



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

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ABSTRACT

Approximately 22,700 Canadian women were expected to be diagnosed with breast cancer in 2012. Despite improvements in screening and adjuvant treatment options, a substantial number of postmenopausal women with hormone receptor positive (HR+) breast cancer will continue to develop metastatic disease during or after adjuvant endocrine therapy. Guidance on the selection of endocrine therapy for patients with HR+ disease that is negative for the human epidermal growth factor receptor 2 (HER2–) and that has relapsed or progressed on earlier nonsteroidal aromatase inhibitor (NSAI) therapy is of increasing clinical importance. Exemestane, fulvestrant, and tamoxifen are approved therapeutic options in this context. Four phase III trials involving 2876 patients—EFFECT, SOFEA, CONFIRM, and BOLERO-2—have assessed the efficacy of various treatment options in this clinical setting. Data from those trials suggest that standard-dose fulvestrant (250 mg monthly) and exemestane are of comparable efficacy, that doubling the dose of fulvestrant from 250 mg to 500 mg monthly results in a 15% reduction in the risk of progression, and that adding everolimus to exemestane (compared with exemestane alone) results in a 57% reduction in the risk of progression, albeit with increased toxicity. Multiple treatment options are now available to women with HR+ HER2– advanced breast cancer recurring or progressing on earlier NSAI therapy, although current clinical trial data suggest more robust clinical efficacy with everolimus plus exemestane. Consideration should be given to the patient's age, functional status, and comorbidities during selection of an endocrine therapy, and use of a proactive everolimus safety management strategy is encouraged.

KEY WORDS

Advanced breast cancer, endocrine therapy, mTOR-inhibitor, nonsteroidal aromatase inhibitor, everolimus, fulvestrant, exemestane, endocrine resistance

1. INTRODUCTION

Approximately 22,700 Canadian women were expected to be diagnosed with breast cancer in 2012, and 5100 women were expected to die of their disease¹. Between 70% and 75% of breast cancers are hormone receptor–positive (HR+) ^{2–4}. Despite significant improvements in outcomes since the early 1990s, a substantial number of women with HR+ breast cancer continue to develop metastatic disease. In the advanced breast cancer (ABC) setting, sequential endocrine therapy (ET) is an optimal treatment strategy for women with reasonably limited and indolent disease; for rapidly progressive or symptomatic disease, chemotherapy is commonly considered optimal^{5,6}. Aromatase inhibitors (AI) have improved ABC outcomes in postmenopausal women in the adjuvant and metastatic settings and have become important options in sequential ET^{7–9}.

Despite the efficacy of ET for HR+ ABC, approximately 30% of women with metastatic disease will have primary resistance to ET, which is commonly defined as recurrence within the first 2 years on adjuvant ET or as progressive disease within 6 months of treatment initiation for advanced disease^{10,11}. Furthermore, many patients with initial response to ET will acquire secondary resistance, commonly defined as disease progression more than 6 months after ET initiation^{11,12}. While there appears to be clinical benefit in combining therapies targeted to the human epidermal growth factor receptor 2 (HER2) with ET in HER2-positive (HER2+) ABC^{13,14}, attempts at combining other receptor tyrosine kinase inhibitors with ET in the HER2-negative (HER2–) setting have met with limited success^{14–16}, highlighting an unmet clinical need in this population.

Sequential ET with selective estrogen receptor modulators, steroidal AI, and estrogen receptor downregulators remains the current standard of care for postmenopausal women with HR+ HER2– ABC. Considering the increased use of nonsteroidal AI (NSAI) therapy in both the adjuvant and the first-line

metastatic setting, the question of which ET to use upon recurrence or progression during prior NSAI therapy is of increasing clinical interest. Historically, high-dose estrogen and megestrol acetate—and the more established selective estrogen receptor modulator tamoxifen—have demonstrated clinical benefit while being reasonably well-tolerated among patients with HR+ ABC^{17–24}. However, megestrol acetate and tamoxifen have not been investigated in large phase III trials for HR+ ABC disease progressing or recurring on NSAI therapy and are therefore not considered in this consensus statement. Exemestane (EXE), a steroidal AI, acts by binding irreversibly to the substrate binding site of aromatase, a mechanism that contrasts with the reversible binding of NSAIs²⁵. Exemestane has demonstrated activity comparable to that of tamoxifen as initial therapy for HR+ metastatic disease in postmenopausal women⁹, is not fully cross-resistant with NSAIs²⁶, and is commonly recommended as the next line of therapy after disease progression on a NSAI. Unlike tamoxifen, the estrogen receptor downregulator fulvestrant is devoid of any agonist activity²⁷. On binding to the estrogen receptor, fulvestrant induces rapid degradation of the estrogen and progesterone receptors^{28,29}. Fulvestrant has demonstrated activity similar to that of tamoxifen when used as initial therapy for metastatic HR+ ABC progressing on prior ET^{17,30–33}.

Researchers studying resistance to ET in HR+ ABC have sought to identify new therapeutic strategies that enhance the efficacy of ETs³⁴. A recently identified mechanism of endocrine resistance is aberrant signalling through the phosphatidylinositol 3 kinase–Akt–mammalian target of rapamycin (mTOR) signalling pathway^{35–37}. Targeted inhibition of this pathway using mTOR inhibitors has therefore become a key clinical research strategy in the attempt to reverse resistance to ET. Three mTOR inhibitors—temsirolimus, sirolimus, and everolimus (EVE)—have been tested in combination with ET in the treatment of HR+ ABC^{10,38–41}. Temsirolimus was not found to improve outcomes when combined with letrozole as initial therapy for women with HR+ ABC^{38,40}; however, sirolimus and EVE have both demonstrated activity when combined with ET in HR+ HER2– patients recurring or progressing on prior ET^{10,39}.

Postmenopausal women with HR+ HER2– ABC recurring or progressing on NSAIs have an unmet clinical need. The present consensus statement weighs available phase III evidence and clinical issues to formulate evidence-based recommendations for ET in this patient population.

2. FORMULATION OF PANEL DISCUSSIONS AND RECOMMENDATIONS

The discussions and author recommendations that follow were developed in a two-step consensus

development process. Authors first participated in a Web-based consensus panel discussion on September 10, 2012, to review and discuss available evidence and to formulate treatment recommendations. The second phase of the development process involved the refinement both of the consensus discussions and of the recommendations with the active involvement of all participants in the iterative manuscript development process.

3. OVERVIEW OF KEY TRIALS OF ET FOR HR+ HER2– ABC PATIENTS RESISTANT TO NSAI THERAPY

Results from four large phase III trials evaluating ET for postmenopausal patients with HR+ ABC that relapsed or progressed on prior NSAI therapy have been reported to date (Figure 1)^{31–33,41}.

The EFECT trial evaluated the safety and efficacy of fulvestrant compared with EXE in patients with advanced disease³¹. This placebo-controlled trial enrolled 693 patients and compared fulvestrant delivered intramuscularly [beginning with a loading dose of 500 mg on day 1, followed by 250 mg on days 14 and 28, and monthly thereafter (F250)] with once-daily oral EXE at 25 mg (Figure 1). The primary endpoint was time to progression (TTP), and baseline patient and disease characteristics were balanced between the treatment arms. The two regimens demonstrated comparable objective response rates (ORR: 7.4% and 6.7%; $p = 0.74$) and TTP (3.7 months in both arms, $p = 0.653$, Table 1). Survival data have yet to be reported³¹.

The SOFEA trial compared both fulvestrant alone and fulvestrant plus anastrozole with EXE. This three-arm trial accrued 750 HR+ patients and compared an intramuscular injection of fulvestrant [beginning with a loading dose of 500 mg, followed by 250 mg on day 15, and monthly thereafter (F250)] plus an oral daily dose of anastrozole 1 mg with F250 plus placebo and with an oral daily dose of EXE 25 mg (Figure 1)³². Baseline patient and disease characteristics were balanced between the treatment arms, and the primary endpoint was progression-free survival (PFS). Compared with EXE, neither F250 alone nor F250 combined with anastrozole resulted in a significantly improved ORR (6.9% vs. 7.4% vs. 3.6%), PFS (4.8 months vs. 4.4 months vs. 3.4 months), or overall survival (OS: 19.4 months vs. 20.2 months vs. 21.6 months; Table 1).

In both the foregoing trials, F250 and EXE were well tolerated, with low rates of treatment discontinuation because of toxicity and low rates of serious adverse events. The most common adverse events of any grade for the SOFEA trial were nausea (43.5% F250 vs. 37.2% EXE), arthralgia (42.6% vs. 46.6%), and lethargy (62.6% vs. 54.3%, Table 1).

The phase III double-blind placebo-controlled CONFIRM trial evaluated the safety and efficacy of

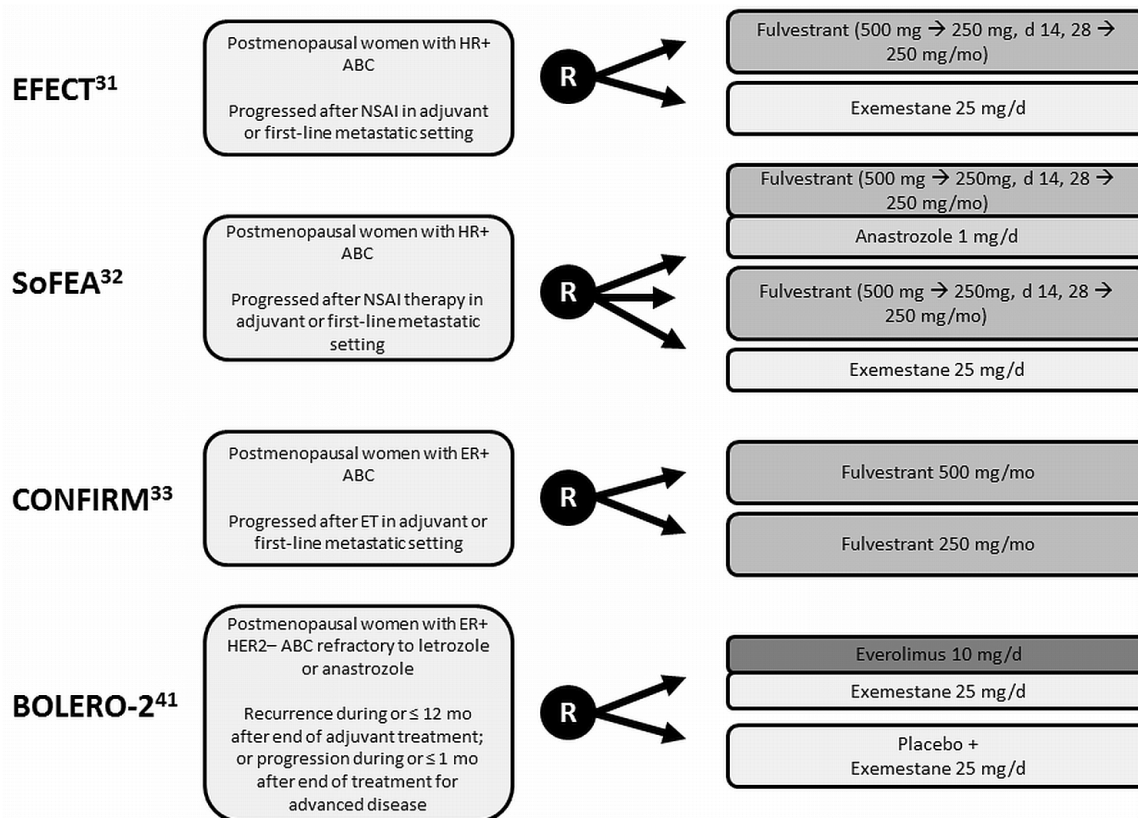


FIGURE 1 Trial design summary. HR+ = hormone receptor–positive; ABC = advanced breast cancer; NSAI = nonsteroidal aromatase inhibitor; R = randomization; ER+ = estrogen receptor–positive; ET = endocrine therapy; HER2– = human epidermal growth factor receptor 2–negative.

doubling the dose of fulvestrant for patients with prior exposure to ET³³. A total of 736 patients with recurrent or progressive disease on either prior AI therapy (42.5%) or prior anti-estrogen therapy (57.5%) were enrolled in the trial. Patients were randomized to receive an intramuscular dose of fulvestrant either 500 mg or 250 mg monthly (F500 vs. F250, Figure 1). The primary endpoint was PFS. Baseline patient and disease characteristics were balanced between the treatment arms. Doubling the dose of fulvestrant did not improve the ORR (9.1% F500 vs. 10.2% F250, $p = 0.795$) or OS (25.1 months vs. 22.8 months, $p = 0.91$, Table i). Patients receiving the higher dose of fulvestrant experienced a statistically significant improvement in median PFS [6.5 months vs. 5.5 months; hazard ratio (HR): 0.80; 95% confidence interval (CI): 0.68 to 0.94; $p = 0.006$], which trended toward significance in patients recurring or progressing on prior AIs (estimated HR: 0.85; 95% CI: 0.67 to 1.08). No substantial differences in the incidence or severity of adverse events were observed in the two arms. With F500, no adverse events with an overall incidence of 40% or greater were observed (Table ii). Although F500 is clearly superior to F250, the optimal dose and schedule of fulvestrant remains unclear^{43,44}.

The placebo-controlled phase III BOLERO-2 trial evaluated the safety and efficacy of adding EVE

to EXE in this patient population⁴¹. A total of 724 patients were randomized 2:1 to either a daily oral dose of EVE 10 mg and EXE 25 mg or to placebo and EXE (Figure 1). The primary endpoint was investigator-assessed PFS. Baseline patient and disease characteristics were balanced between the treatment arms. Results of the primary analysis demonstrated statistically significant improvements in ORR and in both the investigator-assessed and the centrally-reviewed PFS favouring the experimental arm (Table i). Updated outcomes reported at a median follow-up of 18 months confirmed significant improvements in ORR (12.6% vs. 1.7%, $p < 0.0001$) and investigator-assessed median PFS (7.8 months vs. 3.2 months; HR: 0.45; 95% CI: 0.38 to 0.54; $p < 0.0001$) favouring the addition of EVE to EXE⁴⁵. Fewer deaths were reported in the EVE plus EXE arm (OS events: 25.4% vs. 32.2%)⁴⁵, although OS results remain immature at the time of writing. Adverse events observed in the EVE plus EXE arm were consistent with those reported in other studies, with increased toxicity observed for the addition of EVE to EXE⁴¹. Stomatitis and infection were the most common adverse events associated with EVE plus EXE (grade 3 or 4: 8% EVE+EXE vs. 1% placebo+EXE, and 6% vs. 2%; any grade: 56% vs. 11%, and 50% vs. 25%; Table ii).

TABLE 1 Efficacy outcomes: phase III clinical trials of endocrine therapy for advanced breast cancer failing prior nonsteroidal aromatase inhibitors

Reference (trial name)	Treatment regimen	Pts (n)	Median age [years (range)]	HER2 status (% positive/ negative/unknown)	ORR (%)	CBR (%)	Progression-free survival		Overall survival	
							(months)	HR (95% CI)	(months)	HR (95% CI)
Fulvestrant										
Chia <i>et al.</i> , 2008 ³¹ (EFFECT)	Fulvestrant IM, LD 500 mg day 1, 250 mg days 14 and 28, then every 4 weeks	351	63 (38–88)	NR	7.4 ^a (<i>p</i> =0.736)	32.2 ^{ab} (<i>p</i> =0.853)	3.7 ^c	0.93 (0.819 to 1.133) (<i>p</i> =0.6531)	NR	
	Exemestane PO 25 mg daily	342	63 (32–91)	NR	6.7 ^a	31.5 ^{ab}	3.7 ^c		NR	
Johnston <i>et al.</i> , 2012 ³² (SOFEA)	Fulvestrant IM, LD 500 mg day 1, 250 mg day 15, then monthly; plus anastrozole PO 1 mg daily	243	63.8 (57.0–72.0)	7.0/50.2/42.8	7.4 (<i>p</i> =0.82) ^d	33.7 (<i>p</i> =0.58) ^d	4.4	1.00 (0.83 to 1.21) ^d (<i>p</i> =0.98)	20.2	0.95 (0.76 to 1.17) ^d (<i>p</i> =0.61)
	Fulvestrant IM LD 500 mg day 1, 250 mg day 15, then monthly; plus anastrozole- placebo PO	231	63.4 (57.0–73.5)	6.1/61.0/32.9	6.9 (<i>p</i> =0.10) ^e	31.6 (<i>p</i> =0.25) ^e	4.8	0.95 (0.79 to 1.14) ^e (<i>p</i> =0.56)	19.4	1.05 (0.84 to 1.29) ^e (<i>p</i> =0.68)
	Exemestane PO 25 mg daily	249	66.0 (59.2–75.0)	6.8/57.0/36.1	3.6	26.9	3.4		21.6	
Di Leo <i>et al.</i> , 2010 ³³ (CONFIRM)	Fulvestrant IM 500 mg days 0, 14, 28, then every 4 weeks	362	61 (NR)	NR	Overall: 9.1	Overall: 45.6 ^b (<i>p</i> =0.10)	Overall: 6.5	Overall: 0.80 (0.68 to 0.94) (<i>p</i> =0.006) Prior AI: 0.85 (0.67 to 1.08) ^f	Overall: 25.1	Overall: 0.84 (0.69 to 1.03) (<i>p</i> =0.091)

TABLE 1 Continued

Reference (trial name)	Treatment regimen	Pts (n)	Median age [years (range)]	HER2 status (% positive/ negative/unknown)	ORR (%)	CBR (%)	Progression-free survival		Overall survival	
							(months)	HR (95% CI)	(months)	HR (95% CI)
	Fulvestrant IM 250 mg days 0 and 28, then every 4 weeks	374	61 (NR)	NR	Overall: 10.2	Overall: 39.6 ^b	Overall: 5.5	Overall: 22.8		
<i>Everolimus</i>										
Baselga <i>et al.</i> , 2012 ⁴¹ (BOLERO-2)	Everolimus PO 10 mg daily, exemestane PO 25 mg daily	485	62 34–93		9.5 (<i>p</i> <0.001)	79.6 (<i>p</i> <0.001)	6.9	0.43 (0.35 to 0.54) (<i>p</i> <0.001)	NR	
				0.0/100.0/0.0			Central assessment: 10.6	Central assessment: 0.36 (0.27 to 0.47) (<i>p</i> <0.001)		
	Everolimus-placebo PO, exemestane PO 25 mg daily	239	61 (28–90)		0.4	59.0	2.8		NR	
							Central assessment: 4.1			

^a Response-evaluable population: fulvestrant, *n*=270; exemestane *n*=270.
^b Clinical benefit defined as complete response plus partial response plus stable disease ≥ 24 weeks.
^c Time to progression.
^d Fulvestrant plus anastrozole versus fulvestrant plus anastrozole-placebo.
^e Fulvestrant plus anastrozole-placebo versus exemestane.
^f HR and 95% CI estimated from forest plots.
 Pts = patients; HER2 = human epidermal growth factor receptor 2; ORR = objective response rate; CBR = clinical benefit rate; HR = hazard ratio; CI = confidence interval; IM = intramuscular injection; LD = loading dose; NR = not reported; PO = oral.

TABLE II Summary of adverse events of any grade reported at 40% or more frequently^a in phase III endocrine therapy trials

Adverse event	Reference (study name)													
	Chia et al., 2008 ³¹ (EFFECT)		Johnston et al., 2012 ³² (SOFEA)		Di Leo et al., 2010 ³³ (CONFIRM)		Baselga et al., 2012 ⁴¹ Hortobagyi et al., 2011 ⁴² (BOLERO-2)		Eve plus Exe (n=482)		Pbo plus Exe (n=238)			
	Any ^b (%)	Exe (n=340)	Any (%)	Exe (n=247)	Any ^c (%)	Exe (n=361)	Any ^c (%)	Exe (n=374)	Any (%)	Grade 3 (%)	Grade 4 (%)	Any (%)	Grade 3 (%)	Grade 4 (%)
Stomatitis	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Infection	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Nausea	6.8	7.9	43.5 ^e	0.9 ^e	37.2 ^e	3.2 ^e	3.2 ^e	3.2 ^e	3.2 ^e	3.2 ^e	3.2 ^e	27	<1	<1
Arthralgia	3.7	5.6	42.6	3.0	46.6	3.2	3.2	18.8 ^f	2.2 ^f	2.1 ^f	16	1	0	0
Lethargy	3.1 ^g	2.1 ^g	62.6	4.8	54.3	4.5	4.5	NR	NR	NR	NR	NR	NR	NR

^a Adverse events reported at 40% or more often (all grades) in one or more of the included trials; rates of those adverse events are given across all trials, even if less than 40% incidence.
^b Adverse events with more than 2% incidence.
^c Grades 1–4.
^d Grade 3 or higher.
^e Nausea or vomiting.
^f Joint disorders.
^g Asthenia.
 Ful = fulvestrant; Exe = exemestane; F500 = fulvestrant 500 mg; F250 = fulvestrant 250 mg; Eve = everolimus; Pbo = placebo; NR = not reported.

4. PANEL DISCUSSION AND RECOMMENDATIONS

4.1 Management of Postmenopausal Patients with HR+ HER2– ABC Recurring or Progressing on Prior NSAI Therapy

4.1.1 Discussion

In first- and second-line treatment of ABC, PFS and OS are both important measures of clinical benefit. However, clinical trials are often underpowered to effectively evaluate OS as a primary endpoint in the endocrine-sensitive ABC patient population because of sequential treatment options and the protracted post-progression survival interval, which often confound detection of ET-related OS benefits⁴⁶. Determining whether, in this clinical setting, nonsignificant OS differences are a result of limitations in trial design or a true measure of lack of OS benefit is therefore difficult. As a result, PFS as a primary endpoint is gaining importance in first- and second-line settings. However, PFS is often considered a less reliable measure, being more complex and possibly more susceptible to bias and error. Results from trials that control for investigator bias through the use of a double-blind trial design and independent review assessment are therefore considered more reliable⁴⁶.

Four clinical trials have assessed the benefit of ET therapy in postmenopausal women with HR+ disease recurring or progressing on prior NSAI therapy. In all four trials, investigator-assessed PFS was the primary endpoint, and two of them—the CONFIRM and BOLERO-2 trials—reported statistically significant improvements in PFS. Both trials used a double-blind design to control for investigator bias, and the BOLERO-2 results were also independently assessed.

In the CONFIRM trial, patients receiving a higher dose of fulvestrant (F500 compared with F250) experienced a 20% reduction in the risk of progression (HR: 0.80; 95% CI: 0.68 to 0.94) and an incremental gain in median PFS of 1.0 month (6.5 months vs. 5.5 months, $p = 0.006$). In the BOLERO-2 trial, patients receiving EVE plus EXE experienced a reduction in the risk of progression of between 57% and 64% (locally assessed HR: 0.43; 95% CI: 0.35 to 0.54; centrally assessed HR: 0.36; 95% CI: 0.27 to 0.47) and a net gain in median PFS of between 4.1 and 6.5 months (locally assessed: 6.9 months vs. 2.8 months, $p < 0.001$; centrally assessed: 10.6 months vs. 4.1 months, $p < 0.001$)⁴¹. At a median follow-up of 18 months, the OS data remained immature⁴⁵.

Subgroup analyses are used to identify treatment effects in specific populations, but they are often limited in statistical power and may be susceptible to bias related to imbalances in patient or disease characteristics between treatment arms. Investigators conducting the CONFIRM and BOLERO-2 trials carried out preplanned subgroup analyses based on endocrine sensitivity, burden of disease, and age.

Patients in the CONFIRM trial were stratified based on institutional affiliation, and patients in the BOLERO-2 trial were stratified according to the presence or absence of visceral disease and endocrine sensitivity. In CONFIRM, a statistically significant PFS benefit favouring F500 was observed in patients demonstrating resistance to prior ET therapy and in those without visceral disease. Robust statistically significant effects were seen in all subgroups in the BOLERO-2 trial, regardless of burden of disease, endocrine sensitivity, and age.

In both the CONFIRM and BOLERO-2 trials, most patients were described as having endocrine-sensitive disease (63%–67% and 84% respectively), defined as disease recurrence lasting at least 2 years after initiation of adjuvant ET or progression after more than 6 months on ET for advanced disease^{33,41}. Subgroup analyses were conducted for endocrine-sensitive patients in both trials. Overall benefits for EVE plus EXE were confirmed in the subpopulation of 610 endocrine-sensitive patients (estimated HR: 0.43; 95% CI: 0.34 to 0.54; Table III). The overall benefits of F500 were not statistically significant in the endocrine-sensitive population (estimated HR: 0.86; 95% CI: 0.72 to 1.05), but the results are likely similar to those observed in the overall population.

A substantial proportion of patients in both the CONFIRM and BOLERO-2 trials lacked visceral involvement (approximately 45%)^{33,41}. Patients without visceral disease receiving F500 in the CONFIRM trial experienced a 25% reduction in the risk of progression compared with patients receiving F250 (estimated HR: 0.75; 95% CI: 0.57 to 0.95); patients without visceral involvement receiving EVE plus EXE in the BOLERO-2 trial experienced a 59% reduction in the risk of progressive disease (9.9 months vs. 4.2 months; HR: 0.41; estimated 95% CI: 0.30 to 0.56; Table IV)⁴⁵. The benefit of EVE plus EXE was pronounced in patients with bone-only disease; those patients experienced a 67% reduction in the risk of progression and a net median PFS gain of 7.6 months (12.9 months vs. 5.3 months; HR: 0.33; estimated 95% CI: 0.20 to 0.55) compared with those receiving placebo plus EXE⁴⁵. It is notable that EXE alone increased bone turnover and that the addition of EVE reversed the EXE-induced increase in bone resorption and appears to have contributed to a significant reduction in the cumulative incidence of disease progression from bone metastases in patients receiving EVE plus EXE compared with those receiving placebo plus EXE ($p = 0.036$)⁴⁷.

No significant differences in the incidence or severity of adverse events were observed between F500 and F250 in the CONFIRM trial. However, higher rates of trial discontinuation for toxicity were observed when EVE was added to EXE (19% vs. 4%), with increased rates of serious adverse events attributable to treatment (11% EVE+EXE vs. 1% placebo+EXE) and a slightly higher proportion of deaths attributable to adverse events (1% vs. <1%)⁴¹. However, despite

TABLE III Phase III subgroup outcomes by degree of sensitivity to prior endocrine therapy

Reference (study name)	Regimen	Prior ET	Sensitivity to prior ET		Progression-free survival	
			Definition	Proportion (%)	Prior sensitivity	Prior resistance
<i>Fulvestrant</i>						
Chia <i>et al.</i> , 2008 ³¹ (EFFECT)	Fulvestrant 250 mg vs. exemestane	NSAI	≥6 Months before recurrence or progression	61–64	HR: 0.90 (95% CI: 0.73 to 1.08) ^a (TTP, <i>n</i> =434)	HR: 1.01 (95% CI: 0.79 to 1.35) ^a (TTP, <i>n</i> =259)
Johnston <i>et al.</i> , 2012 ³² (SOFEA)	Fulvestrant 250 mg vs. exemestane	NSAI	>1 Year before progression	1–2 Years: 26–35 >2 Years: 27–31	HR: 0.75 (95% CI: 0.54 to 1.06) (1–2 years, <i>n</i> =149) ^b HR: 1.06 (95% CI: 0.75 to 1.50) (>2 years, <i>n</i> =139) ^b	HR: 1.27 (95% CI: 0.84 to 1.91) ^c (<i>n</i> =100)
Di Leo <i>et al.</i> , 2010 ³³ (CONFIRM)	Fulvestrant 500 mg vs. fulvestrant 250 mg	Tamoxifen or AI	>2 Years before recurrence ≥6 Months before progression	63–67	HR: 0.86 (95% CI: 0.72 to 1.05) ^a	HR: 0.72 (95% CI: 0.57 to 0.93) ^{a,d}
<i>Everolimus</i>						
Baselga <i>et al.</i> , 2012 ⁴¹ (BOLERO-2)	Everolimus plus exemestane vs. exemestane	NSAI	≥2 Years before recurrence ≥6 Months before progression	84	HR: 0.43 (95% CI: 0.34 to 0.54) ^a (<i>n</i> =610)	HR: 0.49 (95% CI: 0.30 to 0.81) ^a (<i>n</i> =114)

^a HR and 95% CI estimated from forest plots.

^b Does not include patients receiving NSAIs in the adjuvant setting.

^c Locally advanced or metastatic breast cancer and less than 1 year on NSAI therapy.

^d Poorly responsive or status unknown.

ET = endocrine therapy; NSAI = nonsteroidal aromatase inhibitor; HR = hazard ratio; CI = confidence interval; TTP = time to progression; AI = aromatase inhibitor.

those differences, quality of life was not compromised for patients receiving EVE plus EXE compared with those receiving placebo plus EXE (European Organisation for Research and Treatment of Cancer QLQ-C30 Global Health Status—Time to Definitive Deterioration minimally important difference: 5% change from baseline, 8.3 months vs. 5.8 months, $p = 0.0084$; 10% change from baseline, 11.7 months vs. 8.4 months, $p = 0.1017$)⁴⁸.

4.1.2 Recommendation

Multiple treatment options are available to women with HR+ HER2- ABC recurring or progressing on prior NSAI therapy, including EXE, F250, F500, and EVE plus EXE^{31–33,41}. When considering ET, thought should be

given to disease extent, degree of symptomatology, and duration of clinical benefit on prior ET. For patients with relatively indolent progression and endocrine-sensitive disease for whom ET is indicated, the available evidence supports the use of EVE plus EXE, which may be of particular benefit for patients with bone-only disease. But this combination may not be ideal for all patients; when selecting ET, consideration should be given to patient age, functional status, and extent of comorbidities. Other ET options should be considered in the event that a patient is unable to tolerate EVE.

Because of the increased risk of serious adverse events with the addition of EVE to EXE, together with the potential for early onset of select adverse events,

TABLE IV Phase III subgroup outcomes by burden of disease

Reference (study name)	Regimen	Visceral disease (%)	ORR ^a (%)	Progression-free survival by visceral disease status	
				Yes	No
<i>Fulvestrant</i>					
Chia <i>et al.</i> , 2008 ³¹ (EFFECT)	Fulvestrant 250 mg vs. exemestane	57.0	7.4 vs. 6.7 (<i>p</i> =0.736)	HR: 0.89 (95% CI: 0.75 to 1.10) ^b (TTP, <i>n</i> =395)	HR: 1.00 (95% CI: 0.80 to 1.35) ^b (TTP, <i>n</i> =298)
Johnston <i>et al.</i> , 2012 ³² (SOFEA)	Fulvestrant 250 mg vs. exemestane	Visceral: 60.0 Soft tissue or node: 25.2 Bone: 14.4	6.9 vs. 3.6 (<i>p</i> =0.10)	HR: 0.93 (95% CI: 0.73 to 1.18) (viscera dominant site of relapse, <i>n</i> =288)	HR: 0.79 (95% CI: 0.54 to 1.16) (soft tissue or node, <i>n</i> =121) HR: 1.37 (95% CI: 0.83 to 2.25) (bone, <i>n</i> =69)
Di Leo <i>et al.</i> , 2010 ³³ (CONFIRM)	Fulvestrant 500 mg vs. fulvestrant 250 mg	54.8	9.1 vs. 10.2	HR: 0.80 (95% CI: 0.65 to 1.00) ^b (<i>n</i> =471)	HR: 0.75 (95% CI: 0.57 to 0.95) ^b (<i>n</i> =265)
<i>Everolimus</i>					
Piccart <i>et al.</i> , 2012 ⁴⁵ (BOLERO-2)	Everolimus plus exemestane vs. exemestane	56	12.6 vs. 1.7 (<i>p</i> <0.0001)	6.8 vs. 2.8 months HR: 0.47 (95% CI: 0.38 to 0.60) ^b (<i>n</i> =406)	9.9 vs. 4.2 months HR: 0.41 (95% CI: 0.30 to 0.56) ^b (<i>n</i> =318)

^a Response rates for overall population.

^b HR and 95% CI estimated from forest plot.

ORR = objective response rate; HR = hazard ratio; CI = confidence interval; TTP = time to progression.

careful proactive safety monitoring and toxicity management is strongly recommended for patients on EVE plus EXE, so as to maximize clinical benefit and treatment adherence⁴⁹. For appropriate patients, EVE should begin at the prescribed dose of 10 mg, with a first follow-up appointment within 2 weeks to ensure early detection of hematologic or pulmonary adverse events, oral mucositis, or fatigue. Patients should undergo regular monthly clinical monitoring, including functional inquiry and symptom-directed physical examination, complete blood count and glucose level, and disease imaging every 3 months. For grade 3 adverse events, treatment may be interrupted until resolution and then resumed at the same or a lower dose. In the event of symptomatic pneumonitis, infection should be ruled out, treatment interrupted, and oral corticosteroids administered until symptoms resolve. Resolution may take between 7–10 days, at which point EVE may be reinitiated at a lower dose. Treatment should be discontinued in the event of grade 4 adverse events. If a patient is unable to tolerate EVE plus EXE, treatment with F500 or EXE is also an option.

4.2 Management of ET-Resistant Disease

4.2.1 Discussion

Although fewer in number, endocrine-resistant patients were represented in both the CONFIRM (33%–37%) and the BOLERO-2 (16%) trials^{33,41}. Compared with endocrine-resistant patients receiving F250 in the CONFIRM trial, those receiving F500 experienced a 28% reduction in the risk of progression (estimated HR: 0.72; 95% CI: 0.57 to 0.93), and in the BOLERO-2 trial, compared with patients receiving placebo plus EXE, those receiving EVE plus EXE experienced a 51% reduction in the risk of progression (estimated HR: 0.49; 95% CI: 0.30 to 0.81; Table III). The benefits of EVE plus EXE extended to patients receiving 3 or more lines of prior systemic therapy. These heavily pretreated patients experienced a 59% reduction in the risk of progression (HR: 0.41; estimated 95% CI: 0.32 to 0.53) and incremental median PFS gains of 5.2 months (8.2 months vs. 3.0 months)⁴⁵.

4.2.2 Recommendation

Treatment options in women with HR+ HER2– ABC recurring or progressing on prior NSAI therapy who have

relatively indolent progression and resistant disease are limited to F500, EVE plus EXE, chemotherapy, and EXE^{31–33,41}. For those patients, the magnitude of the clinical benefit, balanced with tolerability and convenience relative to chemotherapy, support the use of EVE plus EXE regardless of prior therapies. Chemotherapy remains the recommended treatment choice for patients with symptomatic visceral disease. Because EVE plus EXE may not be ideal for all patients, consideration should be given to the patient's age, functional status, and comorbidities, and alternative ET options should be considered if a patient is unable to tolerate EVE. A proactive EVE safety management strategy is recommended, and for patients for whom EVE plus EXE is not well tolerated, treatment with F500, EXE alone, or chemotherapy should be considered.

4.3 Treatment of Patients with High Burden of Disease

4.3.1 Discussion

Endocrine therapy is the preferred option for HR+ ABC, even in the presence of visceral disease⁶, and chemotherapy is recommended for patients with rapidly progressive or symptomatic visceral disease^{5,6}. More than half the patients in both the CONFIRM and the BOLERO-2 trials had visceral disease (55%–56%). Among patients with visceral disease in the CONFIRM trial, those receiving F500 (compared with those receiving F250) experienced a 20% reduction in the risk of progression (estimated HR: 0.80; 95% CI: 0.65 to 1.00)³³, and in the BOLERO-2 trial, compared to those receiving placebo plus EXE, those receiving EVE plus EXE experienced a 53% reduction in the risk of progression (PFS: 6.8 months vs. 2.8 months; HR: 0.47; estimated 95% CI: 0.38 to 0.60)⁴⁵ and a significantly improved ORR (9.5% vs. 0.4%, $p < 0.001$) overall⁴¹. Additionally, at a median follow-up of 18 months, patients with extensive visceral involvement and those who had received prior chemotherapy both experienced a 59% reduction in the risk of progression (>3 organs involved: 6.9 months vs. 2.6 months; HR: 0.41; estimated 95% CI: 0.30 to 0.55; prior chemotherapy: 8.2 months vs. 3.2 months; HR: 0.41; estimated 95% CI: 0.33 to 0.52)⁴⁵.

4.3.2 Recommendation

Chemotherapy is recommended for women with HR+ HER2– ABC with symptomatic or rapidly progressive disease^{5,6}. For patients with more indolent visceral disease or those declining chemotherapy, a number of treatment options, including EXE, F250, F500, and EVE plus EXE are available^{31–33,41}. The strength of the evidence and the magnitude of clinical benefit observed in BOLERO-2 supports the use of EVE plus EXE in patients with asymptomatic or minimally symptomatic visceral disease, regardless of disease extent and receipt of prior chemotherapy. A proactive EVE safety management strategy is recommended, and for those in whom

EVE plus EXE is not well-tolerated, treatment with F500, EXE, or chemotherapy should be considered.

4.4 Treatment of Elderly Patients with HR+ Disease Refractory to NSAIs

4.4.1 Discussion

Elderly patients are more likely to have multiple comorbidities that may limit life expectancy or tolerance of therapies⁵⁰. A comprehensive geriatric assessment is an important component in the decision to pursue systemic therapies. A substantial proportion of patients in both the CONFIRM and BOLERO-2 trials were 65 years of age or older (median: 61 years and 61–62 years respectively), and preplanned subgroup analyses in elderly populations were conducted for both trials. In the CONFIRM trial, elderly patients receiving F500 (compared with those receiving F250) experienced a 14% reduction in the risk of progression (HR: 0.86; 95% CI: 0.67 to 1.09) and no observed increase in the rate of adverse events. At 18 months' follow-up, patients receiving EVE plus EXE in the BOLERO-2 trial experienced a 41% (for those 65 years of age or older) and a 55% reduction in the risk of progression (for those 70 years of age or older)⁵¹. The most common adverse events in elderly patients were stomatitis, fatigue, decreased appetite, and diarrhea. Treatment with EVE was also associated with a greater incidence of on-treatment death in elderly women than in younger patients (Pritchard K. Unpublished data, November 2012). Most of the deaths were reported in very elderly patients (70 years of age and older) and might have been associated with comorbidities and overall health status at study entry.

4.4.2 Recommendation

Many treatment options are available to elderly postmenopausal HR+ HER2– patients who have recurrent or progressive disease on prior NSAI therapy, including EXE, F250, F500, and EVE plus EXE^{31–33,41}. Clinical judgment should be used when selecting an ET, and elderly patients should be well informed about the need for early toxicity reporting. Current evidence supports use of EVE plus EXE in conjunction with thorough and proactive adverse event management. In very elderly patients or in those with comorbidities or compromised health status, a dose escalation strategy should be considered, beginning with a starting dose of 5 mg and slowly increasing to a dose of 10 mg with demonstrated tolerance. In the event that an elderly patient is unable to tolerate EVE plus EXE, the use of F500 or another ET regimen is encouraged.

5. RE-BIOPSY

5.1 Discussion

There is evidence that receptor status may change over time and over the course of treatment. Guidelines

from the Advanced Breast Cancer First International Consensus Conference therefore recommend biopsy of a metastatic lesion, if easily accessible, to confirm diagnosis and to evaluate hormone receptor and HER2 expression^{52,53}. In the context of HR+ HER2- disease, a previously HER2- tumour may be found to be HER2+ upon re-biopsy, which would increase the number of treatment options by adding HER2-targeted therapies. In contrast, discovery of a change from HR+ to HR- potentially suggests resistance to ET and a need to try alternative therapies. Regardless of findings, re-biopsy results should be interpreted with caution and within the context of the patient's unique disease and treatment history, because variations in tissue processing and sampling can produce erroneous results.

5.2 Recommendation

The re-biopsy of a tumour once over the course of treatment for advanced disease is a reasonable practice if sample collection is straightforward and does not pose undue risk to the patient. Re-biopsy is strongly encouraged in women whose disease is not following the expected pattern of progression based on tumour receptor profile or in the case of an isolated lesion. Caution should be used when interpreting re-biopsy results, especially in instances in which loss of receptor status expression might result in the withholding of targeted therapy.

6. SUMMARY

With the increased use of NSAI therapy in both the adjuvant and first-line settings, there is a need to identify the optimal sequencing of ET in women with HR+ HER2- ABC who have recurrent or progressive disease on NSAI therapy. Sequential ET remains the goal of treatment for these patients⁵. Four large phase III trials—EFFECT, SOFEA, CONFIRM, and BOLERO-2—assessed the benefits of particular ET regimens in this patient population^{31-33,41}. Those studies demonstrated that F250 and EXE are of comparable efficacy and that, compared with fulvestrant alone, the addition of anastrozole to fulvestrant does not improve outcomes. Data also demonstrate that F500 and EVE plus EXE result in statistically significant improvements in PFS compared with control regimens, with associated reductions of 20% and 57% respectively in the risk of progression. Increasing the dose of fulvestrant from F250 to F500 did not increase toxicity, but an increase in toxicity was seen with the addition of EVE to EXE. Of the many available ET options for patients with HR+ HER2- disease who have experienced disease recurrence or progression on prior NSAI therapy, the rigour of the evidence and the magnitude of the clinical benefit support the use of EVE plus EXE in most clinical cohorts (Figure 2). Consideration should be given to the patient's age, functional status, and comorbidities when selecting an ET, and use of a proactive EVE safety management strategy is encouraged.

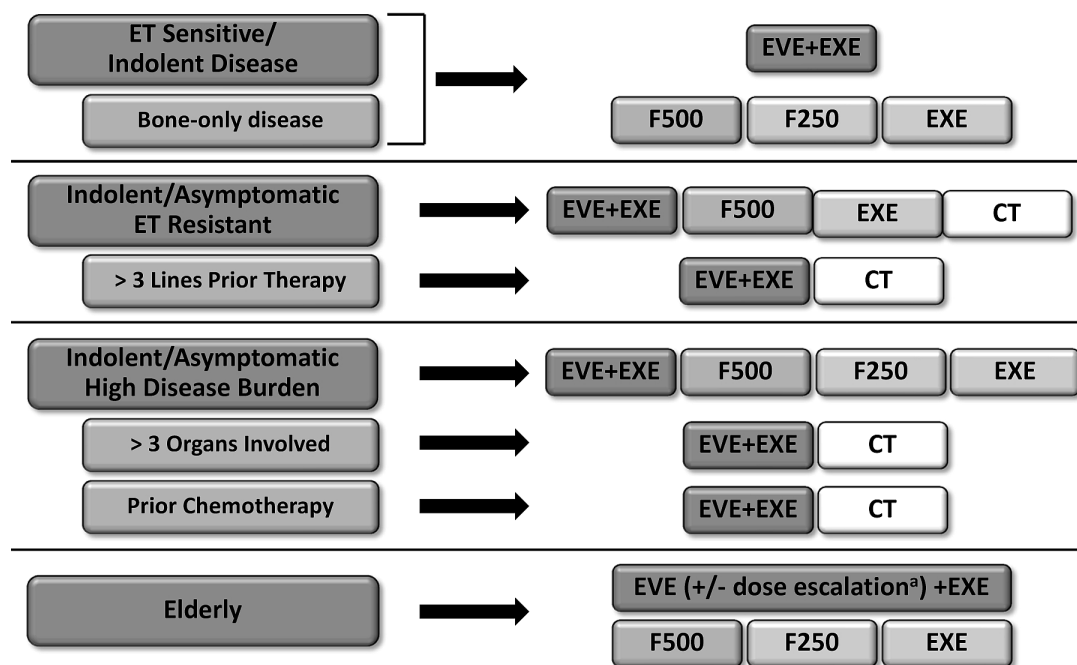


FIGURE 2 Endocrine therapy (ET) treatment guidelines for postmenopausal patients with hormone receptor-positive and human epidermal growth factor receptor 2-negative advanced breast cancer recurring or progressing on prior nonsteroidal aromatase inhibitor therapy. ^a For patients 70 years of age or older, or for those with multiple comorbidities or frailties compromising overall health status, consideration should be given to a reduced starting dose of 5 mg daily, followed by potential dose escalation based on tolerance. EVE = everolimus; EXE = exemestane; F500 = fulvestrant 500 mg; F250 = fulvestrant 250 mg; CT = chemotherapy.

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KIP is a consultant for Roche, Novartis, AstraZeneca, Abraxis, Pfizer, and Amgen, and has received honoraria from Roche, Novartis, AstraZeneca, Abraxis, Pfizer, Boehringer–Ingelheim, and Amgen. KAG is a consultant for Roche, Novartis, AstraZeneca, Pfizer, and Amgen, and has received research funding from Roche. LP is a consultant for Roche and Novartis. She has received honoraria from Roche, Novartis, and Amgen, and research funding from Roche and Pfizer. DR is a consultant for Roche and Novartis, has received honoraria from Roche and Novartis, and has received research funding from Roche. MW is a consultant for Roche, Novartis, and AstraZeneca, and has received honoraria from Novartis, AstraZeneca, and Roche. DM is owner and founder of Kaleidoscope Strategic. SV is a consultant for Novartis, AstraZeneca, Roche, and GlaxoSmithKline, has received honoraria from Novartis, AstraZeneca, and Roche, and has received research funding from Roche and Sanofi-Aventis.

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