, Seagen; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. M. Martin: Financial Interests, Personal, Other, Honoraria: AstraZeneca, Lilly, Amgen, F. Hoffmann-La Roche Ltd, Genentech, Inc, Novartis, Pfizer; Financial Interests, Personal, Advisory Role: AstraZeneca, Amgen, Taiho Oncology, F. Hoffmann-La Roche Ltd, Genentech, Inc, Novartis, PharmaMar, Eli Lilly, Puma Biotechnology, Taiho Oncology, Daiichi Sankyo, Pfizer; Financial Interests, Personal, Speaker’s Bureau: Lilly/ImClone, F. Hoffmann-La Roche Ltd, Genentech, Inc, Pierre Fabre; Financial Interests, Institutional, Research Funding: Novartis, F. Hoffmann-La Roche Ltd, Puma Biotechnology ; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. G.A. Vidal: Financial Interests, Personal, Advisory Role: Arvinas, AstraZeneca, Concerto AI, Daiichi Sankyo, Eli Lilly, Gilead, Hologic, F. Hoffmann-La Roche Ltd, Genentech, Inc, Merck, Myriad Genetics, Novartis, Pfizer, Stemline; Financial Interests, Institutional, Advisory Role: Puma Biotechnology; Financial Interests, Institutional, Research Funding: AstraZeneca, Bristol Myers Squibb, Celcuity, Eli Lilly, Gilead, GSK, Merck, Napo Pharmaceuticals, Novartis, Pfizer, Puma Biotechnology, F. Hoffmann-La Roche Ltd, Genentech, Inc, Tesaro; Financial Interests, Personal, Other, Non-CME: AstraZeneca, Eli Lilly, Gilead; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. L. Moscetti: Financial Interests, Personal, Other, Honoraria: AstraZeneca, Daichii-Sankyo, Eli Lilly, Gilead, Novartis, Pfizer-Seagen; Non-Financial Interests, Personal, Advisory Board: AstraZeneca, Eli Lilly, Pfizer-Seagen; Financial Interests, Personal, Other, Travel fees: Novartis, Pfizer-Seagen; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. K.L. Jhaveri: Non-Financial Interests, Personal, Advisory Role: AstraZeneca, Bicycle Therapeutics, Blueprint Medicines, Daiichi Sankyo, Eisai, Genentech, Inc, Gilead, Lilly/Loxo Oncology, Pfizer, Menarini/Stemline, Novartis, Olema Pharmaceuticals, Ravzebio, Scorpion Therapeutics, Zymeworks; Financial Interests, Institutional, Research Funding: AstraZeneca, Blueprint Medicines, Eisai, Genentech, Inc, Gilead, Lilly/Loxo Oncology, Pfizer, Merck Pharmaceuticals, Novartis, Puma Biotechnology, Rayzebio, Scopion Therapeutics, Zymeworks; Financial Interests, Personal, Other, Travel and Accommodation: AstraZeneca; Financial Interests, Personal, Other, Travel and accommodation: Genentech, Inc, Gilead, Lilly, Pfizer; Non-Financial Interests, Personal, Other, Research support in the form of third-party

writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. A.M. Brufsky: Financial Interests, Personal, Advisory Board: Gilead, AstraZeneca, Novartis, Lilly, Pfizer, Daiichi Sankyo, Roche/Genentech, Puma, Eisai, Merck; Financial Interests, Personal, Other, Consultant: Myriad, Agendia; Financial Interests, Institutional, Local PI: AstraZeneca, Daiichi Sankyo, Lilly, Roche/Genetech; Financial Interests, Institutional, Steering Committee Member: Gilead, Puma. W.J. Gradishar: Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. A. Schneeweiss: Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. N. Niikura: Financial Interests, Personal, Speaker's Bureau: AstraZeneca, Daiichi Sankyo, Eli Lilly Japan, MSD, Pfizer; Financial Interests, Personal, Advisory Role: AstraZeneca; Financial Interests, Personal, Research Funding: Chugai, Daiichi Sankyo, Nippon Kayaku, Pfizer; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. A. Favret: Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. M.S. Alfie: Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. K.S. Lee: Financial Interests, Personal, Advisory Role: AstraZeneca, Daiichi Sankyo, Gilead Sciences, Novartis; Financial Interests, Personal, Advisory Board: Pfizer; Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. S. Khan: Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. M. Feldman: Financial Interests, Personal, Full or part-time Employment: Genentech, Inc; Financial Interests, Personal, Stocks/Shares: F. Hoffmann-La Roche Ltd; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. B. Day: Financial Interests, Personal, Full or part-time Employment: Genentech, Inc; Financial Interests, Personal, Stocks/Shares: F. Hoffmann-La Roche Ltd; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. L. Lam: Financial Interests, Personal, Full or part-time Employment: Genentech, Inc; Financial Interests, Personal, Stocks/Shares: F. Hoffmann-La Roche Ltd; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. W. Darbonne: Financial Interests, Personal, Full or part-time Employment: Genentech, Inc; Financial Interests, Personal, Stocks/Shares: F. Hoffmann-La Roche Ltd; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. P.D. Perez Moreno: Financial Interests, Personal, Full or part-time Employment: Genentech, Inc; Financial Interests, Personal, Stocks/Shares: F. Hoffmann-La Roche Ltd; Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Bena Lim, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. H.S. Rugo: Financial Interests, Personal, Advisory Board, Consultancy/advisory support: NAPO; Financial Interests, Personal, Invited Speaker, Honoraria: Mylan/Viatris, Chugai; Financial Interests, Personal, Advisory Board, Advisory/Consultancy: PUMA, Sanofi; Financial Interests, Personal, Other, Advisory/Consultant: Bristol Myers Squibb; Financial Interests, Institutional, Local PI: Novartis, Lilly, Pfizer, Daiichi, Astra Zeneca, Gilead Sciences, Inc.; Financial Interests, Institutional, Coordinating PI: OBI Pharma, F. Hoffmann-La Roche AG/Genentech, Inc., Merck; Financial Interests, Institutional, Research Grant: Stemline Therapeutics, Ambryx.