CURRENT ONCOLOGY, VOL 20, NO 1 (2013)

Practice Guideline Series

Endocrine therapy for postmenopausal women with hormone receptor–positive HER 2–negative advanced breast cancer after progression or recurrence on nonsteroidal aromatase inhibitor therapy: a Canadian consensus statement

K.I. Pritchard , MD [*], K.A. Gelmon , MD [†], D. Rayson , MD [‡], L. Provencher , MD [§], M. Webster , MD PhD [‖], D. McLeod , BSc [#], S. Verma , MD [**]

[*] *Sunnybrook Odette Cancer Centre and the University of Toronto, Toronto, ON.*

[†] *BC Cancer Agency, Vancouver, BC.*

[‡] *QEII Health Sciences Centre, Halifax, NS.*

[§] *Centre des Maladies du Sein Deschênes–Fabia, CHU de Québec, Hôpital St-Sacrement, Québec City, QC.*

[‖] *Tom Baker Cancer Center, Calgary, AB.*

[#] *Kaleidoscope Strategic, Toronto, ON.*

[**] *Sunnybrook Odette Cancer Centre, Toronto, ON.*

doi: http://dx.doi.org/10.3747/co.20.1316

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 (HER 2–) 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—EFECT , 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 + HER 2– 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.

KEYWORDS: Advanced breast cancer , endocrine therapy , m TOR -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 disease[1]. 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 s) 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 (HER 2) with ET in HER 2-positive (HER 2+) ABC [13,14],

Par Pharm., Inc.
Exhibit 1084
Par Pharm., Inc. v. Novartis AG
Case IPR2016-00084

DOCKET ALARM
Find authenticated court documents without watermarks at docketalarm.com.

attempts at combining other receptor tyrosine kinase inhibitors with ET in the HER 2-negative (HER 2–) setting have met with limited success14–16, highlighting an unmet clinical need in this population.

Sequential ET with selective estrogen receptor modulators, steroidal AI s, and estrogen receptor downregulators remains the current standard of care for postmenopausal women with HR + HER 2– 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 NSAI s25. 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 NSAI s26, 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 receptors28,29. 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 ET s34. A recently identified mechanism of endocrine resistance is aberrant signalling through the phosphatidylinositol 3 kinase–Akt–mammalian target of rapamycin (m TOR) signalling pathway35–37. Targeted inhibition of this pathway using m TOR inhibitors has therefore become a key clinical research strategy in the attempt to reverse resistance to ET . Three m TOR 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 + HER 2– patients recurring or progressing on prior ET 10,39.

Postmenopausal women with HR + HER 2– ABC recurring or progressing on NSAI s 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.

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

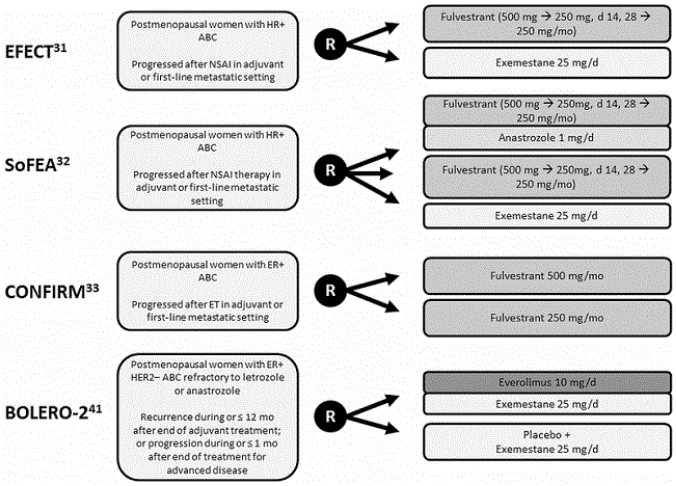

FIGURE 1 *Trial design summary. HR + = hormone receptor–positive; ABC = advanced breast cancer; NSAI = nonsteroidal aromatase inhibitor; R = randomization; ER + = estrogen receptor–positive; ET = endocrine therapy; HER 2– = human epidermal growth factor receptor 2–negative.*

The EFECT trial evaluated the safety and efficacy of fulvestrant compared with EXE in patients with advanced disease[31]. 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 I). Survival data have yet to be reported[31].

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

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

Reference (trial name)	Treatment regimen	Pts (n)	Median age [years (range)][f]	HER2 status (% positive/ negative/unknown)	ORR (%)	CBR (%)	Progression-free survival (months)	Progression-free survival HR (95% CI)	Overall survival (months)	Overall survival HR (95% CI)
Fulvestrant										
Chia *et al.*, 2008[31] (EFECT)	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] (p=0.736)	32.2[a,b] (p=0.853)	3.7[c]	0.93 (0.819 to 1.133) (p=0.6531)	NR	
	Exemestane PO 25 mg daily	342	63 (32–91)	NR	6.7[a]	31.5[a,b]	3.7[c]		NR	
Johnston *et al.*, 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 (p=0.82)[d]	33.7 (p=0.58)[d]	4.4	1.00 (0.83 to 1.21)[d] (p=0.98)	20.2	0.95 (0.76 to 1.17)[d] (p=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 (p=0.10)[e]	31.6 (p=0.25)[e]	4.8	0.95 (0.79 to 1.14)[e] (p=0.56)	19.4	1.05 (0.84 to 1.29)[e] (p=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 *et al.*, 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] (p=0.10)	Overall: 6.5	Overall: 0.80 (0.68 to 0.94) (p=0.006) Prior AI: 0.85 (0.67 to 1.08)[c]	25.1	Overall: 0.84 (0.69 to 1.03) (p=0.091)
	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	
Everolimus										
Baselga *et al.*, 2012[41] (BOLERO-2)	Everolimus PO 10 mg daily, exemestane PO 25 mg daily	485	62 34–93	0.0/100.0/0.0	9.5 (p<0.001)	79.6 (p<0.001)	6.9 Central assessment: 10.6	0.43 (0.35 to 0.54) (p<0.001) Central assessment: 0.36 (0.27 to 0.47) (p<0.001)	NR	
	Everolimus-placebo PO, exemestane PO 25 mg daily	239	61 (28–90)		0.4	59.0	2.8 Central assessment: 4.1		NR	

[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.

The SoFEA trial compared both fulvestrant alone and fulvestrant plus anastrozole with EXE . This threearm 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 I).

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 II).

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

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] (EFECT)		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)					
	Ful (n=351)	Exe (n=340)	Ful (n=230)		Exe (n=247)		F500 (n=361)		F250 (n=374)		Eve plus Exe (n=482)			Pbo plus Exe (n=238)		
	Any[b] (%)	Any[b] (%)	Any (%)	Grades 3 and 4 (%)	Any (%)	Grades 3 and 4 (%)	Any[c] (%)	Grades 3 and 4[d] (%)	Any[e] (%)	Grades 3 and 4[d] (%)	Any (%)	Grade 3 (%)	Grade 4 (%)	Any (%)	Grade 3 (%)	Grade 4 (%)
Stomatitis	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	56	8	0	11	1	0
Infection	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	50	4	2	25	2	0
Nausea	6.8	7.9	43.5[g]	0.9[g]	37.2[g]	3.2[g]	NR	NR	NR	NR	27	<1	<1	27	1	0
Arthralgia	3.7	5.6	42.6	3.0	46.6	3.2	18.8[f]	2.2[f]	18.7[f]	2.1[f]	16	1	0	16	0	0
Lethargy	3.1[g]	2.1[g]	62.6	4.8	54.3	4.5	NR	NR	NR	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.

The phase III double-blind placebo-controlled CONFIRM trial evaluated the safety and efficacy of doubling the dose of fulvestrant for patients with prior exposure to ET 33. 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 AI s (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 unclear43,44.

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 EXE 45. 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 EXE 41. 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).

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

DOCKET ALARM Find authenticated court documents without watermarks at docketalarm.com.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.