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Review of hormone-based treatments in postmenopausal patients with advanced breast cancer focusing on aromatase inhibitors and fulvestrant

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ABSTRACT

Background: Endocrine therapy constitutes a central modality in the treatment of oestrogen receptor (ER)-positive advanced breast cancer.

Purpose: To evaluate the evidence for endocrine treatment in postmenopausal patients with advanced breast cancer focusing on the aromatase inhibitors, letrozole, anastrozole, exemestane and fulvestrant.

Methods: A review was carried out using PubMed. Randomised phase II and III trials reporting on ≥100 patients were included.

Results: 35 trials met the inclusion criteria. If not used in the adjuvant setting, a non-steroid aromatase inhibitor was the optimal first-line option. In general, the efficacy of the different aromatase inhibitors and fulvestrant was similar in tamoxifen-refractory patients. A randomised phase II trial of palbociclib plus letrozole versus letrozole alone showed significantly increased progression-free survival (PFS) when compared with endocrine therapy alone in the first-line setting (20.2 vs 10.2 months). Furthermore, the addition of everolimus to exemestane in the Breast Cancer Trials of OraL EveROlimus-2 (BOLERO-2) study resulted in an extension of median PFS by 4.5 months after recurrence/progression on a non-steroid aromatase inhibitor. However, overall survival was not significantly increased.

Conclusion: Conventional treatment with an aromatase inhibitor or fulvestrant may be an adequate treatment option for most patients with hormone receptor-positive advanced breast cancer. Mammalian target of rapamycin (mTOR) inhibition and cyclin-dependent kinase 4/6 (CDK4/6) inhibition might represent substantial advances for selected patients in some specific settings. However, there is an urgent need for prospective biomarker-driven trials to identify patients for whom these treatments are cost-effective.

INTRODUCTION

Breast cancer is strongly related to age. The highest incidence rates are found in older, postmenopausal women. Approximately 70–80% of breast cancers are oestrogen and/or progesterone receptor (ER/PGR) positive and, thus, potentially sensitive to endocrine therapy.[1]

After menopause, about 90% of the total body oestrogens are synthesised by aromatisation of androstenedione into oestrone, and the production may be blocked by aromatase inhibitors (AIs). The first AI with documented antitumour efficacy was aminoglutethimide. Following this, second-generation and third-generation AIs have been developed. The third-generation inhibitors including letrozole, anastrozole and exemestane have increased potency associated with better clinical efficacy compared with aminoglutethimide or the second-generation inhibitor fadrazole.[2] Pharmacologically, AIs may be subdivided into two classes: non-steroidal AI (NSAI) represented by letrozole and anastrozole, and steroidal AI (SAI) represented only by exemestane. Both groups of AIs block aromatase activity: NSAIs inhibit the aromatase in a reversible manner by binding to the haem moiety of the enzyme, thus preventing androgens from binding to the catalytic site. SAIs bind covalently to the substrate binding site of the aromatase, irreversibly inactivating the enzyme.[2] Apart from AIs, endocrine treatment consists of the selective ER modulator (SERM) tamoxifen and the pure antioestrogen fulvestrant. Tamoxifen has mixed agonistic and antagonistic activity, depending on the target tissue. In contrast, fulvestrant is a complete ER antagonist which in addition introduces a conformational change leading to monomers degrading ER,[3–5] theoretically overcoming resistance driven by the agonist properties of tamoxifen.

The purpose of this review was to evaluate outcome in clinical trials performed in postmenopausal patients with advanced breast cancer treated with various endocrine

regimens, including letrozole, anastrozole, exemestane and fulvestrant.

METHODS

No review protocol exists. However, before initiating the review, we decided on a search strategy in which PubMed was searched for human studies using the 'clinical trial' filter and the following search terms: AI, endocrine therapy and advanced/metastatic breast cancer. In addition, we searched for the specific drugs. Papers from 1980 and onwards were included. In total, 535 articles were identified. Subsequently, we applied the following exclusion criteria: phase I and non-randomised phase II trials, dose-finding studies, studies on first-generation or second-generation AIs, trials including <100 patients, studies reporting on various antihormonal treatments in which it was not possible to distinguish between the different outcomes, preclinical studies and reviews. Articles on exploratory subgroup analyses and studies evaluating the compounds in premenopausal women or including premenopausal and postmenopausal patients were also excluded. Fully published, randomised phase II or III trials in English were included. Full articles were obtained and references were checked for additional material when appropriate. The reference list was updated in October 2015.

Two authors (IK and DLN) independently surveyed the literature. In case of unclarity, a verdict was reached by consensus.

RESULTS

A total of 35 trials were included in the present review.

Studies comparing AIs or fulvestrant with an antioestrogen, megestrol acetate or a first-generation AI

In total, 11 trials were identified, including 1 phase II–III and 10 phase III trials. Results are presented in table 1.

First-line therapy

NSAIs versus tamoxifen

Three phase III studies compared anastrozole with tamoxifen as first-line therapy. The Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability (TARGET) trial including 668 women (43% known hormone receptor (HR) positive) found the two treatments to be equivalent regarding response rate (RR) and time to progression (TTP).[6] The North American Multicenter Randomized trial (NAT) trial included 353 patients among which almost 90% were HR positive. The RR was similar in the two arms; however, anastrozole had a significant advantage over tamoxifen in terms of a nearly doubling of TTP.[7] The two studies had a similar design and were prospectively planned for a combined analysis. Among all included patients, TTP was similar in the two groups. However, a subgroup analysis among HR-positive patients (~60%) revealed a TTP of 10.7 months in the anastrozole group compared with 6.4 months in the tamoxifen group (p=0.022). Median time to death was 40.8 and 41.3 months, respectively.[8 9] Crossover was not preplanned in these studies.

A third trial in ER-positive, hormonal therapy-naïve patients showed significant advantage of anastrozole regarding clinical benefit rate (CBR), TTP and median time to death.[10]

The P025 trial of letrozole versus tamoxifen in 907 patients showed superiority of letrozole, regarding RR and TTP. The findings were irrespective of prior adjuvant antioestrogen treatment.[11 12] The overall survival (OS), however, was not statistically different.[13] Approximately half of the patients in each arm crossed over to the other agent on progression. Thus, OS results might have been confounded. Indeed, a planned statistical analysis 2 years after randomisation showed a 62% vs 57% survival in the letrozole and tamoxifen group, respectively (p=0.0246).[14]

SAI versus tamoxifen

A phase II/III trial comparing exemestane with tamoxifen showed an increased RR after exemestane and early significant differences in progression-free survival (PFS) (Wilcoxon p=0.028). However, this early finding did not translate into a significant benefit in PFS or OS.[15 16]

Fulvestrant (250 mg) versus tamoxifen

A phase III non-inferiority trial including 587 patients compared fulvestrant (250 mg) with tamoxifen. Approximately 78% of the patients were HR positive and ~25% had received adjuvant tamoxifen prior to inclusion. Overall RR and TTP were not significantly different. In addition, a prospectively planned analysis of patients with known HR-positive status showed equal efficacy of the drugs. Estimated OS was 36.9 months in the fulvestrant group and 38.7 months in the tamoxifen group (HR 1.29; p=0.04).[17] In the subgroup of patients who had received adjuvant tamoxifen, the results were similar to those of the whole population.

First-line or second-line therapy

NSAIs versus megestrol acetate

Two phase III trials compared two doses of anastrozole with megestrol acetate in patients who had progressed after tamoxifen. RRs were comparable and no significant difference between the two anastrozole regimens and megestrol acetate regarding TTP and OS on an initial analysis was found.[18 19] However, a planned subsequent analysis found anastrozole 1 mg to be associated with significantly increased OS compared with megestrol acetate (26.7 vs 22.5 months; p<0.025).[20]

Two different doses of letrozole were compared with megestrol acetate as second-line therapy in women previously treated with antioestrogen in two phase III trials. The first study included 602 women (80–85% HR positive). RR was not significantly different among the three treatment regimens. However, patients treated with letrozole 0.5 mg had a significantly longer TTP (5.6 vs

Table 1 Summary of randomised phase II and III studies comparing third-generation aromatase inhibitors or fulvestrant with an antioestrogen, megestrol acetate or a first-generation aromatase inhibitor

Reference	Treatment*	Number of patients	Patient population	Phase	Prior endocrine therapy	Prior chemotherapy for ABC	RR (%) (95% CI)	SD (%) (95% CI)	TTP/PFS (median; months) (95% CI)	OS (median; months) (95% CI)
First-line therapy										
NSAIs vs tamoxifen										
Bonneterre *et al*[6 8]	Anastrozole	340	ER/PGR+ (UK 54/56%)	III (TARGET)	None: 89/88%; >12 months adj	None	32.9	23.2	8.2; ER/PGR+: 8.9	NR
	Tamoxifen	328			TAM: 11/12%		32.6	22.9	8.3 (p=0.941); ER/PGR+: 7.8	
Nabholtz *et al*[7 9]	Anastrozole	171	ER+ (UK 11/11%)	III (NAT)	None: 82/79%; >12 months adj TAM: 18/21%	None	21	38.0	11.1	NR
	Tamoxifen	182					17	28.6	5.6 (p=0.005)	
Milla-Santos *et al*[10]	Anastrozole	121	ER+	III	None	None	35	47	18.0	17.4
	Tamoxifen 40 mg	117					26 (p=0.172)	29	7.0 (HR 0.13; p<0.01)	16.0 (HR 0.64; p=0.003)
Mouridsen *et al*[12–14]	Letrozole	453	ER/PGR+ (UK 34/33%)	III	None: 81/82% >12 months adj	≤1	30	49 (44 to 54) (CBR)	9.4	34
	Tamoxifen	454			TAM: 19/18%		20 (OR 1.71; 1.26 to 2.31; p=0.0006)	38 (34 to 43)	6.0 (p=0.0001)	30 (p=0.53)
SAI vs tamoxifen										
Paridaens *et al*[15 16]	Exemestane	182	Hormone receptor+ (UK 8/5%)	II/III	None: 79/61%; >6 months adj TAM: 21/21%	≤1	46	29.7†	9.9 (8.7 to 11.8)	p=0.821
	Tamoxifen	189					31 (OR 1.85; 1.21 to 2.82; p=0.005)	35.4	5.8 (5.3 to 8.1) (HR 0.84; p=0.121)	
Fulvestrant vs tamoxifen										
Howell 2004 *et al*[17]	Fulvestrant 250 mg	313	ER/PGR+ (UK 18/20%; ER−/PGR− 1/1%)	III	None: 78/75%; >12 months adj TAM: 22/25%	None	31.8	54.3† (CBR)	6.8	36.9 (estimated)
	Tamoxifen	274					33.9 (OR 0.87; 0.61 to 1.24; p=0.45)	62.0 (p=0.026)	8.3 (HR 1.18; p=0.088)	38.7 (HR 1.29; p=0.04)
First-line or second-line therapy										
NSAIs vs megestrol acetate										
Buzdar *et al*[18]	Anastrozole 1 mg	128	ER+ or prior sensitivity to TAM (UK 13/15/13%)	III	PD on antioestrogen‡; adj antioestrogen: 47/42/39%	≤1	10	27	5.6	NR
	Anastrozole 10 mg	130					6	24	4.7	
	Megestrol acetate	128					6	30	4.9	

Continued

Table 1 Continued

Reference	Treatment*	Number of patients	Patient population	Phase	Prior endocrine therapy	Prior chemotherapy for ABC	RR (%) (95% CI)	SD (%) (95% CI)	TTP/PFS (median; months) (95% CI)	OS (median; months) (95% CI)
Jonat *et al*[19]	Anastrozole 1 mg	135	ER/PGR+ (UK 34/39/	III	PD after/on TAM; adj TAM: 49/39	≤1	34.1	34.0 (CBR)	NR	NR
	Anastrozole 10 mg	118	38%)		/42%; first-line TAM: 51/61/58%		33.9	33.9		
	Megestrol acetate	125					32.8	32.8		
Buzdar *et al*[21]	Letrozole 0.5 mg	202	ER/PGR+ (UK 13/15/	III	PD on antioestrogen‡; adj	≤2	21 (15.2 to 26.4)	12.4	5.6 (3.3 to 6.3)	33.1 (26.7 to 39.4)
	Letrozole 2.5 mg	199	13%)		antioestrogen: 47/42/39%; first-line		16 (11.0 to 21.2)	10.6	3.2 (3.0 to 5.3)	26.6 (25.0 to 33.8)
	Megestrol acetate	201			antioestrogen: 53/58/61%		15 (10.0 to 19.9)	8.5	3.4 (3.0 to 5.6)	26.2 (21.7 to 29.9)
Dombernowsky *et al*[22]	Letrozole 0.5 mg	188	ER/PGR+ (UK 45/43/	III	PD on antioestrogen‡; adj	≤1	13 (p=0.004)	14.4	5.1 (p=0.02)	1.34 (risk ratio)
	Letrozole 2.5 mg	174	41%)		antioestrogen: 35/ 33/32%		24	10.9	5.6 (p=0.07)	0.82
	Megestrol acetate	189					16 (p=0.04)	15.3	5.5	1.12
SAI vs megestrol acetate										
Kaufmann *et al*[23]	Exemestane	366	ER/PGR+ (UK+or prior	III	PD on TAM‡; adj TAM: NR	≤1	15	37.4 (CBR)	4.5	Not reached
	Megestrol acetate	404	sensitivity to TAM (UK 33/32%)				012.4 (NS)	34.6 (NS)	3.7 (p=0.037)	27.4 (p=0.039)

For RR, SD, duration of TTP/PFS and OS, the number of decimals reported by the authors is given.
ER/PGR+, HER2: numbers are given when possible.
*Unless stated, doses of tamoxifen, megestrol acetate, anastrozole, letrozole and exemestane were 20, 160, 1, 2.5 and 25 mg, respectively.
†Duration of SD not reported; if not marked, duration of SD reported ≥24 weeks or 6 months.
‡Defined as relapse on adjuvant antioestrogen or within 12 months of stopping treatment or progression on first-line antioestrogen therapy.
ABC, advanced breast cancer; Adj, adjuvant; AI, aromatase inhibitor; CBR, clinical benefit rate; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; NR, not reported; NS, non-significant; NSAI, non-steroid aromatase inhibitor; PD, progressive disease; PFS, progression-free survival; PGR, progesterone receptor; RR, response rate; SAI, steroid aromatase inhibitor; TAM, tamoxifen; TARGET, Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability; TTP, time to progression; OS, overall survival; UK, unknown.

3.4 months) and a decreased risk of treatment failure compared with patients treated with megestrol acetate. Letrozole 0.5 mg showed a trend (p=0.053) towards a survival benefit.[21] The second study included 551 patients. The RR was significantly higher for letrozole 2.5 mg (24%) compared with letrozole 0.5 mg (13%) or megestrol acetate (16%). TTP for letrozole 2.5 mg was superior to letrozole 0.5 mg, but not to megestrol acetate. There was a significant dose effect on OS in favour of letrozole 2.5 mg (p=0.03) compared with letrozole 0.5 mg. The OS was similar in the letrozole 2.5 mg and megestrol acetate arms. However, letrozole was significantly better tolerated than megestrol acetate.[22]

SAI versus megestrol acetate

A randomised phase II trial comparing exemestane with megestrol acetate in patients who had experienced tamoxifen failure showed significantly increased TTP and OS in favour of exemestane.[23]

Studies comparing the individual AIs with each other or with fulvestrant, or combinations

A total of 12 trials were identified: one randomised phase II, nine phase III, one phase III–IV and one study with combined data from two phase III trials. Efficacy results are given in table 2.

First-line therapy

Exemestane versus anastrozole

One phase III trial compared exemestane with anastrozole in the first-line setting among 298 patients. RRs and TTP were identical in the two arms.[24] Likewise, a randomised phase II trial found the clinical activity of the two drugs to be equal.[25]

Fulvestrant (500 mg) versus anastrozole

The Fulvestrant First-Line Study Comparing Endocrine Treatments (FIRST) trial was a phase II trial comparing fulvestrant (500 mg) with anastrozole as first-line treatment. Approximately 25% of the patients had received adjuvant endocrine therapy (the number of patients receiving an AI was not reported).[26 27] RR and CBR were comparable in the treatment arms; however, TTP was 23.4 and 13.1 months, respectively, for fulvestrant and anastrozole, indicating superiority of fulvestrant to anastrozole in this setting. It should be noted that TTP was a secondary end point.

Combination therapy versus single agent

The Fulvestrant and Anastrozole Combination Therapy (FACT) trial compared fulvestrant+anastrozole with anastrozole in 514 women of whom approximately two-thirds had received adjuvant tamoxifen. TTP and OS were identical in the two arms.[28] The Southwest Oncology Group (SWOG) 0226 trial evaluated fulvestrant+anastrozole to anastrozole in 694 patients, of which ~40% had received adjuvant tamoxifen. In the anastrozole monotherapy arm, crossover to fulvestrant after progression was strongly encouraged. The median PFS was 15.0 months in the fulvestrant+anastrozole arm compared with 13.5 months in the anastrozole arm followed by fulvestrant arm (p=0.007). OS was 47.7 and 41.3 months, respectively (p=0.0049), despite the fact that 41% of patients crossed over to fulvestrant after progression.[29]

First-line or second-line therapy

Letrozole versus anastrozole

A phase IIIb/IV trial compared letrozole with anastrozole in patients who had progressed on first-line antioestrogen or were clinically resistant to adjuvant tamoxifen. TTP, the primary end point, was 5.7 months in both arms. However, RR was significantly higher in the letrozole arm (19.1% vs 12.3%; p=0.013).[30]

Fulvestrant (250 mg) versus AIs

Four studies comparing fulvestrant (250 mg) with anastrozole in the first-line or second-line setting were identified. All studies reported similar efficacy of the two drugs with regard to RR and TTP. No survival data were provided.[31–33]

The Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) trial compared fulvestrant (250 mg) with exemestane in patients who had progressed on an NSAI. In 60% of women, the agents were administered as third or higher lines of therapy. No significant difference in efficacy parameters was found.[34]

Combination therapy versus single agent

The Study of Faslodex with or without concomitant Arimidex vs Exemestane following progression on non-steroidal Aromatase inhibitors (SoFEA) trial compared fulvestrant (250 mg)+anastrozole or placebo with exemestane monotherapy in the first-line or second-line setting. A total of 723 patients, previously progressing on an NSAI, were included. No statistically significant differences in outcome were found.[35]

Studies of combinations of AI/fulvestrant and other drugs

Table 3 shows efficacy results of AI/fulvestrant in combinations with other drugs. Nine trials were identified, including five randomised phase II and four phase III studies. Most studies were performed in the first-line or second-line setting including patients known to be HR positive. Human epidermal growth factor receptor 2 (HER2) status was known in many of the studies, some excluding HER2-positive patients.

COX-2 inhibitor

One phase II and one phase III trial evaluated the addition of the cyclooxygenase-2 (COX-2) inhibitor celecoxib to exemestane versus exemestane alone. In both studies, patients were AI naïve. None of the studies found significant differences in PFS.[36 37] Thus, the addition of celecoxib did not add any clinically relevant benefit to exemestane.

Table 2 Summary of randomised phase II and III studies comparing the individual aromatase inhibitors with each other, with fulvestrant, or combinations

Reference	Treatment*	Number of patients	Patient population	Phase	Prior endocrine therapy	Prior chemotherapy for ABC	RR (%) (95% CI)	SD (%) (95% CI)	TTP/PFS (median; months) (95% CI)	OS (median; months) (95% CI)
First-line therapy										
Exemestane vs anastrozole										
Iwata *et al*[24]	Exemestane	149	ER/PGR+ (HER2− 94/94%)	III	None: 83/83%; >12 months adj TAM: 17/17%	None	43.8 (35.3 to 52.8)	31.1	13.8 (10.8 to 16.59	NR
	Anastrozole	149					39.1 (30.6 to 48.1)	38.3	11.1 (10.8 to 16.6)	
Llombart-Cussac *et al*[25]	Exemestane	51	ER/PGR+ (UK 0/4%)	II, randomised	None: 49/50%; >24 months adj TAMs: 51/50%	≤1	36.2 (18.5 to 45.9)	59.6 (CBR)	6.1 (2.4 to 9.6)	19.9 (15.32 to 24.46)
	Anastrozole	52					46.0 (32.2 to 59.8)	68	12.1 (7.3 to 16.8) (HR 1.13; p=0.558)	48.3 (18.3 to 78.3) (HR 1.33; p=0.296)
Fulvestrant vs anastrozole										
Robertson *et al*[26 27]	Fulvestrant 500 mg	102	ER/PGR+ (UK 1/3%) (HER2 2+/3+ 19/18%)	III (FIRST)	None: 72/78%; adj endocrine therapy: 28/22%	None	31.4	41.2	23.4	NR
	Anastrozole	103					31.1	35.0	13.1 (HR 0.66; p=0.01)	
Combination therapy vs single agent										
Bergh *et al*[28]	Fulvestrant 250 mg +anastrozole	258	ER/PGR+	III (FACT)	None: 30/34%; adj TAM: 70/67%; adj AI: 2/1%	None	31.8	55.0 (CBR)	10.8	37.8
	Anastrozole	256					33.6 (OR 0.92; p=0.76)	55.1 (OR 1.0; p=0.99)	10.2 (HR 0.99; p=0.91)	38.2 (HR 1.0; p=1.00)
Mehta *et al*[29]	Anastrozole +fulvestrant 250 mg	349	ER/PGR+ HER2+ 10/9%	III (SWOG 0226)	None: 60/60%; >12 months adj TAM: 40/40%	None	27	73†	15.0 (13.2 to 18.4)	47.7 (43.4 to 55.7)
	Anastrozole → fulvestrant (41%)	345					22 (p=0.26)	70 (p=0.39)	13.5 (12.1 to 15.1) (HR 0.80; p=0.007)	41.3 (37.2 to 45.0) (HR 0.81; p=0.049)
First-line or second-line therapy										
Letrozole vs anastrozole										
Rose *et al*[30]	Letrozole	356	ER/PGR+ (UK 21/8%)	IIIb/IV	PD‡ on antioestrogen; adj antioestrogen: number NR	≤1	19.1 (15.7 to 22.9)	7.9	5.7 (5.1 to 6.0)	NR
	Anastrozole	357					12.3 (9.6 to 15.6) (p=0.013)	10.6	5.7 (4.6 to 6.1) (p=0.92)	
Fulvestrant vs AIs										
Howell *et al*[31]	Fulvestrant 250 mg	222	ER/PGR+ or prior sensitivity to endocrine therapy (UK 23/16%)	III	PD on adj: 56/56%; PD on first-line endocrine therapy: 44/44% no prior AI	≤2	20.7	23.9	5.5	NR
	Anastrozole	229					15.7	29.3	5.1	

Continued

Table 2 Continued

Reference	Treatment*	Number of patients	Patient population	Phase	Prior endocrine therapy	Prior chemotherapy for ABC	RR (%) (95% CI)	SD (%) (95% CI)	TTP/PFS (median; months) (95% CI)	OS (median; months) (95% CI)
Xu *et al*[32]	Fulvestrant 250 mg +placebo	121	ER+	III	PD after adj: NR; PD on first-line antioestrogen therapy: NR	≤2	10	48.2† (CBR)	3.6	NR
	Anastrozole +placebo	113					14	36.1 (OR 0.608; p=0.117)	5.2 (HR 1.314; p=0.101)	
Robertson *et al*[33]	Fulvestrant 250 mg +placebo	206	ER/PGR+ or prior sensitivity to endocrine therapy (UK 6/8%) (ER/PGR− 7/5%)	III	PD on adj antioestrogen therapy: 56/50%; PD on first-line endocrine therapy: 44/50%	No criteria	17.5	24.8	5.4	NR
	Anastrozole +placebo	194					17.5	18.6	3.4 (HR 0.92; p=0.43)	
Robertson *et al*[33]	Fulvestrant 250 mg	428	ER/PGR+ or prior sensitivity to endocrine therapy (UK 15/12%) (ER/PGR− 5/5%)	Combined data from two phase III (0020 and 0021)	PD after adj endocrine therapy: 57/56%; PD on first-line endocrine therapy: 43/44%	NR	19.2	24.3	NR	NR
	Anastrozole	423					16.5 (p=0.32)	24.3		
Chia *et al*[34]	Fulvestrant 250 mg	351	ER/PGR+	III (EFECT)	PD on NSAI‡; 60% ≥2 lines	≤1	7.4	32.2 (CBR)	3.7	NR
	Exemestane	342					6.7 (OR 1.12; p=0.736)	31.5 (OR 1.03; p=0.853)	3.7 (HR 0.963; p=0.6531)	
Combination therapy vs single agent										
Johnston *et al*[35]	Fulvestrant +anastrozole	243	ER/PGR+ HER2− (HER2+ 7/6/7%) (HER2 UK 43/33/36%)	III (SoFEA)	PD on adj NSAI: 17/22/17% first-line NSAI: 83/78/83%	≤1	8	33	4.4 (3.4 to 5.4)	20.2 (17.2 to 22.5)
	Fulvestrant +placebo	231					8	31	4.8 (3.6 to 5.5)	19.4 (16.8 to 22.8)
	Exemestane	249					4 (NS)	23 (NS)	3.4 (3.0 to 4.6) (NS)	21.6 (19.4 to 23.9) (NS)

For RR, duration of TTP/PFS and OS, the number of decimals used by the authors is reported. ER/PGR+, HER2: % positive are given when possible.
*Doses of anastrozole, letrozole and exemestane were 1, 2.5 and 25 mg, respectively.
†Duration of SD not reported; if not marked, duration of SD reported ≥24 weeks or 6 months.
‡Defined as relapse on adjuvant NSAI or within 6 months of stopping treatment or by progression on NSAI for advanced breast cancer.
ABC, advanced breast cancer; Adj, adjuvant; AI, aromatase inhibitor; CBR, clinical benefit rate; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; NR, not reported; NS, non-significant; NSAI, non-steroid aromatase inhibitor; PD, progressive disease; PFS, progression-free survival; PGR, progesterone receptor; RR, response rate; TAM, tamoxifen; TTP, time to progression; OS, overall survival; UK, unknown.

Table 3 Summary of randomised phase II and III trials of endocrine therapy combined with other agents in patients with hormone receptor-positive metastatic breast cancer

Reference	Treatment*	Number of patient	Patient population	Phase	Prior endocrine therapy	Prior chemotherapy for ABC	RR (%)	SD (%)	TTP/PFS (median; months) (95% CI)	OS (median; months) (95% CI)
COX-2 inhibitor										
Dirix *et al*[37]	Exemestane +celecoxib	56	ER/PGR+ or prior sensitivity to hormone receptor therapy (UK 30/38%)	II, randomised	PD on TAM; adj TAM: 62/50%; first-line TAM: 38/50%; no prior AI	≤1	21.5	21.4	5.2	16.4
	Exemestane	55					20	23.6	4.4	16.5
Falandry *et al*[36]	Exemestane +celecoxib	74	ER/PGR+ (UK 7/6%) (HER2+ 4/5%)	III	None: 43/39%; adj TAM: 57/61%; no prior AI	None	24	55†	9.8	NR
	Exemestane +placebo	83					17 (p=0.18)	56	9.8 (p=0.72)	
mTOR inhibitor										
Baselga *et al*[39]; Piccart *et al*[40]	Exemestane +everolimus	485	ER+HER2−	III, BOLERO-2	Refractory NSAI‡; prior AI 100/100%; adj endocrine therapy: 28/28%; first-line endocrine therapy: 72/72%	≤1	7.0†	74.6§	10.6§	31.0
	Exemestane +placebo	239					0.4 (p<0.001)	64.4	4.1 (HR 0.36; p<0.001)	26.6 (p=0.14)
Wolff *et al*[42]	Letrozole +temsirolimus	555	ER+ (95/96%) HER2+ (18/23%)	III (HORIZON)	None: 57/60%; adj endocrine therapy: 43/40%	None	27	NR	8.9 (7.4 to 9.6)	Not estimable
	Letrozole +placebo	555					27		9.0 (7.2 to 9.4) (HR 0.90; p=0.25)	(HR 0.89; p=0.5)
HER1 inhibitor										
Carlson *et al*[45]	Anastrozole +gefitinib	72	ER/PGR +	II, randomised	None: 54/58%; adj endocrine therapy: 46/42%	≤2	25	19	5.3 (3.1 to 10.4)	30.3 (21.2 to 38.9+)
	Fulvestrant 250 mg +gefitinib	69					20	20	5.2 (2.9 to 8.2)	23.9 (15.4 to 33.5)
Martin *et al*[47]	Letrozole/fulvestrant +bevacizumab	190	Hormone receptor+ HER2−	III	None:48/47%; adj endocrine therapy: 52/53%	None	41	77 (CBR)	19.3 (16.5 to 22.1)	52.1
	Letrozole/fulvestrant	184					22	67	14.4 (11.4 to 17.5) (HR 0.83; p=0.126)	51.8 (HR 0.87; p=0.518)

Continued

Table 3 Continued

Reference	Treatment*	Number of patient	Patient population	Phase	Prior endocrine therapy	Prior chemotherapy for ABC	RR (%)	SD (%)	TTP/PFS (median; months) (95% CI)	OS (median; months) (95% CI)
Histone deacetylase inhibitor										
Yardley *et al*[48]	Exemestane +entinostat	64	ER+	II, randomised	PD on NSAI¶; adj endocrine therapy: 52/48%; first-line endocrine therapy: 84/86%	≤1	6.3	28.1† (CBR)	4.3 (3.3 to 5.4)	28.1 (21.2- not reached)
	Exemestane +placebo	66					4.6	25.8	2.3 (1.8 to 3.7) (HR 0.73; p=0.11)	19.8 (17.0 to 26.7) (HR 0.59; p=0.036)
Cyclin-dependent kinase 4/6 inhibitor										
Finn *et al*[49 50]	Letrozole +palbociclib	84	ER+ HER2−	II, randomised	None: 59/55%; adj TAM: 29/30%; adj AI: 12/15%	None	43	38	10.2 (5.7 to 12.6)	Not powered for OS
	Letrozole	81					33	25	20.2 (13.8 to 27.5) (p=0.0004)	
Antiboby directed against MUC1										
Ibrahim *et al*[52]	Letrozole +anti-MUC1 antibody (AS1402)	56	ER/PGR HER2 −	II, randomised	None: 84/80%; >12 months adj AI: 16/20%	None	12.5	57.1†	(HR 0.925)	NR
	Letrozole	54					25.9	50.0		

For RR, duration of TTP/PFS and OS, the number of decimals used by the authors is reported.
ER/PGR+, HER2: % positive are given when possible.
*Doses of anastrozole, letrozole and exemestane were 1, 2.5 and 25 mg, respectively.
†Duration of SD not reported; if not marked, duration of SD reported ≥24 weeks or 6 months.
‡Defined as recurrence during or ≤12 months after adjuvant NSAI or PD during or within 1 month after treatment for advanced breast cancer.
§Central assessment.
¶Defined as relapse after adjuvant therapy administered for ≥12 months or PD on NSAI for MBC administered for ≥3 months.
ABC, advanced breast cancer; Adj, adjuvant; AI, aromatase inhibitor; CBR, clinical benefit rate; COX-2, cyclooxygenase-2; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; MBC, metastatic breast cancer; NR, not reported; NSAI, non-steroid aromatase inhibitor; PD, progressive disease; PFS, progression-free survival, PGR, progesterone receptor; RR, response rate; TAM, tamoxifen; TTP, time to progression, OS, overall survival; UK, unknown.

mTOR inhibitors

Among other mechanisms, endocrine resistance has been attributed to the crosstalk between ER signalling and the phosphatidylinositol 3-kinase (PI3K/protein kinase B (AKT)/mammalian target of rapamycin (mTOR)) pathway. Thus, dual targeting of both pathways may enhance efficacy of endocrine therapy.[38]

The Breast Cancer Trials of OraL EveROlimus-2 (BOLERO-2) study compared exemestane combined with the mTOR inhibitor everolimus with exemestane +placebo in patients previously treated with an NSAI. In total, 724 patients were randomised 2:1. No crossover was allowed. A significant difference in PFS was found favouring everolimus (10.6 vs 4.1 months).[39 40] The trial was stopped early after a prespecified interim analysis found a significantly better PFS for the combination arm. However, OS was similar in the two arms.[40]

A retrospective, exploratory subgroup analysis in patients whose last treatment was in the (neo)adjuvant setting showed a median PFS in the combination arm of 15.2 vs 4.2 months in the exemestane+placebo arm; HR 0.32, 95% CI 0.18 to 0.57. Thus, the addition of everolimus nearly tripled PFS in the first-line setting.[41] In contrast, the Randomized Phase III Placebo-Controlled Trial of Letrozole Plus Oral Temsirolimus as First-Line Endocrine Therapy in Postmenopausal Women With Locally Advanced or Metastatic Breast Cancer (HORIZON) study comparing temsirolimus plus letrozole with letrozole failed to show any difference between treatment arms regarding PFS (9 months in both groups) and OS.[42]

HER1-targeted therapy

Preclinical studies have suggested that activation of the epidermal growth factor receptor (EGFR) pathway might be an important mechanism of endocrine resistance.[43] Approximately 30% of HR-positive patients with breast cancer overexpress EGFR.[44]

In a randomised phase II trial, anastrozole+gefitinib was compared with fulvestrant (250 mg)+gefitinib. The RR, CBR and PFS did not differ for the two regimens. Median OS was 30.3 months for anastrozole+gefitinib vs 23.9 months for fulvestrant+gefitinib.[45] Thus, efficacy rates were not clearly superior to endocrine therapy alone.[46] Furthermore, the combinations had a less favourable safety profile compared with endocrine therapy.

Angiogenesis inhibitors

Preclinical studies have shown that vascular endothelial growth factor (VEGF) induced proliferation in breast cancer cell lines by interfering with the actions of oestrogens. Only one randomised study was identified. In total, 374 patients were randomised to first-line endocrine therapy (letrozole or fulvestrant)±bevacizumab. However, the addition of bevacizumab failed to produce a significant improvement in PFS or OS.[47]

Histone deacetylase inhibitor

A double-blind phase II trial of exemestane versus exemestane plus the histone deacetylase inhibitor entinostat showed no difference in the predefined end point PFS (4.3 vs 2.3 months; p=0.11). However, an exploratory analysis showed improved OS in the experimental arm (28.1 vs 19.8 months; p=0.036).[48] In a subset of patients, an association of histone deacetylase inhibition with protein lysine acetylation and improved clinical outcome was demonstrated.

CDK4/6 inhibitor

The cyclin-dependent kinases (CDKs) are a large family of serine threonine kinases. Together with their regulatory partners, the cyclins, they play a crucial role in cell cycle control. Preclinical studies have shown synergistic effect of CDK inhibitors and tamoxifen as well as efficacy in a model of acquired tamoxifen resistance.[49]

Among several CDK4/6 inhibitors currently in development, palbociclib has been evaluated in a randomised phase II trial of letrozole±palbociclib. Median PFS was 10.2 months in the letrozole group compared with 20.2 months in the palbociclib+letrozole group (p=0.0004). The study was not powered to detect an OS benefit.[50]

Antibody directed against MUC1

MUC1 is an aberrantly glycosylated antigen, overexpressed in ~90% of breast cancers. Preclinical studies have shown a mechanistic interaction between MUC1 and ER, providing a rationale for evaluation of combination therapy.[51] However, a randomised phase II study of letrozole±anti-MUC1 antibody AS1402 failed to demonstrate any benefit of adding AS1402 to letrozole.[52]

Studies of combinations of AI/fulvestrant and HER2-targeting agents

Results from three phase III trials evaluating endocrine therapy in combination with HER2-directed therapy are given in table 4.

Studies have shown significant inverse correlation between HER2 and ER expression. Furthermore, preclinical studies suggest an interaction between the two pathways.[53] In the first-line setting, trastuzumab+anastrozole compared with anastrozole demonstrated significantly increased median PFS (4.8 vs 2.4 months) and increased RR (20.3% vs 6.8%).[54]

A phase III trial compared letrozole with letrozole plus the dual HER1/EGFR and HER2 tyrosine kinase inhibitor lapatinib in 1286 patients with HR-positive metastatic breast cancer as first-line therapy. In 219 HER2-positive patients, the addition of lapatinib reduced the risk of disease progression (p=0.019) and increased median PFS (8.2 vs 3.0 months).[55] Finally, a phase III trial including 295 patients with advanced breast cancer previously treated with an AI compared fulvestrant (250 mg) plus lapatinib with fulvestrant plus placebo. In the total patient population, no differences

Table 4 Summary of phase II and III trials of HER2-directed therapy in combination with endocrine therapy in patients with HER2-positive hormone receptor-positive metastatic breast cancer

Reference	Treatment*	Number of patients	Patient population	Phase	Prior endocrine therapy	Prior chemotherapy for ABC	RR (%) (95% CI)	SD (%) (95% CI)	TTP/PFS (median; months) (95% CI)	OS (median; months) (95% CI)
NSAI; trastuzumab										
Kaufman *et al*[54]	Anastrozole +trastuzumab	103	ER/PGR+ HER2+	III	None: 37/29%; adj TAM: 60/66%; first-line endocrine therapy:3/5%; no prior HER-directed therapy	None	20.3	42.7 (33.0 to 52.9)	4.8	28.5
	Anastrozole	104					6.8 (p=0.018)	27.9 (19.5 to 37.5) (CBR)	2.4 (HR 0.63; p=0.0016)	23.9 (p=0.325)
NSAI; lapatinib										
Johnston *et al*[55]	Letrozole +lapatinib	642 (111 HER2+)	ER/PGR+ HER2+ 17/17%	III	None: 51/43%; adj endocrine therapy: 49–57%; prior AI ≤1%; prior HER2-directed therapy ≤1%	None	28 (HER2+)	48 (HER2+, CBR)	8.2 (HER2+)	32.3 (HER2+)
	Letrozole +placebo	644 (108 HER2+)					15 (OR 0.4; 0.2 to 0.9; p=0.021)	29 (OR 0.2 to 0.8; p=0.003)	3.0 (HR 0.71; p=0.019)	33.3 (HR 0.74; p=0.113)
Fulvestrant; lapatinib										
Burstein *et al*[56]	Fulvestrant 500 mg +lapatinib	146 (24 HER2+)	ER/PGR+ HER2+ 16/21%	III	Prior TAM: 57/57%; prior AI: 97/97%; setting NR; prior trastuzumab: 2/3%	≤1	38 (14 to 70) (HER2+)	38	4.7 (HER2+)	30.0 (HER2+)
	Fulvestrant 500 mg +placebo	145 (30 HER2+)					16 (5 to 45)	25	3.8 (HR 1.04; p=0.37)	26.4 (HR 0.91; p=0.25)

For RR, duration of TTP/PFS and OS, the number of decimals used by the authors is reported.
ER/PGR+, HER2: % positive are given when possible.
*Doses of anastrozole and letrozole were 1 and 2.5 mg, respectively.
ABC, advanced breast cancer; adj, adjuvant; AI, aromatase inhibitor; CBR, clinical benefit rate; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; NR, not reported; NSAI, non-steroid aromatase inhibitor; PFS, progression-free survival; PRG, progesterone receptor; RR, response rate; SAI, steroid aromatase inhibitor; TAM, tamoxifen; TTP, time to progression; OS, overall survival.

in PFS or OS were found. In 54 HER2-positive patients, however, the addition of lapatinib resulted in a longer median PFS (5.9 vs 3.3 months).[56]

DISCUSSION

Guidelines unanimously recommend endocrine therapy as first choice in patients with HR-positive, HER2-negative disease independent of metastatic site, unless rapid response is needed or in case of doubts regarding the endocrine responsiveness of the tumour.[57 58] This strategy is partly based on consensus between specialists[3] and partly on a Cochrane review published in 2003 and updated in 2010.[59] No studies published after 2000 have addressed this question.

Treatment selection

First-line therapy

In general, trials evaluating the different AIs and/or fulvestrant were conducted before the time of systematic HER2 analyses; thus, patients with unknown HR status were included in some of the trials. In addition, studies were conducted at a time when the use of adjuvant AI was uncommon.

In the first-line setting, NSAIs were more effective than tamoxifen regarding TTP,[7 8 10 13] whereas the difference between exemestane and tamoxifen was limited and depended on the statistical test used.[15 16] Except for the P025 trial in which a significant OS benefit was found for letrozole compared with tamoxifen,[60] no OS benefit was demonstrated in the trials.

A recent meta-analysis of six trials including 2560 patients[6 7 10 15 16 61] comparing an AI with tamoxifen found a significant difference favouring AI regarding RR and CBR. However, a trend towards improved survival was non-significant.[62] In contrast, two meta-analyses showed a significant OS benefit of AIs compared with other endocrine therapies.[63 64] Thus, if not used in the adjuvant setting or if discontinued >12 months, an NSAI is the preferred option in all guidelines.[57 58] None of the guidelines recommend one NSAI over another. Pharmacokinetic data have shown letrozole to be a more potent suppressor of total body aromatisation and plasma oestrogen levels than anastrozole.[65] On the other hand, other data suggested that once a certain threshold of AI was reached, differences in oestrogen suppression were not associated with clinically significant differences in efficacy.[66] Increasingly, AIs have become an integral component of standard care of postmenopausal patients in the adjuvant setting.[67 68] Most studies, however, were conducted at a time when adjuvant treatment consisted of tamoxifen. Thus, evidence for first-line recommendations after an adjuvant AI is lacking. Anyhow, European Society for Medical Oncology (ESMO) guidelines suggest that preferably, an NSAI should be used after progression on an SAI and vice versa, whereas National Comprehensive Cancer Network (NCCN) does not distinguish between the AIs.[57]

The efficacy of fulvestrant (250 mg) did not differ from that of tamoxifen in the first-line setting. Results were independent of prior adjuvant tamoxifen. However, as supported by findings in clinical trials, the recommended dose of fulvestrant is 500 mg which is why these results should be interpreted with caution.[69–72] The 500 mg schedule was approved by the Food and Drug Administration (FDA) in 2010. Thus, guidelines underscore that fulvestrant (500 mg) has demonstrated superiority compared with anastrozole in the first-line setting. However, no recommendations for fulvestrant exist. More data are awaited. Of note, all guidelines regard tamoxifen as an acceptable first-line therapy.

Later lines of therapy

Single-agent or combined endocrine therapy

In general, the efficacy of the different AIs and fulvestrant was similar in tamoxifen-refractory patients. No study fulfilling the search criteria investigated the impact of treatment sequence. Only one small randomised trial (substudy of TARGET) including 60 patients investigated the impact of the treatment sequence.[73] Data suggested that an antioestrogen might be active after an AI. However, the study was not powered to draw firm conclusions. An issue of particular interest is the lack of cross-resistance between SAI and NSAI provided that the NSAI is given upfront. In general, studies reporting on this phenomenon included few patients,[25 74–76] but findings across different studies seem to consent that no cross-resistance exists. This is supported by one randomised trial,[34] in which exemestane was compared with fulvestrant after failure of an NSAI; no significant differences in efficacy parameters were reported. For the reverse sequence, that is NSAI after failure of an SAI, only one study was identified in which a 55% RR of an NSAI after prior exposure to exemestane was reported.[74]

Differences in binding ability, including different binding sites at the aromatase enzyme, kinetics (reversibility) and androgen-agonistic effects, might potentially explain the findings. However, the pharmacologic and molecular mechanisms behind the phenomenon remain unclear.[76]

A limited number of small phase II studies and retrospective studies have demonstrated activity of AIs and fulvestrant in the third-line setting.[77–79] Importantly, the response to previous therapy had little impact on efficacy of the drugs. The results might be due to selection bias and small number of patients. Anyhow, results suggested that the drugs might be active in latter lines of therapy.

In the SWOG 0226 trial, the combination of anastrozole and fulvestrant (250 mg) increased PFS compared with anastrozole alone (15 vs 13.5 months). The combination therapy also increased the median OS by ~6 months despite the fact that 41% of patients crossed over to fulvestrant after progression.[29] The FACT trial, which also compared anastrozole±fulvestrant (250 mg) as first-line therapy, found no difference in outcome.[28] A

possible explanation for the discordant results could be that a higher percentage of patients had received prior hormonal therapy in the FACT trial (66–70% in FACT vs 40% in SWOG). Thus, a subanalysis of the SWOG trial did not show a significant improvement in PFS in patients who had received adjuvant tamoxifen.[29] In addition, the FACT trial was slightly smaller and included patients with local recurrence only, as well as patients who had recurrence while on adjuvant endocrine therapy.

No guidelines consider combination hormonal therapy to be a standard first-line treatment option. However, in postmenopausal patients who have not received prior hormonal therapy, this option deserves further investigation.

Generally, guidelines do not definitively recommend specific endocrine treatment cascades, particularly regarding the best treatment option following progression on first-line therapy.[57 67]

Endocrine therapy combined with other agents

Studies on endocrine therapy in combination with inhibitors of angiogenesis, COX-2 inhibitors and HER1 inhibitors did not show any benefit of the combinations.

The histone deacetylase inhibitor entinostat in combination with exemestane is currently evaluated in a phase III study (NCT02115282). Results are expected in July 2017.

The addition of everolimus to exemestane in the pivotal BOLERO-2 study undoubtedly resulted in a clinically meaningful extension of median PFS by ~4.5 months after recurrence or progression on an NSAI. An exploratory analysis of first-line therapy showed a nearly tripled PFS. However, data on OS failed to show any significant difference between the two regimens, although an absolute difference of almost 4.5 months was observed. In total, 55% of patients experienced grade 3 or 4 side effects in the everolimus arm, and 29% discontinued everolimus because of lack of tolerability. Overall, the number of serious adverse events (SAEs) did not differ from numbers seen in trials including chemotherapy challenging the strategy of applying the most tolerable regimen first.[80] Thus, the safety profile may limit practical use and compliance. The randomised phase II study BOLERO-6 comparing everolimus plus exemestane with everolimus alone with capecitabine (NCT01783444) might provide some answers.

A similar effect of addition of everolimus was found in a randomised phase II study of tamoxifen±everolimus including 111 HER2-negative, HR-positive postmenopausal women with metastatic breast cancer and prior exposure to an AI. The benefit of everolimus was mainly seen in women with acquired resistance to an AI.[81]

In contrast, the phase III HORIZON study evaluating the addition of temsirolimus to letrozole failed to show any benefit of the combination.[42] The discordant results are not well understood. A possible explanation could be the intermittent doses used in the HORIZON study. Also, a high rate of toxic effects in this study leading to dose reductions/cessation of temsirolimus could affect the outcome. However, the key difference between the two studies was differences in the study populations. In the HORIZON study, 58% were AI naïve and it was unlikely that acquired resistance was evident in many of the patients. Thus, it has been hypothesised that mTOR inhibitors are more effective in patients previously exposed to endocrine therapy.

A recent meta-analysis compared everolimus plus exemestane with fulvestrant 250 and 500 mg, respectively. The combination of everolimus and exemestane appeared more efficacious than fulvestrant with regard to PFS. A subgroup analysis of patients who had received prior AI showed similar results.[82]

Yet, there are no predictive biomarkers to identify patients who benefit from addition of an mTOR inhibitor.

Recent treatment guidelines from a range of countries recommend addition of everolimus to exemestane for patients recurring/progressing during or following an NSAI even in the presence of visceral disease.[57 58 83 84]

Currently, three specific CDK4/6 inhibitors palbociclib, abemaciclib and ribociclib are being tested in clinical trials. More recently, the randomised phase II PALbociclib: Ongoing trials in the Management of breast cAncer (PALOMA)-1 trial showed an almost double PFS after addition of palbociclib to letrozole.[50] On 3 February 2015, the US FDA granted accelerated approval to palbociclib for use in combination with letrozole.[85] To confirm the impressive results, the phase III study (PALAMO-2) is ongoing and results are expected in October 2016 (NCT01740427). Recently, the phase III PALAMO-3 trial including 521 premenopausal and postmenopausal patients with advanced breast cancer who were randomised to fulvestrant+palbociclib or placebo±goserelin demonstrated a significant increase in PFS (9.2 vs 3.8 months, HR 0.42, 95% CI 0.32 to 0.56; p<0.001). The number of deaths at the time of the analysis was insufficient to assess OS.[86]

Several phase III studies are in progress with all three CDK4/6 inhibitors in HR-positive, HER2-negative breast cancer. The observed toxicities so far are predominantly hematological, characterised by limited neutropenia. Other common adverse events were infections, fatigue and gastrointestinal toxicity. The toxicities seem manageable. Currently, data are too limited to differentiate between the compounds. No predictive biomarkers to identify patients who benefit from addition of a CDK4/6 inhibitor are available.[87]

Studies of combinations of AI/fulvestrant and HER2-targeting agents

Approximately half of the patients with HER2-positive breast cancer are also HR positive. Concomitant treatment with anastrozole and therapy directed against HER2 provided a significantly better outcome. The

Study of the Efficacy and Safety of Letrozole Combined With Trastuzumab in Patients With Metastatic Breast Cancer (eLEcTRA) study (92 patients) evaluating letrozole±trastuzumab confirmed these finding.[88] Nonetheless, combination chemotherapy with HER2-directed therapy as first-line treatment is generally preferred.[57 89]

Future perspectives

A major limitation of endocrine therapy is intrinsic and acquired resistance. Although expression of ER is strongly predictive of response to endocrine therapies, approximately one-third of ER-positive cancers do not respond or relapse after an initial response.[90] In the past decade, there have been major efforts to understand the molecular mechanism responsible for development of endocrine resistance.[91 92] Drug resistance to single-agent therapy might be driven by pathway reactivation, suggesting that one limitation lies in the inability to fully block the pathway. mTOR and CDK4/6 inhibition might represent ways to overcome this. Furthermore, future strategies currently under evaluation include combining endocrine therapy with inhibitors of growth factor receptors or downstream signalling pathways. For a comprehensive review, see Palmieri *et al*.[93] On the other hand, ER-positive breast cancer is biologically heterogeneous, and many patients have long-lasting benefit of endocrine monotherapy.[94] Yet, prognostic biomarkers to identify patients who will do well with endocrine therapy alone as well as biomarkers to predict benefit from combination therapy are lacking.

CONCLUSION

Conventional treatment with an AI or fulvestrant may be an adequate treatment option for the majority of patients. mTOR and CDK4/6 inhibition might represent substantial advances for patients with HR-positive, HER2-negative advanced breast cancer. However, there is an urgent need for prospective biomarker-driven trials to identify patients for whom the treatments are cost-effective.

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REFERENCES

1. Torre LA, Bray F, Siegel RL, *et al*. Global cancer statistics, 2012. *CA Cancer J Clin* 2015;65:87–108.
2. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. *N Engl J Med* 2003;348:2431–42.
3. Cardoso F, Bischoff J, Brain E, *et al*. A review of the treatment of endocrine responsive metastatic breast cancer in postmenopausal women. *Cancer Treat Rev* 2013;39:457–65.
4. Carlson RW. The history and mechanism of action of fulvestrant. *Clin Breast Cancer* 2005;6(Suppl 1):S5–8.
5. Ciruelos E, Pascual T, Arroyo Vozmediano ML, *et al*. The therapeutic role of fulvestrant in the management of patients with hormone receptor-positive breast cancer. *Breast* 2014;23:201–8.
6. Bonneterre J, Thurlimann B, Robertson JF, *et al*. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 2000;18:3748–57.
7. Nabholtz JM, Buzdar A, Pollak M, *et al*. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol* 2000;18:3758–67.
8. Bonneterre J, Buzdar A, Nabholtz JM, *et al*. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* 2001;92:2247–58.
9. Nabholtz JM, Bonneterre J, Buzdar A, *et al*. Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. *Eur J Cancer* 2003;39:1684–9.
10. Milla-Santos A, Milla L, Portella J, *et al*. Anastrozole versus tamoxifen as first-line therapy in postmenopausal patients with hormone-dependent advanced breast cancer: a prospective, randomized, phase III study. *Am J Clin Oncol* 2003;26:317–22.
11. Mouridsen H, Gershanovich M, Sun Y, *et al*. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. *J Clin Oncol* 2001;19:2596–606.
12. Mouridsen H, Sun Y, Gershanovich M, *et al*. Superiority of letrozole to tamoxifen in the first-line treatment of advanced breast cancer: evidence from metastatic subgroups and a test of functional ability. *Oncologist* 2004;9:489–96.
13. Mouridsen H, Gershanovich M, Sun Y, *et al*. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003;21:2101–9.
14. Mouridsen HT, Chaudri-Ross HA. Comment on "Anastrozole (Arimidex) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results" by J.-M. Nabholtz *et al*. *Eur J Cancer* 2004;40:1095–6.
15. Paridaens R, Dirix L, Lohrisch C, *et al*. Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. *Ann Oncol* 2003;14:1391–8.
16. Paridaens RJ, Dirix LY, Beex LV, *et al*. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. *J Clin Oncol* 2008;26:4883–90.
17. Howell A, Robertson JF, Abram P, *et al*. Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: a multinational, double-blind, randomized trial. *J Clin Oncol* 2004;22:1605–13.
18. Buzdar AU, Jones SE, Vogel CL, *et al*. A phase III trial comparing anastrozole (1 and 10 milligrams), a potent and selective aromatase inhibitor, with megestrol acetate in postmenopausal women with advanced breast carcinoma. Arimidex Study Group. *Cancer* 1997;79:730–9.
19. Jonat W, Howell A, Blomqvist C, *et al*. A randomised trial comparing two doses of the new selective aromatase inhibitor anastrozole (Arimidex) with megestrol acetate in postmenopausal patients with advanced breast cancer. *Eur J Cancer* 1996;32A:404–12.
20. Buzdar AU, Jonat W, Howell A, *et al*. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study Group. *Cancer* 1998;83:1142–52.
21. Buzdar A, Douma J, Davidson N, *et al*. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol* 2001;19:3357–66.
22. Dombernowsky P, Smith I, Falkson G, *et al*. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and

tolerability compared with megestrol acetate. *J Clin Oncol* 1998;16:453–61.
23. Kaufmann M, Bajetta E, Dirix LY, *et al*. Exemestane improves survival in metastatic breast cancer: results of a phase III randomized study. *Clin Breast Cancer* 2000;1(Suppl 1):S15–18.
24. Iwata H, Masuda N, Ohno S, *et al*. A randomized, double-blind, controlled study of exemestane versus anastrozole for the first-line treatment of postmenopausal Japanese women with hormone-receptor-positive advanced breast cancer. *Breast Cancer Res Treat* 2013;139:441–51.
25. Llombart-Cussac A, Ruiz A, Anton A, *et al*. Exemestane versus anastrozole as front-line endocrine therapy in postmenopausal patients with hormone receptor-positive, advanced breast cancer: final results from the Spanish Breast Cancer Group 2001–03 phase 2 randomized trial. *Cancer* 2012;118:241–7.
26. Robertson JF, Lindemann JP, Llombart-Cussac A, *et al*. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. *Breast Cancer Res Treat* 2012;136:503–11.
27. Robertson JF, Llombart-Cussac A, Rolski J, *et al*. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. *J Clin Oncol* 2009;27:4530–5.
28. Bergh J, Jonsson PE, Lidbrink EK, *et al*. FACT: an open-label randomized phase III study of fulvestrant and anastrozole in combination compared with anastrozole alone as first-line therapy for patients with receptor-positive postmenopausal breast cancer. *J Clin Oncol* 2012;30:1919–25.
29. Mehta RS, Barlow WE, Albain KS, *et al*. Combination anastrozole and fulvestrant in metastatic breast cancer. *N Engl J Med* 2012;367:435–44.
30. Rose C, Vtoraya O, Pluzanska A, *et al*. An open randomised trial of second-line endocrine therapy in advanced breast cancer. Comparison of the aromatase inhibitors letrozole and anastrozole. *Eur J Cancer* 2003;39:2318–27.
31. Howell A, Robertson JF, Quaresma Albano J, *et al*. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol* 2002;20:3396–403.
32. Xu B, Jiang Z, Shao Z, *et al*. Fulvestrant 250 mg versus anastrozole for Chinese patients with advanced breast cancer: results of a multicentre, double-blind, randomised phase III trial. *Cancer Chemother Pharmacol* 2011;67:223–30.
33. Robertson JF, Osborne CK, Howell A, *et al*. Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: a prospective combined analysis of two multicenter trials. *Cancer* 2003;98:229–38.
34. Chia S, Gradishar W, Mauriac L, *et al*. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. *J Clin Oncol* 2008;26:1664–70.
35. Johnston SR, Kilburn LS, Ellis P, *et al*. Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial. *Lancet Oncol* 2013;14:989–98.
36. Falandry C, Debled M, Bachelot T, *et al*. Celecoxib and exemestane versus placebo and exemestane in postmenopausal metastatic breast cancer patients: a double-blind phase III GINECO study. *Breast Cancer Res Treat* 2009;116:501–8.
37. Dirix LY, Ignacio J, Nag S, *et al*. Treatment of advanced hormone-sensitive breast cancer in postmenopausal women with exemestane alone or in combination with celecoxib. *J Clin Oncol* 2008;26:1253–9.
38. Ciruelos Gil EM. Targeting the PI3K/AKT/mTOR pathway in estrogen receptor-positive breast cancer. *Cancer Treat Rev* 2014;40:862–71.
39. Baselga J, Campone M, Piccart M, *et al*. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2012;366:520–9.
40. Piccart M, Hortobagyi G, Campone M, *et al*. Everolimus plus exemestane for hormone receptor-positive (HR+), human epidermal growth factor receptor-2 negative (HER2-) advanced breast cancer (BC): overall survival results from BOLERO-2. Presented at EBCC-9; 19–21 March 2014; Glasgow, UK, 2014.
41. Beck JT, Hortobagyi GN, Campone M, *et al*. Everolimus plus exemestane as first-line therapy in HR(+), HER2(−) advanced breast cancer in BOLERO-2. *Breast Cancer Res Treat* 2014;143:459–67.
42. Wolff AC, Lazar AA, Bondarenko I, *et al*. Randomized phase III placebo-controlled trial of letrozole plus oral temsirolimus as first-line endocrine therapy in postmenopausal women with locally advanced or metastatic breast cancer. *J Clin Oncol* 2013;31:195–202.
43. Nicholson RI, McClelland RA, Gee JM, *et al*. Epidermal growth factor receptor expression in breast cancer: association with response to endocrine therapy. *Breast Cancer Res Treat* 1994;29:117–25.
44. Klijn JG, Berns PM, Schmitz PI, *et al*. The clinical significance of epidermal growth factor receptor (EGF-R) in human breast cancer: a review on 5232 patients. *Endocr Rev* 1992;13:3–17.
45. Carlson RW, O'Neill A, Vidaurre T, *et al*. A randomized trial of combination anastrozole plus gefitinib and of combination fulvestrant plus gefitinib in the treatment of postmenopausal women with hormone receptor positive metastatic breast cancer. *Breast Cancer Res Treat* 2012;133:1049–56.
46. Gutteridge E, Agrawal A, Nicholson R, *et al*. The effects of gefitinib in tamoxifen-resistant and hormone-insensitive breast cancer: a phase II study. *Int J Cancer* 2010;126:1806–16.
47. Martin M, Loibl S, von Minckwitz G, *et al*. Phase III trial evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for advanced breast cancer: the letrozole/fulvestrant and avastin (LEA) study. *J Clin Oncol* 2015;33:1045–52.
48. Yardley DA, Ismail-Khan RR, Melichar B, *et al*. Randomized phase II, double-blind, placebo-controlled study of exemestane with or without entinostat in postmenopausal women with locally recurrent or metastatic estrogen receptor-positive breast cancer progressing on treatment with a nonsteroidal aromatase inhibitor. *J Clin Oncol* 2013;31:2128–35.
49. Finn RS, Dering J, Conklin D, *et al*. PD 0332991, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Res* 2009;11:R77.
50. Finn RS, Crown JP, Lang I, *et al*. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 2015;16:25–35.
51. Wei X, Xu H, Kufe D. MUC1 oncoprotein stabilizes and activates estrogen receptor alpha. *Mol Cell* 2006;21:295–305.
52. Ibrahim NK, Yariz KO, Bondarenko I, *et al*. Randomized phase II trial of letrozole plus anti-MUC1 antibody AS1402 in hormone receptor-positive locally advanced or metastatic breast cancer. *Clin Cancer Res* 2011;17:6822–30.
53. Shou J, Massarweh S, Osborne CK, *et al*. Mechanisms of tamoxifen resistance: increased estrogen receptor-HER2/neu cross-talk in ER/HER2-positive breast cancer. *J Natl Cancer Inst* 2004;96:926–35.
54. Kaufman B, Mackey JR, Clemens MR, *et al*. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2-positive, hormone receptor-positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol* 2009;27:5529–37.
55. Johnston S, Pippen J Jr, Pivot X, *et al*. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol* 2009;27:5538–46.
56. Burstein HJ, Cirrincione CT, Barry WT, *et al*. endocrine therapy with or without inhibition of epidermal growth factor receptor and human epidermal growth factor receptor 2: a randomized, double-blind, placebo-controlled phase III trial of fulvestrant with or without lapatinib for postmenopausal women with hormone receptor-positive advanced breast cancer-CALGB 40302 (Alliance). *J Clin Oncol* 2014;32:3959–66.
57. Cardoso F, Costa A, Norton L, *et al*. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Breast* 2014;23:489–502.
58. Gradishar WJ. Treatment of metastatic breast cancer. *J Natl Compr Canc Netw* 2014;12(5 Suppl):759–61.
59. Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. *Cochrane Database Syst Rev* 2003;(2):CD002747.
60. Mouridsen HT. Letrozole in advanced breast cancer: the PO25 trial. *Breast Cancer Res Treat* 2007;105(Suppl 1):19–29.
61. Mouridsen H, Chaudri-Ross HA. Efficacy of first-line letrozole versus tamoxifen as a function of age in postmenopausal women with advanced breast cancer. *Oncologist* 2004;9:497–506.
62. Xu HB, Liu YJ, Li L. Aromatase inhibitor versus tamoxifen in postmenopausal woman with advanced breast cancer: a literature-based meta-analysis. *Clin Breast Cancer* 2011;11:246–51.

63. Gibson L, Lawrence D, Dawson C, *et al*. Aromatase inhibitors for treatment of advanced breast cancer in postmenopausal women. *Cochrane Database Syst Rev* 2009;(4):CD003370.
64. Mauri D, Pavlidis N, Polyzos NP, *et al*. Survival with aromatase inhibitors and inactivators versus standard hormonal therapy in advanced breast cancer: meta-analysis. *J Natl Cancer Inst* 2006;98:1285–91.
65. Geisler J, Haynes B, Anker G, *et al*. Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. *J Clin Oncol* 2002;20:751–7.
66. Sainsbury R. Aromatase inhibition in the treatment of advanced breast cancer: is there a relationship between potency and clinical efficacy? *Br J Cancer* 2004;90:1733–9.
67. Gradishar WJ, Anderson BO, Blair SL, *et al*. Breast cancer version 3.2014. *J Natl Compr Canc Netw* 2014;12:542–90.
68. Senkus E, Kyriakides S, Penault-Llorca F, *et al*. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2013;24(Suppl 6):vi7–23.
69. Ohno S, Rai Y, Iwata H, *et al*. Three dose regimens of fulvestrant in postmenopausal Japanese women with advanced breast cancer: results from a double-blind, phase II comparative study (FINDER1). *Ann Oncol* 2010;21:2342–7.
70. Di Leo A, Jerusalem G, Petruzelka L, *et al*. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. *J Clin Oncol* 2010;28:4594–600.
71. Di Leo A, Jerusalem G, Petruzelka L, *et al*. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. *J Natl Cancer Inst* 2014;106:djt337.
72. Pritchard KI, Rolski J, Papai Z, *et al*. Results of a phase II study comparing three dosing regimens of fulvestrant in postmenopausal women with advanced breast cancer (FINDER2). *Breast Cancer Res Treat* 2010;123:453–61.
73. Thurlimann B, Hess D, Koberle D, *et al*. Anastrozole ('Arimidex') versus tamoxifen as first-line therapy in postmenopausal women with advanced breast cancer: results of the double-blind cross-over SAKK trial 21/95--a sub-study of the TARGET (Tamoxifen or 'Arimidex' Randomized Group Efficacy and Tolerability) trial. *Breast Cancer Res Treat* 2004;85:247–54.
74. Bertelli G, Garrone O, Merlano M, *et al*. Sequential treatment with exemestane and non-steroidal aromatase inhibitors in advanced breast cancer. *Oncology* 2005;69:471–7.
75. Harper-Wynne C, Coombes RC. Anastrozole shows evidence of activity in postmenopausal patients who have responded or stabilised on formestane therapy. *Eur J Cancer* 1999;35:744–6.
76. Lonning PE. Lack of complete cross-resistance between different aromatase inhibitors; a real finding in search for an explanation? *Eur J Cancer* 2009;45:527–35.
77. Carlini P, Michelotti A, Ferretti G, *et al*. Clinical evaluation of the use of exemestane as further hormonal therapy after nonsteroidal aromatase inhibitors in postmenopausal metastatic breast cancer patients. *Cancer Invest* 2007;25:102–5.
78. Chin YS, Beresford MJ, Ravichandran D, *et al*. Exemestane after non-steroidal aromatase inhibitors for post-menopausal women with advanced breast cancer. *Breast* 2007;16:436–9.
79. Franco S, Perez A, Tan-Chiu E, *et al*. Response to fulvestrant in heavily pretreated postmenopausal women: a single-center experience. *Breast Cancer Res Treat* 2004;88:103–8.
80. Brufsky AM, Hurvitz S, Perez E, *et al*. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* 2011;29:4286–93.
81. Bachelot T, Bourgier C, Cropet C, *et al*. Randomized phase II trial of everolimus in combination with tamoxifen in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer with prior exposure to aromatase inhibitors: a GINECO study. *J Clin Oncol* 2012;30:2718–24.
82. Bachelot T, McCool R, Duffy S, *et al*. Comparative efficacy of everolimus plus exemestane versus fulvestrant for hormone-receptor-positive advanced breast cancer following progression/recurrence after endocrine therapy: a network meta-analysis. *Breast Cancer Res Treat* 2014;143:125–33.
83. Harbeck N, Marschner N, Untch M, *et al*. Second International Consensus Conference on Advanced Breast Cancer (ABC2), Lisbon, 11/09/2013: The German Perspective. *Breast Care (Basel)* 2014;9:52–9.
84. Pritchard KI, Gelmon KA, Rayson D, *et al*. Endocrine therapy for postmenopausal women with hormone receptor-positive her2-negative advanced breast cancer after progression or recurrence on nonsteroidal aromatase inhibitor therapy: a Canadian consensus statement. *Curr Oncol* 2013;20:48–61.
85. Dhillon S. Palbociclib: first global approval. *Drugs* 2015;75:543–51.
86. Turner NC, Ro J, Andre F, *et al*. Palbociclib in hormone-receptor-positive advanced breast cancer. *N Engl J Med* 2015.
87. Dukelow T, Kishan D, Khasraw M, *et al*. CDK4/6 inhibitors in breast cancer. *Anticancer Drugs* 2015;26:797–806.
88. Huober J, Fasching PA, Barsoum M, *et al*. Higher efficacy of letrozole in combination with trastuzumab compared to letrozole monotherapy as first-line treatment in patients with HER2-positive, hormone-receptor-positive metastatic breast cancer—results of the eLEcTRA trial. *Breast* 2012;21:27–33.
89. Kumler I, Nielsen DL. Trials of bevacizumab in breast cancer–a safety review. *Expert Opin Drug Saf* 2012;11(Suppl 1):S37–48.
90. Davies E, Hiscox S. New therapeutic approaches in breast cancer. *Maturitas* 2011;68:121–8.
91. Garcia-Becerra R, Santos N, Diaz L, *et al*. Mechanisms of resistance to endocrine therapy in breast cancer: focus on signaling pathways, miRNAs and genetically based resistance. *Int J Mol Sci* 2012;14:108–45.
92. Johnston SR. New strategies in estrogen receptor-positive breast cancer. *Clin Cancer Res* 2010;16:1979–87.
93. Palmieri C, Patten DK, Januszewski A, *et al*. Breast cancer: current and future endocrine therapies. *Mol Cell Endocrinol* 2014;382:695–723.
94. Carey LA, Perou CM. Palbociclib—taking breast-cancer cells out of gear. *N Engl J Med* 2015;373:273–4.