RESEARCH ARTICLE

Fulvestrant 250mg versus Anastrozole 1 mg in the Treatment of Advanced Breast Cancer: a Meta-Analysis of Randomized Controlled Trials

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Abstract

Objective: Most patients with advanced breast cancer experience resistance to endocrine treatment and eventual disease progression. This meta-analysis was designed to compare the efficacy and tolerability of fulvestrant 250mg with anastrozole 1mg in postmenopausal women with advanced breast cancer. Methods: Electronic literature databases (Cochrane Library, Medline, and Embase) were searched for randomized controlled trials (RCTs) published prior to August 2013. Only RCTs that compared fulvestrant 250mg to anastrozole 1mg in postmenopausal women with advanced breast cancer were selected. The main outcomes were time to treatment failure (TTF), time to progression (TTP), duration of response (DOR), clinical benefit rate, and tolerability. Results: Four RCTs covering 1,226 patients (fulvestrant, n=621; anastrozole, n=605) were included in the meta-analysis. Fulvestrant increased the DOR compared to anastrozole (HR =1.31, 95% confidence interval [CI] 1.13–1.51). There was no statistically significant difference between fulvestrant and anastrozole in terms of TTF (HR=1.02, 95%CI 0.89–1.17), complete response (RR=1.79, 95%CI, 0.93–3.43), and partial response (RR=0.91, 95%CI 0.69–1.21). As for safety, there was no statistical significance between the two groups for common adverse events. Conclusion: Fulvestrant 250mg is as effective and well-tolerated as anastrozole 1mg treatment for advanced breast cancer in postmenopausal women whose disease progressed after prior endocrine treatment. Thus, fulvestrant may serve as a reasonable alternative to anastrozole when resistance is experienced in breast cancer cases.

Keywords: Fulvestrant - anastrozole - advanced breast cancer - meta-analysis

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Introduction

Breast cancer remains one of the most frequently diagnosed malignancies in women. Treatments for advanced breast cancer include chemotherapy, endocrine therapy and possibly surgery and radiation therapy. Despite the advances in hormonal therapy, most patients with advanced breast cancer experienced a resistance to endocrine treatment and eventually lead to disease progress. The estrogen receptor (ER), progesterone receptor r (PgR), human epidermal growth factor receptor-2 (HER-2), and Ki67 as a surrogate of intrinsic subtype classification (Goldhirsch et al., 2011). The positive HER-2 is a predictor of worse disease free survival rate and high recurrence rate in patients with breast cancer (Najafi et al., 2013; Jia et al., 2014). Therefore, it is very urgent to identify and evaluate new hormonal agents that are effective after disease progression.

Anastrozole, the third-generation aromatase inhibitor has been used ahead of tamoxifen as a second-line treatment for advanced breast cancer (Winer et al., 2005). However, most patients with advanced disease will eventually lead to progressing, so there is a requirement for new agents without cross-resistance. Fulvestrant is a steroidal analogue of oestrogen which completely inhibits ER signaling and lacks cross-resistance with other antioestrogens. Fulvestrant also decreases expression of the PgR (Robertson et al., 2001).

Many subsequent studies have compared the efficacy and tolerability between fulvestrant with anastrozole (Howell et al., 2002; Osborne et al., 2002; Robertson et al., 2009). Based on the previously published clinical evidence, a well-designed meta analysis (Valachis et al., 2010) showed that fulvestrant was similarly effective and well tolerated as the third-generation aromatase inhibitors in the treatment of postmenopausal women with advanced breast cancer, however, there was substantial heterogeneity in the types of aromatase inhibitors. The recent publication of two new RCTs (Xu et al., 2011; Carlson et al., 2012) that compared the efficacy and tolerability of fulvestrant with anastrozole in advanced breast cancer patients instigated our efforts to perform a

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Table 1. General Characteristics of Studies Included in the Meta-analysis

First author	Year	Design	Patient Population	Participants	Age: median/ mean or range	Fulvestrant group	Anastrozole	Outcomes	Quality Assessment
Howell et al	2002	Randomized, international, multicenter, parallelgroup, phase III trial	Postmenopausal women with locally advanced or metastatic breast cancer whose disease had progressed during adjuvant endocrine therapy or first-line endocrine therapy for advanced disease.	Fulvestrant: 222; Anastrozole: 229	63(mean); 64(mean)	Fulvestrant 250 mg (IM) once monthly	Anastrozole 1 mg/day orally	TTP, OR, DOR, and safety	B
Osborne et al	2002	Randomized double-blind, double dummy, parallel-group study	Postmenopausal women with locally advanced or metastatic breast cancer whose disease had progressed during adjuvant endocrine therapy or first-line endocrine therapy for advanced disease.	Fulvestrant: 206; Anastrozole: 194	63(mean); 62(mean)	Fulvestrant 250 mg (IM) once monthly	Anastrozole 1 mg/day orally	TTP, OR, DOR, and safety	B
Xu et al	2011	Double blind, double-dummy, randomised phase III study	Postmenopausal women with ER-positive advanced breast cancer who had relapsed or progressed following previous adjuvant anti-oestrogen therapy.	Fulvestrant: 121; Anastrozole: 113	53.4 (8.3); 54.8 (9.8)	Fulvestrant 250 mg (IM) every 4 weeks	Anastrozole 1 mg daily p.o. monthly	TTP,OR, TTF, and safety	B
Carlson et al	2012	Randomized, double-blind, placebo-controlled trial	Postmenopausal women with ER+and/or PgR+ recurrent or metastatic breast cancer. Patients had not received prior endocrine therapy and prior aromatase inhibitor, ER down-regulator	Fulvestrant: 72; Anastrozole: 69	58 (34–90); 63 (35–91)	Fulvestrant 250 mg intramuscularly every 4 weeks plus gefitinib; 500 mg/d orally was modified to use a starting dose of gefitinib of 250 mg/d	Anastrozole 1 mg orally daily plus gefitinib 500 mg/d was modified to use a starting dose of gefitinib of 250 mg/d.	OR and safety	

focused meta-analysis using the accumulated clinical evidence.

The objective of this meta-analysis is to compare the efficacy and safety of administration fulvestrant 250mg and anastrozole 1mg in postmenopausal women with advanced breast cancer using the most comprehensive, up-to-date clinical data available in the public literature.

Materials and Methods

Search strategy

Systematic literature searches were conducted in PubMed, Embase, and the Cochrane Library published prior to August 2013. All databases were searched without language restrictions. Potentially relevant randomized controlled trials (RCTs) were identified by various combinations of the following search terms: fulvestrant OR faslodex, anastrozole, breast OR mammary, tumor OR malignant OR carcinoma OR cancer and ovarian failure. When multiple publications were identified for the same population, only the most recent publication was selected. In addition, we searched the existing meta-analyses and scanned the cited references in published studies to identify any additional eligible trials.

Trial selection

Trials satisfying the following criteria were included in the meta-analysis: 1) RCTs comparing fulvestrant 250mg versus anastrozole 1mg in postmenopausal women with advanced breast cancer; and 2) the fulvestrant and anastrozole arms had to differ only by fulvestrant and anastrozole. Trials were excluded based upon the following criteria: 1) the presence of life-threatening metastatic visceral disease; 2) any concurrent medical illness or laboratory abnormalities; 3) reviews, letters, abstract, and case reports.

Types of outcome measures

The primary outcome measures were time to treatment failure (TTF), time to progression (TTP), objective response, and duration of response (DOR). Secondary outcome measure was the rate of adverse events. TTF is defined as the earliest occurrence of disease progression or withdrawal of study treatment for any reason, including death from any cause. TTP was defined as the time from randomization until objective disease progression or death from any cause before progression. Objective response was defined as the proportion of all treated patients with measurable disease at baseline who had a best objective tumor response of either complete response or partial response after treatment; DOR is defined as responding patients only as the period of time from randomization to the first observation of disease progression or death.

Data extraction and quality assessment

Two reviewers (DD Gong and CF Man) independently extracted the data from each trial using a standardized form with predefined criteria that had been developed for this meta-analysis and which included the following items: 1) baseline demographics: author, and year of publication; 2) participants: sample size and age; 3) fulvestrant intervention; 4) anastrozole intervention; 5) duration of intervention; 6) outcome measures; and 7) adverse events. Discrepancies between the extracted datasets were resolved by discussion.

The methodological quality of each study was assessed in accordance with the guidelines in the Cochrane reviewers' handbook (Higgins JPT, 2009). The following trial design features were assessed: 1) measured or unmeasured baseline characteristics due to the method by which trial participants had been selected or assigned; 2) care provided apart from the intervention being evaluated; 3) method by which outcomes were ascertained, diagnosed, and verified; and 4) withdrawal or exclusion of participants throughout the course of the trial. If all quality criteria were met, the trial was considered to have low risk of bias (score: A). If one or more of the quality criteria were only partially met, the trial was considered to have moderate risk of bias (score: B), and if one or more criteria not met, the trial was considered to have high risk of bias (score: C).

Statistical analysis

Risk ratio (RR) and 95% confidence interval (CI) were computed for objective response and adverse events of endpoints as dichotomous outcomes. Hazard ratios (HRs) were summarized, and their corresponding standard errors were calculated to analyze the time-to-event data as generic inverse variance outcomes.

Table 2. Summary of the Common Adverse Events of the Included Trials in the Meta-analysis

Adverse events	Number. of studies	Participants number	Adverse events in fulvestrant arm	Adverse events in anastrozole arm	OR	95%CI	Heterogeneity		*P*-value
							I^2 statistic(%)	*P*	
Nausea	4	1238	140	147	0.93	0.76-1.13	0	0.43	0.45
Vomiting	3	1004	68	77	0.86	0.64-1.17	0	0.49	0.34
Anorexia	3	779	56	53	1.03	0.74-1.42	24	0.27	0.88
Constipation	2	856	53	45	1.14	0.79-1.66	0	0.45	0.49
Diarrhea	2	545	90	91	0.96	0.61- 1.51	75	0.05	0.75
Bone pain	4	1090	82	75	1.07	0.80-1.43	34	0.21	0.66
Cough	2	631	30	34	0.83	0.53-1.32	0	0.35	0.44
Headache	2	856	65	71	0.88	0.65- 1.20	0	1	0.43
Vasodilatation/Hot flash	3	1090	80	77	1.01	0.76-1.34	0	0.62	0.96
Asthenia	3	1090	110	126	0.84	0.67-1.05	0	0.72	0.12
Arthralgia	2	382	19	17	1.11	0.61-2.01	56	0.13	0.74

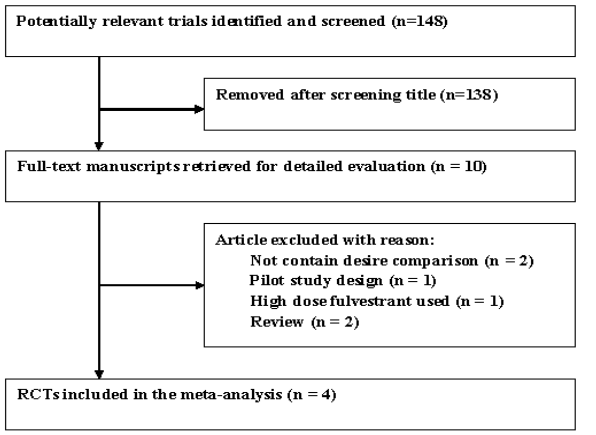

Figure 1. Flow Chart of Trial Selection Process for Meta-analysis

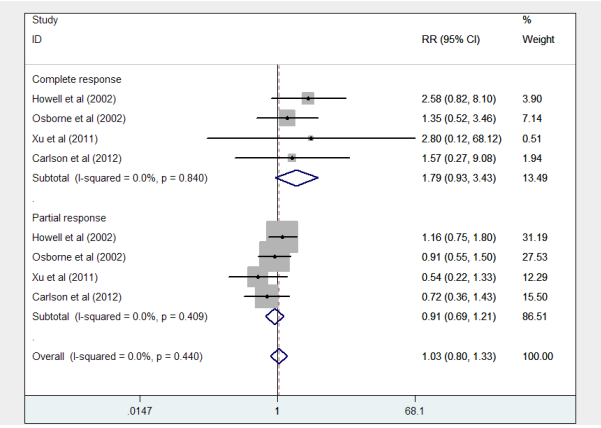

Figure 2. Forest Plots Showing RR of Complete Response and Partial Complete Rate of Eligible Trials Comparing Fulvestrant with Anastrozole

Heterogeneity of effect sizes across studies was assessed by using the Cochrane Q statistic and the I^2 statistic. If $p>0.10$ or $I^2<50\%$ were taken as indicators in the same scale of outcomes using a fixed-effect model. If $p\leq0.10$ or $I^2>50\%$ were taken as indicators in different scales of outcomes using a random effect model, based on the suggestion of the Cochrane Handbook for Systematic Review of Interventions (Higgins et al., 2003).

Potential publication bias was assessed by both Begg's rank correlation test (Begg and Mazumdar, 1994) and Egger's linear regression test (Egger et al., 1997) with $p<0.10$ indicating statistical significance. Finally, sensitivity analysis was used to investigate the influence of a single study on the overall risk estimate, and was carried out by sequentially omitting one study at each turn with the metaninf algorithm in STATA. A *p*-value of <0.05 was considered statistically significant. All analyses were performed with STATA statistical software (version 12.0; STATA Corp LP, College Station, TX, USA).

Results

Literature search

A total of 1276 potentially relevant publications were identified by the initial electronic search. After reviewing the full-texts, only four trials (Howell et al., 2002; Osborne et al., 2002; Xu et al., 2011; Carlson et al., 2012) met the inclusion criteria (Figure 1).

Baseline characteristics and risk of bias for the individual trials

Characteristics of the four RCTs are listed in Table 1. Four trials (Howell et al., 2002; Osborne et al., 2002; Xu et al., 2011; Carlson et al., 2012) were composed of 1226 postmenopausal advanced breast cancer patients, including 621 who had received fulvestrant and 605 who had received anastrozole. Patients were treated with fulvestrant 250mg dosages intramuscular or oral administration of anastrozole 1 mg/day monthly. All of the included trials were classified as having low or moderate risk of bias according to the methodological quality assessment.

Objective response

Objective response data were available from all the included trials, the complete response rate was 3.86% (24 out of 621 patients) in fulvestrant arm in comparison with 2.1% (13 out of 605 patients) in anastrozole arm; partial response rate was 14.5% (90 out of 621 patients) in the fulvestrant arm in comparison with 14.4% (87 out of 605 patients) in anastrozole arm.

As it shown in Figure 2 A, for complete response rate analysis, there was no heterogeneity ($I^2=0\%$, $p=0.840$) among the four trials, we used the fixed-effect model method. The RR was in favor of the fulvestrant treatment [versus. anastrozole: RR=1.79, 95% CI 0.93–3.43)] in increasing the complete response rate, although this was not significant ($p= 0.08$). For partial response rate

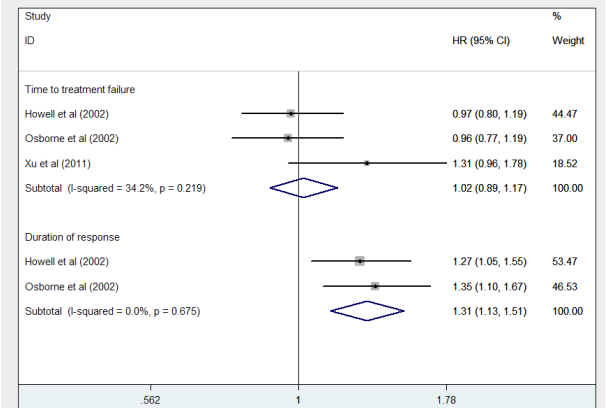

Figure 3. Forest Plots Showing HR of Time to Treatment Failure and Duration of Response of Eligible Trials Comparing Fulvestrant with Anastrozole

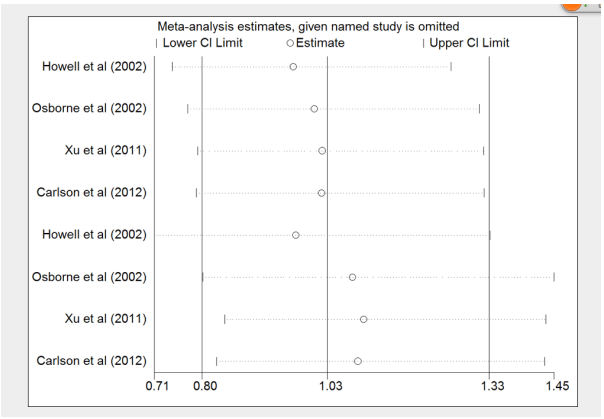

Figure 4. RR and 95% CI by Omitting Each Study from the Included Trials of Complete Response and Partial Complete Rate

analysis, there was no heterogeneity (I^2=0%, p=0.409), administration of fulvestrant was not associated with increased partial response rate [versus. anastrozole: RR=0.91, 95% CI, 0.69–1.21)], and the difference were not significant (p= 0.525).

TTF and DOR

TTF data were available from three trials (Howell et al., 2002; Osborne et al., 2002; Xu et al., 2011) involving 1085 patients. There was not statistically significant in TTF [versus. anastrozole: HR=1.02, 95% CI 0.89–1.17)] in a fixed-effect model. The heterogeneity among the three trials was not obvious (I^2=34.2%, p=0.219). DOR data were available from two trials (Howell et al., 2002; Osborne et al., 2002) involving 851 patients. There was statistically significant in DOR [versus. anastrozole: HR=1.31, 95% CI 1.13–1.51] in a fixed-effect model. There were no heterogeneity between the two trials (I^2=0%, p=0.675).

TTP

TTP data were available from three trials (Howell et al., 2002; Osborne et al., 2002) involving 1085 patients. In the trial of Howell et al (Trial 020) (Howell et al., 2002) and Osborne et al (Trial 021) (Osborne et al., 2002), TTP data were reported by HR and 95.14%CI. There was no statistically significant difference in TTP between fulvestrant and anastrozole (HR=0.98, 95.14% CI 0.80–1.21 in Trial 020; HR=0.92, 95.14%CI 0.74–1.14 in Trial 021, separately). There was also no statistical difference between the treatment groups (HR=1.314, 95% CI 0.948–1.822) in Xu et al report (Xu et al., 2011). Due to the heterogeneity in statistical methods, we did not pooled the TTP.

Adverse events

All the included RCTs reported adverse events experienced by patients in the treatment groups. The common adverse events included nausea, vomiting, anorexia, constipation, diarrhea, hot flush/vasodilatation, headache, bone pain, cough, arthralgia, etc. There was no statistical significance between the two groups for the common adverse events. The detail summary of adverse events of fulvestrant and anastrozole was shown in Table 2.

Sensitivity and publication bias analysis for objective response

As shown in Figure 4, the quantitative summary measure of RR (95% CI) for objective response changed very little by sequential omission of individual trials. Neither the Begg's rank correlation test (p=0.454) nor the Egger's linear regression test (p=0.326) showed any evidence of publication bias for the trials reporting RR of complete response rate and partial response rate.

Discussion

The major findings of the current meta-analysis provide evidence that administration of fulvestrant can significantly increase the DOR comparing with those treated with anastrozole in postmenopausal patients with advanced breast cancer. However, there was no difference in terms of complete response rate, partial response rate, TTF, and TTP. As for safety, there was no statistical significance between the two groups for the common adverse events.

Treatment of breast cancer in postmenopausal women with hormone-responsive tumors is based on two aspects: prevention of estrogen binding to the estrogen receptor using an antiestrogen, or lowering of estrogen levels using an aromatase inhibitor. Tamoxifen has also been shown to be highly effective in oestrogen receptor (ER)-positive postmenopausal advanced breast cancer for many years. Unfortunately, resistance to tamoxifen treatment will eventually lead to the disease recurs or progress in most patients with advanced breast cancer (Motamedi et al., 2012). Standard follow-up treatments are the aromatase inhibitors, including anastrozole. Anastrozole are now increasingly used ahead of tamoxifen in advanced and adjuvant settings (Fisher et al., 1998). However, most patients with advanced disease still recur or progress, therefore it is urgent to identify new agents without cross-resistance

Fulvestrant is a steroidal analogue of oestrogen which completely inhibits ER signalling with a novel mode of action, distinct from that of tamoxifen or any other antiestrogen. In the current meta-analysis, treatment

with fulvestrant increased the DOR compared with anastrozole (HR=1.31; 95%CI 1.13–1.51). Fulvestrant showed a numerical improvement in TTF compared with anastrozole; however, the pooled analyses of TTF showed no statistically significant. There was also no statistically significant difference between fulvestrant and anastrozole in terms of complete response, and partial response.

Dose-dependent clinical activity has been observed for fulvestrant. Evidence suggest that doses of fulvestrant higher than 250mg may have greater pharmacodynamic activity against the ER pathway (Robertson, 2007). Patients receiving fulvestrant at 500mg showed a higher response rate than those receiving fulvestrant at the approved dose (Howell and Sapunar, 2011). In Robertson's study (Robertson et al., 2009) , high dose fulvestrant (double the approved dose) was associated with significantly longer TTP (HR= 0.63, 95% CI 0.39 –1.00). There were 29.4% patients in the high dose fulvestrant group had progressed compared with 41.7% of those in the anastrozole group. The CONFIRM study (Di Leo et al., 2010) showed a statistical significant improvement in PFS with fulvestrant 500 mg. The NEWEST study (Kuter et al., 2012) indicated that fulvestrant 500 mg regimen reduced the expression of ER and PgR and increased overall response. Both doses were well tolerated with no unexpected adverse events. A recent published network meta-analysis (Cope et al., 2013) demonstrated that fulvestrant 500 mg is expected to be more efficacious than fulvestrant 250 mg. Above data supported higher dose of 500 mg might be more effective. However, not all the evidences support this conclusion. FINDER1 (Ohno et al., 2010) and FINDER2 (Pritchard et al., 2010) study showed fulvestrant approved dose, loading dose or high dose had similar efficacy and tolerability in postmenopausal women with advanced breast cancer. Whether the increment of dose regimen improves patients'outcome is still controversial. More well-designed RCTs are needed to determine of the optimum fulvestrant dose regimen.

Clinical trials evaluating the clinical efficacy of fulvestrant in combination with anastrozole has been conducted. However, two RCTs comparing intramuscular fulvestrant 250 mg monthly in combination with daily anastrozole (1 mg) to anastrozole alone as first line therapy in women with metastatic postmenopausal ER-positive breast cancer have exerted conflicting results. Bergh et al. (2012) reported no significant improvement of PFS or OS with combination therapy. Another study reported by Mehta et al. (2012) showed a significant improvement of both PFS and OS. Therefore, additional benefit of the combination with fulvestrant at a dose of 250 mg monthly therapy is not robust.

Despite the efficacy of fulvestrant and anastrozole treatment with advanced breast cancer in postmenopausal patients, a major concern of both patients and treating physicians is the potential side effects of those drugs. The frequently reported adverse events were nausea, vomiting, anorexia, constipation, diarrhea, hot flush/vasodilatation, headache, bone pain, cough, arthralgia, and injection-site pain. Most adverse events were mild. Even at the high dose of 500 mg/month in Robertson's study (Robertson et al., 2009), fulvestrant were still well tolerated. Only three patients in each group (fulvestrant, 3.0%; anastrozole, 2.9%) discontinued treatment because of adverse effects. The most common adverse events of high dose fulvestrant were bone pain (13.9%), nausea (10.9%), arthralgia (9.9%), constipation (9.9%), vomiting (8.9%), and dyspnea (8.9%). The current meta-analysis found no statistically significant differences for the common adverse events between fulvestrant and anastrozole. In a Japanese trial, the total doses administered in the first month were 500, 1000 and 1500 mg, respectively. All three fulvestrant dose regimens were well tolerated, with no emerging safety concerns (Pritchard et al., 2010).

Although only RCTs were included in the current meta-analysis, several potential limitations exist that may have impacted the results. First, only English languages RCTs were identified. It is possible that some relevant clinical data published in other languages may have been overlooked. Second, there was considerable heterogeneity in the design and modes of treatment used in each study. Such as in Xu et al' s study (Xu et al., 2011), more patients in the fulvestrant group (32%) than in the anastrozole group (24%) had undergone two previous rounds of chemotherapy, potentially giving those patients in the fulvestrant 250 mg group a worse prognosis. Third, the limited number of eligible trials is not enough to perform further subgroup analysis, such as based on ER and/or PgR analysis.

In conclusion, fulvestrant 250mg is as effective and safe as anastrozole 1mg for patients with advanced breast cancer. Fulvestrant provides an additional choice for the management of women with advanced breast cancer resistant to anastrozole. However, additional well-designed trials with hormone status of patient and line are needed to clarify which patients should be more appropriate.

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