REVIEW

Clinical utility of fulvestrant in the treatment of breast cancer: a report on the emerging clinical evidence

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Abstract: Fulvestrant is the first selective estrogen receptor (ER) downregulator available in clinical practice. It is a pure antiestrogen with no agonistic effects, leading to degradation of ER alpha, with activity in tamoxifen-resistant breast cancer (BC) models. Pharmacokinetic and pharmacodynamic studies and several postmarketing clinical trials led to the definition of the optimal dose at 500 mg intramuscularly on days 1, 15, and 29 and then every 28 days. Targeting ER alpha, fulvestrant is a cornerstone of treatment in luminal BCs, whose growth is largely driven by the ER pathway. In endocrine therapy-naïve patients with hormone receptor-positive, HER2– advanced BC (ABC), fulvestrant yielded significantly longer progression-free survival compared to anastrozole in the Phase III FALCON study. Due to its mechanism of action and pharmacokinetic properties, fulvestrant is an ideal backbone for combination therapies. Preclinical studies have shown synergism with drugs acting on signaling pathways involved in the development of endocrine resistance, among which the cyclin D/cyclin-dependent kinase 4-6/retinoblastoma pathway and the phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of rapamycin pathway, contributing to overcoming or delaying endocrine resistance. In the Phase III PALOMA-3 trial, a combination of the cyclin-dependent kinase 4/6 inhibitor palbociclib with fulvestrant significantly improved progression-free survival over fulvestrant alone in women with hormone receptor positive, HER2– ABC progressing during prior endocrine therapy. This led to approval of the combination in this clinical setting. Similar results were obtained with abemaciclib and ribociclib. Combination with pan-PI3K inhibitors, though showing some efficacy, was hampered by the toxicity of these agents, and studies in combinations with more selective inhibitors of the α-catalytic subunit of PI3K are ongoing. Fulvestrant has shown partial activity also in patients with tumors harboring mutations of the *ESR1* gene. It is thus a key drug in the treatment of ABC, whose role in combination with new targeted agents is still evolving.

Keywords: advanced breast cancer, endocrine therapy, metastatic, selective estrogen receptor downregulator, SERD, combination therapy

Introduction

Among neoplasms in women, breast cancer (BC) ranks first in incidence worldwide, first in mortality in less developed regions, and second in more developed ones.[1] Although BC mortality is decreasing and the overall survival (OS) of metastatic disease is increasing, due to diagnostic and therapeutic improvements, the disease in its metastatic stage remains virtually incurable.

Different BC subtypes can be identified by "omics" techniques,[2] first and foremost the "intrinsic" BC subtypes defined by gene-expression profiling.[3,4] These include

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four main classes: the luminal A and luminal B tumors, whose growth is largely driven by the estrogen receptor (ER) pathway, and the human epidermal growth factor receptor 2 (HER2)-enriched and basal-like subtypes, which are not affected by the ER pathway. Luminal A tumors show high expression of genes related to the ER pathway (eg, *ESR1*, *GATA3*) and low expression of genes associated with cell proliferation, while luminal B tumors have lower expression of genes of the ER pathway and higher expression of genes associated with the cell cycle (eg, *CCND1*, encoding cyclin D1) and proliferation (eg, *MKI67*, encoding Ki67), as well as higher expression of growth-factor-receptor genes, including *HER2*.[2,5,6] A surrogate definition of these subtypes is used in clinical practice, based on tumor expression of ER, progestin receptor (PR), the proliferative marker Ki67, and HER2, assessed by immunohistochemistry.[7]

Current strategies for slowing cancer progression in women with luminal BC

Given the role of the ER pathway in luminal BC, first-choice treatment is usually endocrine therapy, although endocrine resistance, either primary (relapse while in the first 2 years of adjuvant endocrine therapy or progression within first 6 months of first-line endocrine therapy for metastatic disease) or acquired (relapse while on adjuvant endocrine therapy after the first 2 years, relapse within 12 months of completing adjuvant endocrine therapy, or disease progression ≥6 months after initiating endocrine therapy for metastatic disease), is a major obstacle to disease control.[8] Several agents are available, the most important being: tamoxifen, a selective ER modulator with antagonistic but also partially agonistic action on ER; aromatase inhibitors (AIs), which inhibit the aromatase enzyme converting androgens into estrogens; and fulvestrant, a selective ER downregulator/degrader (SERD) with purer antagonistic and irreversible action on ER. Nonetheless, primary or acquired endocrine resistance ultimately affects all metastatic luminal BCs, often subtended by known biological alterations, such as cross talk between ER and growth-factor receptors,[9] mutations/hyperactivity of the phosphatidylinositol 3-kinase (PI3K)/[10] protein kinase B (Akt)/[11] mammalian target of rapamycin (mTOR)[12] pathway, hyperactivity of the cyclin D1[13]/cyclin-dependent kinase (CDK) 4 and 6[14]/retinoblastoma (RB)[15] pathway and ESR1 gene mutations.[16] Several drug-combination strategies are being developed to overcome or delay the onset of endocrine resistance: combinations of endocrine agents with growth-factor-receptor inhibitors, CDK4/6 inhibitors,

PI3K inhibitors, or use of SERDs potentially active also in the presence of mutated ER.

Fulvestrant is the first SERD to enter the clinical arena and represents a key compound for endocrine treatment of BC and a suitable backbone for combination therapy with new targeted agents. In this paper, we review pharmacological properties and preclinical and clinical studies of fulvestrant alone and in combination with other agents, and provide a perspective on its current and future role in BC treatment.

Pharmacology, mode of action, pharmacokinetics of fulvestrant
Pharmacology

Fulvestrant (ICI 182,780) is a steroidal molecule derived from 17β-estradiol by substitution of a hydrogen atom with an alkylsulfinylamide side chain in position 7α.[17] Fulvestrant acts as ERα antagonist, binding ERα competitively with estradiol, with a binding affinity that is 89% that of estradiol (much greater than the affinity of tamoxifen, which is 2.5% that of estradiol).[17]

The ERα molecule is composed of different domains: a ligand-binding domain (binding 17β-estradiol), a DNA-binding domain, a hinge or dimerization domain, and two transactivating domains (ligand-independent activation function [AF]-1 and the ligand-dependent AF2).[18–20] ERα has different mechanisms of action: 1) working as a transcription factor (classical genomic action): activating specific "estrogen-response elements" in the promoters of target genes; 2) binding and activating other transcription factors (nonclassical genomic action); 3) being activated in a ligand-independent way by cross talk with receptor tyrosine-kinase pathways; or 4) exerting "nongenomic" actions whereby estrogens activate membrane-bound G protein coupled ERs (GPER, also known as GPR30) and their downstream signaling. Control of ER actions involves AF-domain recruitment of coregulators. While AF2 is activated by estrogen in ligand-dependent processes,[21] AF1 is activated by growth factors through activation of the mitogen activated protein kinase (MAPK).[22]

Binding of fulvestrant to ERα hampers ER dimerization,[23] inhibits ER nuclear translocation[24] and activation, and promotes ER degradation (ER downregulation), yielding complete inhibition of ERα signaling. Blocking both AF1 and AF2 (while selective ER modulators inhibit only AF2), fulvestrant is a pure ERα antagonist, lacking any agonist activity, including any effect on the endometrium.[25,26] Contrary to its action on ERα, fulvestrant causes a stabilization of ERβ, a receptor isoform with growth-inhibitory properties, in BC cell lines.[27,28]

Preclinical studies have shown that fulvestrant downregulates the expression of ERα in ER-positive BC cell lines[29] without reducing ERα gene (*ESR1*) transcripts and inhibits transcription of ER-responsive genes.[30] Fulvestrant can also block the nongenomic actions of estradiol on GPER.[31] These processes result in potent inhibition of the growth of ER-positive human BC cell lines,[17] with activity also in tamoxifen-resistant lines[32–34] and lack of cross-resistance with tamoxifen.[35] The antitumor activity of fulvestrant was confirmed in xenograft models of ER-positive BC[17,36] and found to be more effective than tamoxifen or estrogen withdrawal.[37]

Pharmacodynamics

Pharmacodynamic (PD) studies in women with early BC treated with a short preoperative course of short-acting fulvestrant and assessing biomarker changes between baseline biopsies and surgical samples have shown substantial reduction in the expression levels of ER, PR, and Ki67.[29,38] In a randomized study comparing a single injection of long-acting fulvestrant at different doses (50, 125, or 250 mg) with oral daily tamoxifen or placebo for 2–3 weeks before surgery, fulvestrant showed a dose-dependent reduction in ER, PR, and Ki67 expression in primary BC. ER downregulation at the 250 mg dose was significantly higher compared to the tamoxifen arm, and tamoxifen produced an increase in PR expression, underlying the different mechanism of action.[39]

A further study involved 32 patients with advanced BC (ABC) treated with first-line fulvestrant 250 mg monthly who underwent repeated tumor biopsies.[40] The clinical benefit (CB) rate (objective response [OR] or stable disease [SD] ≥6 months) was 81% and duration of response (DOR) was 25.8 months. Fulvestrant produced a decrease in Ki67 in 79% of tumors, and lower Ki67 predicted longer DOR. ER and PR significantly decreased in all tumors, and there was loss of epidermal growth factor receptor (EGFR) and MAPK phosphorylation in 65% of tumors. At disease progression, ER remained low (although still present), while there was some recovery of Ki67 and EGFR/MAPK activity in 45%–67% of the patients.

The NEWEST (neoadjuvant endocrine therapy for women with estrogen-sensitive tumors) randomized, open-label, Phase II study compared high-dose (HD) fulvestrant (500 mg on days 0, 14, and 28, then every 28 days) with fulvestrant 250 mg every 28 days administered for 16 weeks prior to surgery in 211 postmenopausal women with ER-positive local ABC.[41] The primary objective was to compare reductions in Ki67 on tumor biopsy after 4 weeks of treatment. HD fulvestrant produced a greater reduction in Ki67 (78.8% versus 47.4%,

P<0.0001) at 4 weeks, as well as a greater reduction in ER expression (25.0% versus 13.5%, *P*=0.0002). OR rates, assessed at week 16 by 3D ultrasound, were 22.9% and 20.6% for fulvestrant 500 and 250 mg, respectively.

Pharmacokinetics

Fulvestrant is supplied as 250 mg/5 mL vials of long-acting compound for intramuscular (IM) injection, its low solubility limiting further drug concentration, and was initially approved at a dose of 250 mg every 28 days. It is slowly absorbed after IM injection, with 99% bound to plasma lipoproteins and volume of distribution of 3–5 L/kg.[42] Fulvestrant metabolism involves multiple transformations, similarly to endogenous steroids, and cytochrome p450 3A4 (CYP3A4 appears involved in its oxidation. Despite that, there are no known interactions with other drugs, including inducers and inhibitors of CYP3A4, and fulvestrant does not inhibit other CYP enzymes. Elimination is largely via the feces as metabolites and less than 1% through the urine.[42] Fulvestrant has not been studied in patients with severe hepatic or renal impairment. Drug exposure may increase in the presence of mild–moderate liver impairment, and use with caution or dose reductions are recommended in these cases. No dose reductions are required in cases of mild or moderate renal impairment.[42] Race, age, and body weight do not affect drug exposure significantly.

Early pharmacokinetic (PK) analyses at the initially approved dose (IAD) and schedule, with monthly depot IM injections of fulvestrant 250 mg, showed maintenance of therapeutic concentrations up to 28 days and an increase in mean area under the concentration–time curve (AUC) after repeated doses.[43,44] Further PK evaluations were done in Phase III studies with fulvestrant IAD. After a single dose, the mean time to peak plasma concentration (T_{max}) was 7 days, the mean AUC from day 0 to day 28 (AUC_{28}) 148 μg*day/L, the mean maximum plasma concentrations (C_{max}) 8.2 μg/L, and the mean minimum plasma concentration 2.6 μg/L.[45] After repeated doses, the steady-state trough-concentration geometric mean increased from about 2.5 to about 6.5 μg/L over the first 6 months, reaching steady-state concentrations in the range of 6–9 μg/L. PK data are adequately described by a two-compartment kinetic model, with a biexponential decline, estimated disposition half-life of about 50 hours and steady-state AUC_{28} of about 300 μg*day/L.[45–47]

The acknowledgment of a greater than twofold increase in steady-state concentrations and AUC_{28} over the first 6 months of therapy and the known dose-dependent downregulation of ERα expression prompted the investigation of different

dosing schedules to achieve therapeutic steady-state levels more rapidly and avoid potential early disease progressions due to inadequate drug levels. Based on PK models, a loading dose (LD) regimen involving the administration of 500 mg IM at day 0, followed by 250 mg IM on days 14 and 28, then 250 mg IM every 28 days, and an HD regimen of 500 mg IM on days 0, 14, and 28, then every 28 days were developed and tested in subsequent clinical trials.[48] Comparison of PK parameters among the three regimens (IAD, LD, and HD) showed dose-proportional C_{max} and AUC and faster achievement of steady-state concentrations with LD and HD within 1 month from treatment start.[49–52]

Efficacy studies for fulvestrant as monotherapy or in combination therapy
Studies at the IAD
Initial studies were conducted at the IAD of 250 mg IM monthly (every 28±3 days), in patients with hormone receptor (HR)-positive ABC pretreated with endocrine therapy, and have been reviewed in detail elsewhere.[53,54] Phase II studies, like the Swiss Group for Clinical Cancer Research SAKK 21/00 trial and the North Central Cancer Treatment Group N0032 trial, reported CB rates of 30%–35%.[55,56] Compassionate use programs showed CB in chemotherapy-pretreated patients, in more advanced lines of endocrine treatment, and in HER2-positive tumors.[57,58] The main randomized clinical trials with fulvestrant are summarized in Table 1.

Two randomized Phase III trials, the open-label trial 0020[59] carried out in Europe, Australia, and South Africa (n=451 patients) and the North American double-blind double-dummy trial 0021[60] (n=400), compared fulvestrant IAD with anastrozole, in postmenopausal patients with endocrine-sensitive ABC (HR-positive, relapsed after ≥12 months of adjuvant endocrine therapy, or with prior CB ≥3 months in the first-line metastatic setting) progressing after prior endocrine therapy mainly with tamoxifen. In a prospectively planned combined analysis of the two trials on 851 patients,[61] the median time to progression (TTP) was 5.5 months with fulvestrant and 4.1 months with anastrozole, with hazard ratio of 0.95 (95.14% CI 0.82–1.10; *P*=0.48), fulfilling criteria for noninferiority of fulvestrant relative to anastrozole (upper one-sided confidence limit for TTP hazard ratio ≤1.25), but not that of superiority. OR and CB rates did not differ between the two arms within subgroups of patients with or without visceral metastases.[62] DOR was in favor of fulvestrant,[61] but there were no differences in OS.[63] These results led to registration of fulvestrant for treatment of patients with ABC relapsing or progressing on prior antiestrogen therapy.

In the first-line setting, fulvestrant IAD was compared with tamoxifen in a randomized Phase III trial in postmenopausal patients with HR-positive/unknown ABC previously untreated for advanced disease and who had completed adjuvant endocrine therapy from ≥12 months.[64] Contrary to what expected from preclinical studies, TTP was inferior, although not significantly, with fulvestrant compared to tamoxifen (median 6.8 and 8.3 months, hazard ratio 1.18, 95% CI 0.98–1.44; *P*=0.088). In a prospectively planned subset analysis of patients with HR-positive tumors (≈78%), median TTP was 8.2 and 8.3 months (hazard ratio 1.10, 95% CI 0.89–1.36; *P*=0.39), showing similar efficacy of the two drugs, although inferiority of fulvestrant could not be ruled out (upper 95% CI >1.25). Only an exploratory unplanned subset analysis of patients with both ER-positive and PR-positive tumors showed results consistent with noninferiority of fulvestrant (hazard ratio 0.85, 95% CI 0.63–1.15; *P*=0.31).

Studies with LD and high dose
Based on PD and PK studies showing dose-related drug exposure and biological effects, trials with higher doses of fulvestrant were conducted. The randomized Phase II Faslodex Investigation of Dose Evaluation in Estrogen Receptor-Positive Advanced Breast Cancer (FINDER) trials 1[49] and 2,[50] carried out in Japanese and non-Japanese patients respectively, compared fulvestrant IAD with LD and HD in postmenopausal women with HR-positive ABC recurring or progressing after prior endocrine therapy, reporting a trend toward improved efficacy with HD and LD compared to the IAD. They set the ground for the large confirmatory Phase III study Comparison of Fulvestrant In Recurrent or Metastatic Breast Cancer (CONFIRM), comparing fulvestrant HD versus the IAD in 736 postmenopausal women with ER-positive ABC who experienced disease progression during adjuvant or first-line endocrine therapy or within 1 year from completion of adjuvant endocrine therapy, about two-thirds of whom had acquired endocrine resistance and a third had primary resistance.[65] PFS was significantly longer with the HD compared to the IAD (hazard ratio 0.80, 95% CI 0.68–0.94; *P*=0.006). Neither OR/CB rates nor adverse events (AEs) differed significantly between the two arms. At the final analysis, median OS was 26.4 months for the HD and 22.3 months for the IAD (hazard ratio 0.81, 95% CI 0.69–0.96; *P*=0.02).[66] A post hoc analysis confirmed the improved PFS with fulvestrant HD versus IAD in both first-line and second-line treatment of ABC.[67] Results of these studies led to worldwide approval of the HD as the standard fulvestrant dose.

In the TransCONFIRM substudy, genome-wide transcriptomic analysis was conducted on primary tumor samples from 134 patients with Affymetrix microarrays (Santa Clara, CA, USA).[68] High expression of most genes in the EGF-signaling pathway and FOXA1 transcription-factor network strongly predicted decreased PFS. An exploratory multivariate Cox analysis identified a set of 37 genes, among them the known regulator of ER activity *TFAP2C*, whose expression was independently associated with PFS.

The LD of fulvestrant was compared with exemestane in the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) randomized, double-blind, Phase III trial in 693 postmenopausal women with HR-positive ABC progressing or recurring after nonsteroidal AI (NSAI).[51] TTP, OR, and CB were similar in the two arms, both in patients with AI-sensitive and AI-resistant tumors, although an unplanned retrospective analysis on AI-sensitive patients (OR or SD ≥6 months from first-line AI for ABC; approximately 60% of the entire patient population) suggested a possible benefit in TTP with fulvestrant.

Fulvestrant HD was compared with anastrozole as first-line treatment for HR-positive ABC in the randomized, open-label, Phase II study Fulvestrant First-Line Study Comparing Endocrine Treatments (FIRST), which enrolled 205 postmenopausal women.[69] The primary end point, CB rate, did not differ between arms, but median TTP was 23.4 months with fulvestrant and 13.1 months with anastrozole (hazard ratio 0.66, 95% CI 0.47–0.92; *P*=0.01).[70] Median OS was 54.1 months with fulvestrant and 48.4 months with anastrozole (hazard ratio 0.70, 95% CI 0.50–0.98; *P*=0.04).[71] These results were confirmed in the randomized, double-blind, Phase III Fulvestrant and Anastrozole Compared in Hormonal Therapy Naive Advanced Breast Cancer (FALCON) study comparing fulvestrant HD with anastrozole in 462 endocrine therapy-naïve, postmenopausal women with HR-positive ABC.[72] Median PFS (the primary end point) was 16.6 months with fulvestrant and 13.8 months with anastrozole (hazard ratio 0.797, 95% CI 0.637–0.999; *P*=0.0486). OR and CB rates did not differ between the two arms, while DOR and duration of CB were longer with fulvestrant. The median OS was not reached in either arm, and the hazard ratio for death was 0.88 (95% CI 0.63–1.22, *P*=0.43). Benefit from fulvestrant was similar across most prespecified patient subgroups, but differed between patients with visceral versus those with nonvisceral disease: the PFS hazard ratio was 0.59 (95% CI 0.42–0.84) in patients with nonvisceral disease (median PFS 22.3 months with fulvestrant versus 13.8 months with anastrozole), and 0.99

(95% CI 0.74–1.33) in patients with visceral disease (median PFS 13.8 months with fulvestrant versus 15.9 months with anastrozole, post hoc interaction test *P*=0.009). Most AE rates were similar between the two arms, but arthralgia was more common with fulvestrant (17%) than with anastrozole (10%). The FALCON study established fulvestrant HD as the most efficacious endocrine agent in postmenopausal women with HR-positive ABC not previously treated with endocrine therapy.

Fulvestrant has been tested at even higher doses, of 750 mg IM, in premenopausal patients, to counteract higher premenopausal estradiol levels, with evidence of activity.[73] Nonetheless, due to the difficulty of administration of the large volume of drug solution, this dosage was not further developed, and use in premenopausal women requires combination with a gonadotropin-releasing hormone (GnRH) analog. The use of fulvestrant in male BC has been reported mainly in small case series, with evidence of activity.[74] In a pooled analysis on 31 cases reported in the literature, the OR rate was 26% and the rate of SD 48%.[75]

Studies of combination therapy with other endocrine agents

Because fulvestrant is a competitive inhibitor of ERα, lowering estradiol levels can increase its activity, as shown by preclinical studies.[76] However, studies combining fulvestrant and AIs have produced contradictory results. A randomized presurgical PD study compared fulvestrant HD plus anastrozole versus either agent alone administered for 2–3 weeks before surgery in 121 patients with operable, HR-positive BC.[77] All treatments significantly reduced ER, PR, and Ki67 expression, and the combination reduced ER more than anastrozole alone, but not more than fulvestrant alone. The randomized Phase III Fulvestrant and Anastrozole Combination Therapy (FACT) trial compared fulvestrant LD plus anastrozole with anastrozole alone in 514 women with HR-positive BC at first relapse. About two-thirds had received adjuvant tamoxifen (only eight received adjuvant NSAIs), and disease relapse occurred within 12 months from the end of adjuvant therapy in half of them; a third received no adjuvant endocrine therapy. There were no differences in efficacy between the two arms.[78] The similar randomized Phase III SWOG 0226 trial enrolled 694 postmenopausal women with previously untreated HR-positive ABC, stratified according to prior adjuvant endocrine therapy (40% had received adjuvant tamoxifen and 60% no adjuvant endocrine therapy).[79] This trial showed better PFS and OS with the combination, without any increase in

Table 1 Main randomized clinical trials in postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer

Study acronyms	Study	Single-agent fulvestrant				
		Design	n	Menopausal status*	Treatment	ET line**
0020	Howell et al[59]	OL Phase III	451	Post	Fulvestrant IAD vs anastrozole	1st–2nd
0021	Osborne et al[60]	DB Phase III	400	Post	Fulvestrant IAD vs anastrozole	1st–2nd
0025	Howell et al[64]	DB Phase III	587 (HR+/unknown) 459 HR+	Post	Fulvestrant IAD vs tamoxifen	1st
CONFIRM	Di Leo et al[65,66]	DB Phase III	736	Post	Fulvestrant HD vs fulvestrant IAD	1st–2nd
EFECT	Chia et al[51]	DB Phase III	693	Post	Fulvestrant LD vs exemestane	1st–2nd
FIRST	Robertson et al[69–71]	OL Phase II	205	Post	Fulvestrant HD vs anastrozole	1st
FALCON	Robertson et al[72]	DB Phase III	462	Post	Fulvestrant HD vs anastrozole	1st
		Fulvestrant + other endocrine agents				
FACT	Bergh et al[78]	OL Phase III	514	Pre/post	Fulvestrant LD + anastrozole vs anastrozole	1st
SWOG 0226	Mehta et al[79]	OL Phase III	694	Post	Fulvestrant LD + anastrozole vs anastrozole	1st
SoFEA	Johnston et al[80]	DB Phase III	723	Post	Fulvestrant LD + anastrozole vs fulvestrant LD + placebo Fulvestrant LD + placebo vs exemestane	1st–2nd
		Fulvestrant + inhibitors of growth-factor-receptor pathways				
CALGB 40302/ ALLIANCE	Burstein et al[87]	DB Phase III	295	Post	Fulvestrant HD + lapatinib vs fulvestrant HD + placebo	1st–2nd
		Fulvestrant + inhibitors of MAPK–ERK1/2 and PI3K–mTOR pathways				
SAKK 21/08	Zaman et al[90]	DB Phase II	46	Post	Fulvestrant HD + selumetinib vs fulvestrant HD + placebo	1st–2nd
BELLE 2	Baselga et al[95]	DB Phase III	1,147	Post	Fulvestrant HD + buparlisib vs fulvestrant HD + placebo	1st–2nd
BELLE 3	Di Leo et al[96]	DB Phase III	432 (2:1)	Post	Fulvestrant HD + buparlisib vs fulvestrant HD + placebo	2nd–4th
FERGI	Krop et al[98]	DB Phase II	168	Post	Fulvestrant HD + pictilisib vs fulvestrant HD + placebo	1st–4th
PrECOG 0102	Kornblum et al[102]	DB Phase II	131	Post	Fulvestrant HD + everolimus vs fulvestrant HD + placebo	1st–3rd
		Fulvestrant + CDK4/6 inhibitors				
PALOMA 3	Turner et al[104–109]	DB Phase III	521 (2:1)	Pre/post	Fulvestrant HD + palbociclib vs fulvestrant HD + placebo	1st–3rd
MONARCH 2	Sledge et al[111]	DB Phase III	669 (2:1)	Pre/post	Fulvestrant HD + abemaciclib vs fulvestrant HD + placebo	1st–2nd
		Fulvestrant + angiogenesis inhibitors and multitargeting tyrosine-kinase inhibitors				
LEA	Martín et al[117]	OL Phase III	380	Post	Fulvestrant HD or letrozole vs fulvestrant HD or letrozole + bevacizumab	1st
CTK1258A2210	Musolino et al[119]	DB Phase II	97	Post	Fulvestrant HD + dovitinib vs fulvestrant HD + placebo	1st–2nd

Notes: *Premenopausal patients also received a GnRH analog; **for advanced disease; ***disease progression while on or ≤12 months after the end of adjuvant endocrine therapy or ≤1 month after the end of endocrine therapy for advanced disease.
Abbreviations: ET, endocrine therapy; CBR, clinical benefit rate; PFS, progression-free survival; TTP, time to progression; OS, overall survival; DCR, disease-control rate; DB, double-blind; OL, open-label; IAD, initially approved dose; LD, loading dose; HD, high dose; MAPK, mitogen activated protein kinase; HER2, human epidermal growth factor receptor 2; GnRH, gonadotropin-releasing hormone; PI3K, phosphatidylinositol 3-kinase; mTOR, mammalian target of rapamycin; NA, not assessed; ERK, extracellular signal-regulated kinase; NS, not significant.

PD to prior ET***	Primary end point	CBR (%)	Median TTP/PFS (months)	HR (95% CI)	Median OS	HR (95% CI)
Yes	TTP	43.5 vs 40.9 (P=0.51)	5.5 vs 4.1	0.95 (0.82–1.10), P=0.48	NA	NA
Yes	TTP					
No	TTP	54 vs 62	6.8 vs 8.3	1.18 (0.98–1.44), P=0.088	36.9 vs 38.7	1.29 (1.01–1.64), P=0.04
		57 vs 63	8.2 vs 8.3	1.10 (0.89–1.36), P=0.39	39.3 vs 40.7	1.16 (0.88–1.54), P=0.30
Yes	PFS	45.6 vs 39.6	5.5 vs 6.5	0.80 (0.68–0.94), P=0.006	26.4 vs 22.3	0.81 (0.69–0.96), P=0.02
Yes	TTP	32.2 vs 31.5	3.7 vs 3.7	0.93 (0.819–1.133), P=0.65	NA	NA
No	CBR	72.5 vs 67.0 (P=0.386)	23.4 vs 13.1	0.66 (0.47–0.92), P=0.01	54.1 vs 48.4	0.70 (0.50–0.98), P=0.04
No	PFS	78 vs 74 (P=0.3045)	16.6 vs 13.8	0.797 (0.637–0.999), P=0.0486	NA	NA
Yes/no	TTP	55.0 vs 55.1 (P=0.99)	10.8 vs 10.2	0.99 (0.81–1.20), P=0.91	37.8 vs 38.2	1.0 (0.76–1.32), P=1.00
No	PFS	73 vs 70	15.0 vs 13.5	0.80 (0.68–0.94), P=0.007	47.7 vs 41.3	0.81 (0.65–1.00), P=0.05
Yes	PFS	34 vs 32 (P=0.75)	4.4 vs 4.8	1.00 (0.83–1.21), P=0.98	20.2 vs 19.4	0.95 (0.76–1.17), P=0.61
		32 vs 27 (P=0.27)	4.8 vs 3.4	0.95 (0.79–1.14), P=0.56	19.4 vs 21.6	1·05 (0.84–1.29), P=0.68
Yes	PFS	NA	4.7 vs 3.8	1.04 (0.82–1.33), P=0.37	30.0 vs 26.4	0.91 (0.68–1.21), P=0.25
Yes	DCR	NA	3.7 vs 5.6	NA	22.9 vs 19.4	NA
Yes	PFS	43.8 vs 42.0	6.9 vs 5.0	0.78 (0.67–0.89), P=0.00021	NA	NA
Yes	PFS	25 vs 15	3.9 vs 1.8	0.67 (0.53–0.84), P=0.0003	NA	NA
Yes	PFS	24.7 vs 17.7 (P=0.27)	6.6 vs 5.1	0.74 (0.52–1.06), P=0.096	NA	NA
Yes	PFS	NA	10.4 vs 5.1	0.60 (0.40–0.92), P=0.02	NA	NA
Yes	PFS	67 vs 40 (P<0.0001)	9.5 vs 4.6	0.46 (0.36–0.59), P<0.0001	NA	NA
Yes	PFS	72.2 vs 56.1 (P<0.001)	16.4 vs 9.3	0.553 (0.449–0.681), P<0.001	NA	NA
Yes/no	PFS	67 vs 77 (P=0.041)	14.4 vs 19.3	0.83 (0.65–1.06), P=0.126	51.8 vs 52.1	0.87 (0.58–1.32), P=0.518
Yes	PFS	NA	5.5 vs 5.5	0.68 (0.41–1.14), NS	NA	NA

toxicity. In an unplanned subgroup analysis, the combination was significantly better only in patients who had not received prior tamoxifen, although the interaction between the treatment arm and adjuvant endocrine therapy was not significant. The three-arm randomized trial Study of Faslodex with or without concomitant Arimidex vs Exemestane (SOFEA) trial compared fulvestrant LD plus anastrozole with fulvestrant LD plus placebo and with exemestane alone in 723 patients with HR-positive ABC who progressed after at least 12 months of adjuvant NSAI or at least 6 months of NSAI first-line treatment for ABC.[80] There were no differences in PFS among the three arms, but in a retrospective analysis patients with *ESR1* mutations showed better PFS with fulvestrant than with exemestane.[81] Based on these data, the combination of fulvestrant plus anastrozole may be offered to endocrine therapy-naïve patients.[8] Nevertheless its prescription is off-label in some countries, and the preferred fulvestrant combination is likely with other targeted agents.

Studies of combination therapy with drugs targeting growth-factor-receptor pathways

The cross talk between the ER pathway and several growth-factor-signaling pathways is a common mediator of endocrine resistance.[9] Fulvestrant, degrading ER, may block this cross talk and potentially work better than tamoxifen in HER2-over-expressing BC, and has shown some activity as monotherapy in HER2-positive, HR-positive BC.[82] Preclinical studies found that the combination of fulvestrant with EGFR, HER2, or pan-HER inhibitors may be synergistic and overcome or delay the development of fulvestrant resistance,[83,84] although clinical experiences with these combinations have been mostly disappointing. The EGFR inhibitor gefitinib has been combined with fulvestrant plus anastrozole in a small randomized Phase II neoadjuvant study, leading to a significant reduction in Ki67 after 3 weeks of therapy,[85] but the clinical utility of this combination seems limited.[86] The dual HER1–HER2 tyrosine-kinase inhibitor lapatinib did not improve results when added to fulvestrant in the randomized Phase III study CALGB 40302/Alliance in 295 patients with HR-positive ABC with any HER2 status pretreated with one or two lines of endocrine therapy for ABC and sensitive to previous AIs. Similar results were obtained in the small subgroup (18%) with HER2-positive disease.[87] The monoclonal antibody ganitumab, targeting the insulin-like growth factor receptor 1 (IGF-1R), did not improve PFS and worsened OS, when added to fulvestrant or exemestane in a randomized Phase II study.[88]

Studies of combination therapy with drugs targeting the MAPK–ERK1/2 and PI3K–Akt–mTOR pathways

Activation of signaling pathways downstream of growth-factor receptors, including MAPK–ERK1/2[89] and PI3K–Akt–mTOR,[10–12] is also implicated in endocrine resistance. MAPK–ERK1/2 phosphorylates AF1, leading to ligand-independent ER activation, and ERK1/2 activation is involved in fulvestrant resistance.[89] The activity and safety of the MAP2K MEK1/2 inhibitor selumetinib in combination with fulvestrant were assessed in a randomized, double-blind, Phase II clinical trial in postmenopausal women with HR-positive, HER2-negative ABC progressing after one line of endocrine therapy with an aromatase inhibitor.[90] The main end point, CB rate, was worse with selumetinib than with placebo.[91] A possible biological explanation of these results is that MEK inhibition reduces the activation of PTEN, leading to accumulation of phosphatidylinositol-3-phosphate and activation of Akt.[91]

Mutations of *PIK3CA*, the gene encoding the p110α catalytic subunit of PI3K, are the most frequent mutations in luminal BC and often lead to constitutive activity of the enzyme.[2] In preclinical studies, the combination of fulvestrant HD and PI3K inhibitors showed synergistic activity and delayed endocrine resistance.[92,93]

A combination of the pan-PI3K inhibitor buparlisib (BKM120) targeting all 4 isoforms of PI3K (α, β, γ, and δ) with fulvestrant HD[94] was compared with fulvestrant HD plus placebo in the randomized, double-blind, Phase III study BELLE-2 in 1,147 postmenopausal women with HR-positive, HER2-negative ABC progressing on or shortly after (≤12 months in the adjuvant and ≤1 month in the metastatic setting) prior AI.[95] Median PFS was 6.9 months with buparlisib and 5.0 months with placebo (hazard ratio 0.78, 95% CI 0.67–0.89; *P*=0.0002). In a planned exploratory subgroup analysis, PFS was significantly longer in the buparlisib arm in patients with *PIK3CA* mutations detected in circulating tumor DNA (ctDNA), but not in those with wild-type *PIK3CA*. The companion randomized (2:1), double-blind, Phase III trial BELLE-3 compared fulvestrant HD plus buparlisib with fulvestrant HD plus placebo in 432 postmenopausal women with HR-positive, HER2-negative ABC pretreated with an AI and relapsing ≤30 days after the end of treatment with an endocrine agent in combination with an mTOR inhibitor (mostly everolimus).[96] As activation of mTOR elicits a negative feedback inhibiting PI3K and Akt, mTOR inhibition, releasing this negative feedback, leads to activation of PI3K and Akt, and ultimately to resistance to mTOR inhibitors.[97] The BELLE-3

trial aimed to assess the potential of PI3K inhibition to revert resistance to mTOR inhibitors and endocrine therapy. The combination of fulvestrant and buparlisib significantly improved PFS (median 3.9 versus 1.8 months, hazard ratio 0.67, 95% CI 0.53–0.84; one-sided P=0.0003). Benefit from buparlisib was greater in patients with *PIK3CA*-mutant tumors than in those with wild-type *PIK3CA*, either when PIK3CA status was assessed on ctDNA or on primary tumor tissue, although the treatment by PIK3CA status-interaction test was significant only for PIK3CA status assessed on tumor tissue. Buparlisib benefit was also marginally greater in patients with visceral disease than in those without and in patients who had no CB from previous mTOR inhibitor than in those who had CB. Despite the hints of efficacy, because of the toxicity of buparlisib (transaminitis, hyperglycemia, rash, mood disorders) the development of this regimen has been abandoned in favor of combinations with more selective, α-specific PI3K inhibitors.

Pictilisib, another pan-PI3K inhibitor, was evaluated in the randomized, double-blind, Phase II clinical trial FERGI comparing fulvestrant HD plus pictilisib with fulvestrant HD plus placebo in postmenopausal women with HR-positive, HER2-negative ABC resistant to AI.[98] Two cohorts of patients were recruited: 168 patients with any PIK3CA status and 61 with *PIK3CA*-mutant tumors. No significant differences in PFS or other end points were found between the two arms in both cohorts. Frequent dose modifications for toxicity could have reduced the efficacy of pictilisib. Studies are ongoing combining fulvestrant with α-specific PI3K inhibitors, which have been shown to be active on *PIK3CA*-mutant tumors, such as alpelisib[99] and taselisib.[100] In the double blind phase III Sandpiper study 516 postmenopausal patients with HR-positive, HER2-negative, PIK3CA mutated ABC, who had disease recurrence or progression during or after an aromatase inhibitor, were randomized 2:1 to fulvestrant plus taselisib (a beta-sparing PI3K inhibitor active on mutant PIK3CA) or fulvestrant plus placebo. Median PFS was 7.4 versus 5.4 months (hazard ratio 0.7, 95% CI 0.56–0.89, P=0.0037), respectively. This came at the cost of increased grade ≥3 and serious adverse events, mainly gastro-intestinal and hyperglycemia, attributed to partial delta and gamma PI3K isoforms inhibition.[101]

The pan-Akt allosteric inhibitor MK2206 has been tested in combination with anastrozole and/or fulvestrant in a Phase IB study, yielding a CB in eleven of 30 (36.7%) patients with HR-positive, HER2-negative ABC.[102] The mTOR inhibitor everolimus in combination with fulvestrant HD was compared with placebo plus fulvestrant HD in the randomized, double-blind, Phase II trial PrECOG 0102 in 130 postmenopausal women with HR-positive, HER2-negative

ABC progressing on AI. PFS was significantly improved from a median of 5.1 months with placebo to 10.4 months with everolimus (hazard ratio 0.61, 95% CI 0.40–0.92; P=0.02).[103]

Studies of combination therapy with drugs targeting the cyclin D–CDK4/6–Rb pathway

Alterations of genes involved in the cyclin D–CDK4/6–Rb pathway are frequent in BC and contribute to endocrine resistance.[2,15,93] CDK4/6 inhibitors are active particularly in luminal BC cell lines, synergize with endocrine agents, and contribute to overcome or delay endocrine resistance.[14,104] Three CDK4/6 inhibitors have undergone clinical development: palbociclib, ribociclib, and abemaciclib. In the randomized, double-blind, Phase III PALOMA-3 trial, 521 women with HR-positive, HER2-negative ABC progressing during or shortly after (≤12 months in the adjuvant and ≤1 month in the metastatic setting) prior endocrine therapy were randomized 2:1 to palbociclib plus fulvestrant HD versus placebo plus fulvestrant HD, with premenopausal women receiving also a GnRH agonist.[105,106] Seventy-nine percent of patients had acquired endocrine resistance and 21% had primary resistance. Median PFS was 9.5 months with palbociclib versus 4.6 months with placebo (hazard ratio 0.46, 95% CI 0.36–0.59; P<0.0001). The OR rate, time to response, and CB rate were also significantly improved. Benefit was independent of the degree of endocrine sensitivity, menopausal status,[107] visceral metastases,[108] *PIK3CA*, and *ESR1* status (mutated vs wild-type).[81] AEs were more frequent with the combined treatment, particularly leuconeutropenia, but toxicity was manageable[109] and quality of life (QoL) better in the palbociclib arm.[110] Results from the PALOMA-3 trial have led to the approval of the combination of fulvestrant plus palbociclib (plus a GnRH agonist in premenopause) in women with HR-positive, HER2-negative ABC who have received prior endocrine therapy.

A combination of fulvestrant and palbociclib with trastuzumab and pertuzumab (plus GnRH agonist in premenopause) has been explored as neoadjuvant treatment in a Phase II trial in patients with HER2-positive, ER-positive early, or local ABC, with reduction in Ki67 as the main end point.[111] In 30 evaluable patients, geometric mean Ki67 expression significantly decreased from 31.9 at baseline to 4.3 at week 2 (assessed on tumor biopsies) and was 12.1 at surgery. Clinical OR was achieved in 97% of patients, and the rate of pathological complete response in the breast and axilla was 27%, highlighting the potential of chemotherapy-free regimens to induce tumor eradication in some cases.

Table 2 Selected ongoing clinical trials with fulvestrant in breast cancer

ClinicalTrials.gov ID (other ID)	Main inclusion criteria	Design	Treatment		
Neoadjuvant setting					
NCT02955394 (16-1042.cc)	HER2−/ER+/AR+ postmenopausal LABC	Phase II, randomized (2 arms), open-label	Enzalutamide + fulvestrant	Fulvestrant	
NCT03236974 (D6090C00002)	HER2−/ER+ postmenopausal EBC	Phase I, randomized (2 arms), open-label	Fulvestrant	AZD9496	
NCT02760030 (OSU-15266)	HER2−/HR+ vulnerable or frail EBC	Phase II, single arm, open-label	Palbociclib + fulvestrant		
NCT03447132 (ICRG1201; SAFIA)	HER2−/HR+ EBC	Phase III, randomized (2 arms), double-blind	Palbociclib + fulvestrant	Placebo + fulvestrant	
Metastatic setting					
NCT02953860 (16-1001.cc)	HER2−/HR+ MBC	Phase II, single arm, open-label	Enzalutamide + fulvestrant		
NCT03393845 (BTCRC-BRE16-042)	HER2−/HR+ LABC or MBC	Phase II, single arm, open-label	Pembrolizumab + fulvestrant		
NCT03056755 (CBYL719X2402)	HER2−/HR+ MBC progressed on CDK4/6 inhibitor	Phase II, nonrandomized (2 cohorts), open-label	Alpelisib + fulvestrant	Alpelisib + letrozole	
NCT03294694 (17-285)	HER2−/HR+ MBC	Phase I, nonrandomized (2 cohorts), open-label	PDR001 + ribociclib	PDR001 + ribociclib + fulvestrant	
NCT03344536 (17-379)	HER2−/HR+ MBC with FGFR amplifications	Phase IB–II, single-group assignment, open-label	Debio 1347 + fulvestrant		
NCT03238196 (VICC BRE 16126)	HER2−/HR+ FGFR amplified postmenopausal MBC	Phase IB, single-arm, open-label	Erdafitinib + palbociclib + fulvestrant		
NCT03241810 (MM-121-02-02-10; SHERBOC)	HER2−/HR+ heregulin positive postmenopausal MBC	Phase II, randomized (2 arms), double-blind	Seribantumab + fulvestrant	Placebo + fulvestrant	
NCT02964507 (201973)	HER2−/HR+ MBC	Phase I–II, single-arm open-label (Phase I) followed by randomized (2 arms) double-blind (Phase II)	GSK525762 + fulvestrant (Phase I)	GSK525762 + fulvestrant (Phase II)	Placebo + fulvestrant (Phase II)
NCT02049957 (C31001)	HER2−/ER+ postmenopausal MBC	Phase IB–II, nonrandomized (2 arms), open-label	MLN0128 + exemestane	MLN0128 + fulvestrant	
NCT03425838 (BOOG 2017-03; SONIA)	HER2−/HR+ LRBC or MBC	Phase III, randomized (2 arms), open-label	NSAI + CDK4/6 inhibitor (first line) followed by fulvestrant (second line)	NSAI (first line) followed by fulvestrant + CDK4/6 inhibitor (second line)	
NCT02763566 (I3Y-CR-JPBQ; MONARCH plus)	HER2−/HR+ postmenopausal LRBC or MBC	Phase III, randomized (4 arms), double-blind	Abemaciclib + NSAI / Placebo + NSAI	Abemaciclib + fulvestrant / Placebo + fulvestrant	
NCT03289039 (17-318)	HER2+/ER+ MBC	Phase II, randomized (2 arms), open-label	Neratinib + fulvestrant	Neratinib	
NCT02983071 (GIT38-02)	HER2−/HR+ LABC or MBC after endocrine failure	Phase I–II, nonrandomized (2 dosing cohorts), open-label	GIT38 (CDK4/6 inhibitor) + fulvestrant		
NCT02684032 (B2151009)	HER2−/ER+ MBC	Phase IB, nonrandomized (2 cohorts), open-label	Gedatolisib + palbociclib + letrozole	Gedatolisib + palbociclib + fulvestrant	
NCT03322215 (PASIPHAE)	HER2−/HR+ postmenopausal endocrine-resistant LABC or MBC	Phase II, randomized (2 arms), open-label	Palbociclib + fulvestrant	Capecitabine	

Trial	Population	Study design	Treatment arms	Additional arms
NCT02756364 (C31006)	HER2-/HR+ MBC progressed on AI	Phase II, single-arm, open-label	MLN0128 + fulvestrant	
NCT02028507 (PEARL)	HER2-/ER+ postmenopausal MBC	Phase III, randomized (2 cohorts), open-label	Exemestane + palbociclib (cohort I) Fulvestrant + palbociclib (cohort II)	Capecitabine (cohort I) Capecitabine (cohort II)
NCT02028507 (GEICAM/2013-02; PEARL)	HER2-/HR+ postmenopausal AI-resistant MBC	Phase III, randomized (2 cohorts), open-label	Palbociclib + exemestane (cohort I) Palbociclib + fulvestrant (cohort II)	Capecitabine (cohort I) Capecitabine (cohort II)
NCT03007979 (201612098)	HER2-/HR+ MBC	Phase II, nonrandomized (2 arms), open-label	Palbociclib (with alternative dosing schedule) + letrozole	Palbociclib (with alternative dosing schedule) + fulvestrant
NCT02530411 (2014/VCC/0013; FURVA)	HER2-/ER+ postmenopausal AI-resistant MBC	Phase II, randomized (2 arms), double-blind	Vandetanib + fulvestrant	Fulvestrant
NCT03280563 (CO39611; MORPHEUS)	HER2-/HR+ postmenopausal LABC or MBC	Phase IB-II, randomized (4 arms) open-label (stage 1), single-arm, open-label (stage 2)	Fulvestrant (stage 1) Atezolizumab + cobimetinib (stage 1) Atezolizumab + ipatasertib + fulvestrant (stage 1)	Atezolizumab + fulvestrant (stage 1) Atezolizumab + bevacizumab + fulvestrant or other endocrine therapy (stage 2)
NCT02057133 (I3Y-MC-JPBH)	MBC	Phase IB, nonrandomized (different groups), open-label	Abemaciclib + letrozole or anastrozole or tamoxifen or exemestane or everolimus or trastuzumab or LY3023414 + fulvestrant	
NCT02947685 (AFT-38; PATINA)	HER2+/HR+ MBC	Phase III, randomized (2 arms), open-label	Palbociclib + trastuzumab/pertuzumab + letrozole or anastrozole or exemestane or fulvestrant	Trastuzumab/pertuzumab + letrozole or anastrozole or exemestane or fulvestrant
NCT02384746 (D13036)	HER2-/ER+ postmenopausal LABC or MBC progressed on fulvestrant	Phase I, single-arm, open-label	MLN9708 + fulvestrant	
NCT02860000 (MC1431)	HER2-/ER+ postmenopausal endocrine-resistant LABC or MBC	Phase II, randomized (2 arms), open-label	Alisertib + fulvestrant	Alisertib
NCT03377101 (I0194)	HER2-/HR+ endocrine-resistant MBC	Phase II, randomized (2 arms), open-label	Copanlisib + palbociclib + fulvestrant	Palbociclib + fulvestrant
NCT02970682 (EVG001BC)	HER2-/ER+ MBC	Phase II, nonrandomized (3 cohorts), open-label	SFX01 + AI or tamoxifen or fulvestrant	
NCT03147287 (17-101; PACE)	HER2-/HR+ LRBC or MBC previously exposed to CDK4/6 + endocrine therapy	Phase II, randomized (3 arms), open-label	Palbociclib + fulvestrant Palbociclib + avelumab + fulvestrant	Fulvestrant
NCT03182634 (ICR-CTSU/2015/10056; plasma MATCH)	LRBC or MBC where the targetable mutation is identified through ctDNA	Phase II, nonrandomized (4 cohorts), open-label	Fulvestrant Neratinib + fulvestrant	AZD5363 AZD5363 + fulvestrant
NCT03430466 (kbcrnb001)	HER2-/HR+ menopausal EBC	Phase II, single arm, open-label	Durvalumab + tremelimumab + fulvestrant	

Notes: When not specified, studies enrolled pre-, peri- (with ovarian suppression), and post-menopausal patients. New drug classes: alisertib, aurora A kinase inhibitor; AZD5363, pan-Akt inhibitor; AZD9496, nonsteroidal oral SERD; copanlisib, pan-class I PI3K inhibitor; Debio 1347, pan-FGFR inhibitor; erdafitinib, pan-FGFR inhibitor; GIT38, CDK4/6 inhibitor; gedatolisib, PI3K/mTOR inhibitor; GSK525762, BET inhibitor; ipatasertib, pan-Akt inhibitor; LY3023414, PI3K/mTOR inhibitor; MLN0128, mTORC1/2 inhibitor; MLN9708 (ixazomib), proteasome inhibitor; PDR001, anti-PD-1 antibody; seribantumab, anti-ErbB3 antibody; SFX01, antioxidant; vandetanib, inhibitor of VEGFR, EGFR and RET.
Abbreviations: EBC, early breast cancer; LABC, locally advanced BC; LRBC, locoregionally recurrent BC; MBC, metastatic breast cancer; AI, aromatase inhibitor; ER, estrogen receptor; FGFR, fibroblast growth factor receptor; ctDNA, circulating tumor DNA; HER2, human epidermal growth factor receptor 2; AR, androgen receptor.

The randomized (2:1), double-blind, Phase III clinical trial MONARCH 2 compared fulvestrant HD plus abemaciclib with fulvestrant HD plus placebo in 669 women with HR-positive, HER2-negative ABC progressing during or ≤12 months after the end of adjuvant endocrine therapy or during first-line endocrine therapy for ABC, 25% of whom had primary endocrine resistance.[112] Median PFS was 16.4 months with abemaciclib versus 9.3 months with placebo (hazard ratio 0.553, 95% CI 0.449–0.681; *P*<0.001). The OR rate in patients with measurable disease was 48.1% with abemaciclib and 21.3% in the placebo arm (*P*<0.001). Benefit from abemaciclib was independent of type of endocrine resistance. Abemaciclib added some toxicity, particularly in terms of diarrhea and neutropenia, albeit manageable. Based on these results, abemaciclib has been approved by the US Food and Drug Administration (and is under evaluation by the European Medicines Agency) in combination with fulvestrant for treatment of women with HR-positive, HER2-negative ABC with disease progression following endocrine therapy. In the recently published double blind phase III Monaleesa-3 study 726 post-menopausal patients with HR-positive, HER2-negative ABC, who were treatment-naïve for ABC or had received up to one line of endocrine therapy for ABC, were randomized 2:1 to fulvestrant plus ribociclib or fulvestrant plus placebo. Median PFS was 20.5 months versus 12.8 months (hazard ratio 0.593, 95% CI 0.480–0.732, *P*<0.001), respectively, and ORR was also improved. Results were similar in patients treatment-naïve and in those pretreated with endocrine therapy for ABC. The combination of ribociclib plus fulvestrant represents therefore another option for first- or second-line treatment in HR-positive, HER2-negative ABC.[113]

Preclinical studies show the potential efficacy of a triple combination with an endocrine agent plus a CDK4/6 inhibitor and a PI3K inhibitor, both in vitro and in patient-derived tumor xenografts.[114,115] Phase IB/II studies are exploring such triple-drug combination with fulvestrant, ribociclib, and PI3K inhibitors (eg, alpelisib and buparlisib)[116] or PI3K/mTOR inhibitors (eg, gedatolisib)[117] (Table 2).

Studies of combination therapy with angiogenesis inhibitors and multitargeting tyrosine-kinase inhibitors

The combination of an endocrine agent, either fulvestrant or letrozole, with the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab was compared with endocrine therapy alone in the randomized, open-label, Phase III trial letrozole/fulvestrant and avastin

(LEA) in 374 postmenopausal women with HR-positive, HER2-negative ABC in a first-line metastatic setting. The combination failed to improve PFS significantly, which was the primary end point, although there was an improvement in OR and CB rates.[118] Similarly, the multitargeting tyrosine-kinase inhibitor vandetanib, inhibiting VEGFR2, EGFR, and RET (rearranged during transfection), was tested in a randomized, double-blind, Phase II trial in combination with fulvestrant in postmenopausal patients with bone-predominant, HR-positive metastatic BC, with no improvement in bone-turnover markers or PFS or CB rates.[119] The efficacy of the multitargeting tyrosine-kinase inhibitor dovitinib, inhibiting the fibroblast growth factor receptors (FGFRs) 1–3, VEGFR1–3, and other tyrosine-kinase receptors in combination with fulvestrant was assessed in a randomized, double-blind, Phase II study in postmenopausal patients with HR-positive, HER2-negative ABC that had progressed during or after prior endocrine therapy.[120] Patients were stratified by FGF pathway-amplification status (amplification of FGFR1, 2, and/or 3 versus no amplification), with subset analyses conducted according to a Bayesian design. The study was closed in advance after recruitment of 31 patients with FGF-pathway amplification and 66 without, due to low frequency of FGF pathway-amplified cases. In the full population, the PFS hazard ratio of 0.68 (95% CI 0.41–1.14) favoring dovitinib did not meet the criteria for superiority, and the same held true in the FGF pathway-unamplified subgroup (PFS hazard ratio 0.69). On the contrary, the PFS hazard ratio of 0.64 (95% CI 0.22–1.86) favoring dovitinib in the FGF pathway-amplified subgroup met the efficacy criteria. Dovitinib thus had promising activity in the FGF pathway-amplified subgroup, although the small sample precludes definitive conclusions, and efficacy in the FGF pathway-unamplified subgroup cannot be excluded.

Combination with other agents

In a Phase II randomized trial, bortezomib added to fulvestrant led to marginal improvement in PFS over fulvestrant alone.[121] Preclinical studies have shown synergism among fulvestrant and several chemotherapeutic agents,[122,123] and a single-arm Phase II trial of fulvestrant plus metronomic capecitabine reported a median PFS of 15 months.[124]

Safety and tolerability

Fulvestrant is well tolerated. The CONFIRM study[65] reported the following grade 1–4 AEs with fulvestrant HD: gastrointestinal 20.2%, joint disorders 18.8%, injection-site reactions 13.6%, hot flashes 8.3%, urinary tract infection 2.2%,

ischemic cardiovascular disorders 1.4%, thromboembolic events 0.8%, vaginitis 0.8%, osteoporosis 0.3%, and weight gain 0.3%. Grade ≥3 AEs were gastrointestinal disturbances 2.2%, joint disorders 2.2%, thromboembolic events 0.6%, injection-site reactions 0.3%, and urinary tract infection 0.3%. Serious AEs (SAEs) occurred in 9.7% of patients, but only 2.2% were causally related to the study treatment, and grade 5 SAEs occurred in 1.4% of patients.[66] Comparing fulvestrant with anastrozole, data from the FALCON study showed a similar rate of SAEs (13%). Grade ≥3 AEs were reported in 22% of patients receiving fulvestrant and 18% of those receiving anastrozole, and grade 5 AEs were 3% in both arms and not deemed causally related to treatment. The rate of arthralgia/back pain was 26% with fulvestrant and 18% with anastrozole.[72] Other AEs were fatigue, hypertension, headache, insomnia, transaminitis, cough, anemia, dyspnea, and peripheral edema.

Patient-focused perspectives, such as QoL, patient satisfaction/ acceptability, adherence, and uptake

The good tolerability and efficacy of fulvestrant lead to maintained QoL. In the FALCON trial, health-related QoL, measured by the Trial Outcome Index (TOI) and the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) total score, showed similar improvements in approximately a third of patients in the fulvestrant and anastrozole arms, and the time to deterioration did not differ significantly between arms.[125] Similarly, no significant differences were found between fulvestrant and exemestane in terms of QoL in the EFECT trial.[51] On the other hand, in PALOMA-3, adding palbociclib to fulvestrant significantly delayed the deterioration of global QoL and pain.[110] In the CONFIRM trial, no differences were found in TOI scores between the two fulvestrant dosages.[65] Treatment compliance with fulvestrant may be supported by its monthly IM administration, often provided at outpatient clinics, although patient preference for IM compared with oral administration has not been assessed and could change from patient to patient and over time.

Conclusion

Fulvestrant, the first SERD approved for clinical use in HR-positive ABC, is the single most active endocrine agent in untreated postmenopausal patients in the first-line metastatic setting, and is particularly suitable for combination therapy, due to the lack of significant drug interactions. It has more recently been approved for treatment in combination with the CDK4/6 inhibitors palbociclib (plus a GnRH agonist in premenopause) or abemaciclib (for the moment only in the US) in women with HR-positive, HER2-negative ABC who have received prior endocrine therapy.

Fulvestrant is now indicated as one of the first lines of endocrine therapy for ABC by all major guidelines, although the preferred sequence of endocrine agents in the metastatic setting has not been defined and may vary from patient to patient. Among the available drugs, those more commonly considered for first-line therapy in postmenopause are fulvestrant alone, AIs alone, and AIs plus CDK4/6 inhibitors. While CDK4/6 inhibitors have shown benefit, when added to an AI, in all subgroups, the real need for a combination treatment in all patients at the frontline is questioned, and the choice should consider disease-related (eg, disease-free interval, biological features, number and site of metastases), patient-related (performance status, age, comorbidity, patient preferences, compliance), and treatment-related (toxicity, suitability, acceptability) aspects. For postmenopausal patients relapsing during or shortly after (≤12 months) adjuvant AI therapy, fulvestrant plus palbociclib is a logical choice. For those with de novo ABC and those not pretreated with an AI or relapsing >1 year from the end of adjuvant AI, frontline treatment could be an AI plus CDK4/6 inhibitor, or also fulvestrant alone or even an AI alone in selected cases. As fulvestrant has been studied mainly in postmenopausal patients, its use in premenopause requires the association with a GnRH analog and regulatory aspects may vary in different countries. Further roles for fulvestrant are anticipated in combination with other targeted therapies like inhibitors of the PI3K–Akt–mTOR pathway. Meanwhile, new oral SERDs are being developed and will likely be licensed in the next few years.

Disclosure

AR has acted in an advisory role for Pfizer Pharmaceutical and received travel and accommodation expenses and speaker honoraria from Roche and Novartis. The other authors report no conflicts of interest in this work.

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