MADRID 2026 ESMO congress

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Retrospective exploratory biomarker (BM) analyses from evERA breast cancer (BC): A phase III trial of giredestrant (GIRE) + everolimus (E) in patients (pts) with oestrogen receptor-positive, HER2-negative advanced BC (ER+, HER2– aBC) in the post-CDK4/6 inhibitor (i) setting

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Background

In evERA BC (NCT05306340) GIRE, a next-generation oral full ER antagonist and degrader, + E significantly improved progression-free survival (PFS) vs standard-of-care endocrine therapy (SOC ET) + E in the post-CDK4/6i setting in ER+, HER2– aBC (Mayer ESMO 2025). We report exploratory BM analyses to characterise the relationship between genomic alterations (GAs) and PFS.

Methods

Pts were randomised 1:1 to daily GIRE + E or tamoxifen/exemestane/fulvestrant + E until disease progression/unacceptable toxicity. Baseline plasma-derived circulating tumour (ct) DNA was evaluated prospectively by FoundationOne®Liquid CDx. *ESR1* variants, ct fraction (cTF) and other genomic variants were assessed.

Results

Baseline ctDNA was evaluable in 365/373 enrolled pts. The most common GAs were in *TP53* (42%), *PIK3CA* (32%), *GATA3* (18%) and *RB1* (18%). cTF, evaluable in 363 pts, was well balanced between arms; 67% had high (≥ 1%) cTF. PFS for subgroups is shown in the Table. Of 207 pts with *ESR1* mutations, the most common variants were D538G and Y537X, detected in 57% and 60% cases, respectively. Seventy-one pts (34%) had > 1 *ESR1* variant. Most (119 pts') *ESR1*-mutated (m) tumours had ≥ 1 clonal *ESR1* variant detected, with an increased number of variants per pt associated with higher cTF. PFS benefit of GIRE + E was generally consistent regardless of key oncogenic pathway alterations.Table: 2RO

ctDNA-evaluable	GIRE + E, n	SOC ET + E, n	PFS unstratified HR (95% CI)
Overall			
cTF ≥ 1%	116	126	0.52 (0.39–0.70)
cTF < 1%	60	61	0.61 (0.40–0.94)
*TP53*m	81	71	0.65 (0.45–0.93)
*TP53*nmd	97	116	0.49 (0.36–0.68)
*PIK3CA*m	64	51	0.55 (0.36–0.83)
*PIK3CA*nmd	114	136	0.58 (0.43–0.78)
*GATA3*m	31	34	0.80 (0.48–1.35)
*GATA3*nmd	147	153	0.53 (0.41–0.70)
*RB1*m	36	28	0.65 (0.38–1.12)
*RB1*nmd	142	159	0.53 (0.41–0.70)
*ESR1*m			

ctDNA-evaluable	GIRE + E, n	SOC ET + E, n	PFS unstratified HR (95% CI)
cTF ≥ 1%	80	80	0.45 (0.31–0.65)
cTF < 1%	21	25	0.32 (0.16–0.68)
Specific residue of *ESR1* mutation			
D538	56	61	0.58 (0.38–0.89)
Y537	60	64	0.35 (0.22–0.54)
L536	14	12	0.67 (0.28–1.63)
E380	16	10	0.30 (0.11–0.83)

CI, confidence interval; HR, hazard ratio; nmd, no mutation detected.

Conclusions

Baseline GAs in evERA BC were consistent with a post-CDK4/6i ER+, HER2– aBC population. Higher cTF was associated with worse prognosis, but GIRE + E maintained greater PFS benefit vs SOC ET + E, regardless of cTF status in the overall and *ESR1*m populations. PFS benefit was observed across all *ESR1* variants, independent of clonality and across poor prognostic subgroups (eg *TP53*, *GATA3*, *RB1*).

Clinical trial identification

NCT05306340.

Editorial acknowledgement

Research support in the form of third-party medical writing assistance for this abstract, furnished by Lidija Garan, PhD, of Nucleus Global, an Inizio Company, was provided 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

S.M. Tolaney: Financial Interests, Personal, Other, Consulting: Aadi BioPharma, Hengrui, Avenzo Therapeutics, Atkis Oncology, Celcuity, Samsung Bioepis, Tempus; Financial Interests, Personal, Advisory Board, Ad board participation: Artios, Bicycle Therapeutics; Financial Interests, Personal, Advisory Board, Ad Board Participant/Consultant: AstraZeneca, Eli Lilly; Financial Interests, Personal, Advisory Board, Advisory Board participation: Bayer, Sumitovant Biopharmaceuticals, Natera; Financial Interests, Personal, Other, Consultant: Blueprint Medicines, Boundless Bio, Denali Therapeutics; Financial Interests, Personal, Advisory Board, Ad board participant: Bristol-Myers Squibb; Financial Interests, Personal, Advisory Board, Ad board participant/consultant: Daichii Sankyo, Eisai, Genentech/Roche, Gilead, Novartis, SeaGen; Financial Interests, Personal, Advisory Board, Advisory Board participation/consulting: Menarini/Stemline, BeOne Medicines; Financial Interests, Personal, Advisory Board, Ad Board participant/consultant: Merck; Financial Interests, Personal, Advisory Board, Ad board participant/Consultant: Pfizer; Financial Interests, Personal, Advisory Board, Advisory board participation: Reveal Genomics, Launch Therapeutics; Financial Interests, Personal, Advisory Board, Advisory board/consulting: Jazz Pharma; Financial Interests, Personal, Advisory Board: Tango Therapeutics, Systimmune, eFFECTOR, Cullinan Oncology, Arvinas, Boehringer Ingelheim; Financial Interests, Personal, Advisory Board, Ad Board participation: Summit Therapeutics; Financial Interests, Personal, Advisory Board, ad board participation: BioNTech, Circle Pharma; Financial Interests, Personal, Advisory Board, Ad board/consulting participation: Zuellig Pharma; Financial Interests, Personal, Advisory Board, ad board/consulting participation: Johnson&Johnson/Ambrx; Financial Interests, Personal, Advisory Board, Advisory Board participation and consulting activities: Mersana Therapeutics; Financial Interests, Personal, Advisory Board, Steering Committee: Olema Pharmaceuticals; Financial Interests, Institutional, Coordinating PI, And steering committing: AstraZeneca; Financial Interests, Institutional, Local PI, And steering committee: Eli Lilly, Jazz Pharmaceuticals; Financial Interests, Institutional, Local PI: Pfizer, SeaGen, Novartis, Nanostring, Bristol Myers Squibb, Daiichi Sankyo; Financial Interests, Institutional, Funding: Exelixis, OncoPep; Financial Interests, Institutional, Coordinating PI, and steering committee: Gilead; Financial Interests, Institutional, Local PI, and steering committee: Merck, Genentech/Roche, Stemline/Menarini; Other, Other, Travel Support: Eli Lilly, Gilead Sciences, Jazz Pharmaceuticals, Arvinas, Roche – Genentech, AstraZeneca. J. Liang: 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 Lidija Garan, 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: Roche – Genentech; Financial Interests, Personal, Stocks/Shares: Hoffmann-La Roche; Non-Financial Interests, Institutional, Proprietary Information:

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Vidal: Financial Interests, Personal, Advisory Board: Roche/Genetech, Novartis, Eli Lilly, Gilead, Puma, Pfizer, Stemline, Biotheranautics; Financial Interests, Personal, Invited Speaker, Travel and Housing cost as well as cost for speaking to employees at annual meetings: Gilead, Lilly, AstraZeneca, Pfizer, Roche/Genentech; Financial Interests, Personal, Full or part-time Employment, Spouse is an employee: Novartis; Financial Interests, Personal, Stocks/Shares, Spouse is an employee: novartis; Financial Interests, Institutional, Funding: Roche/Genetech, Puma, Celcuity, Merck, BMS, Eli Lilly, GTx inc, AstraZeneca, Pfizer, Gilead, Tesaro, Halozyme, GSK, Natera; Non-Financial Interests, Member: ASCO. L. Moscetti: Non-Financial Interests, Personal, Other, Research support in the form of third-party writing assistance for this abstract, furnished by Lidija Garan, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. 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A.M. Brufsky: Financial Interests, Personal, Advisory Board: Gilead, Astrazeneca, Novartis, Lilly, Pfizer, Daiichi Sankyo, Roche/Genentech, Puma, Merck, Bria-Cell; Financial Interests, Personal, Other, Consultant: Agendia; Financial Interests, Personal, Stocks/Shares: Celcuity, Ataraxis; Financial Interests, Institutional, Local PI: Astrazeneca, Daiichi Sankyo, Lilly, Roche/Genetech; Financial Interests, Institutional, Steering Committee Member: Gilead, Puma. W.J. Gradishar: Financial Interests, Personal, Advisory Board: AstraZeneca, Roche, Novartis, Lilly; Financial Interests, Personal, Advisory Board, Advisory board: Menarini-Stemline. A. Schneeweiss: Financial Interests, Personal, Invited Speaker: Aurikamed, Boehringer Ingelheim, Fresenius Kabi, Lilly, med update, Menarini-Stemline, neoConnect, streamed up, SYNLAB, AstraZeneca, Daiichi Sankyo, Pfizer, hig5md, onkowissen.de, Roche, Gilead Sciences; Financial Interests, Personal, Writing Engagement: Georg Thieme Verlag, Zuckschwerdt Verlag. J.A. O'Shaughnessy: Financial Interests, Personal, Advisory Board: Agendia, Amgen, Aptitude Health, AstraZeneca, Eisai, G1 Therapeutics, Lilly, Merck, Novartis, Pfizer, Puma, Roche, Daiichi Sankyo, Gilead Sciences, Pierre Fabre Pharmaceuticals, Sanofi, BioNtech, Dava Oncology, Genentech, Seagen, Stemline Therapeutics, Duality, Bristol Myers Squibb, Ellipses, Exact Science, Guardant Health, Hibercell, Jazz Pharmaceuticals, Johnson and Johnson, Menarini-Stemline, Mersana Therapeutics, Natera, Summit Therapeutics, Tempus, TerSera Therapeutics, AADI Bioscience. M. Dieterich: Financial Interests, Personal, Full or part-time Employment: F. Hoffmann-La Roche Ltd; 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 Lidija Garan, 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 Lidija Garan, PhD, of Nucleus Global, an Inizio Company, and funded by F. Hoffmann-La Roche Ltd, Basel, Switzerland: F. Hoffmann-La Roche Ltd. T. Fernando: Financial Interests, Personal, Full or part-time Employment: Genentech, Inc; Financial Interests, Personal, Stocks/Shares: F. 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