Health-related quality of life from a phase III randomized trial of fulvestrant 500 mg versus anastrozole for hormone receptor-positive advanced breast cancer (FALCON)

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Running header: FALCON HRQoL

Word count: 2376 (2500 maximum)

Abstract word count: 250 (250 maximum)

Tables and figures: 6 main display items (5 figures, 1 table);

2 supplementary figures

References: 25 (40 maximum)

Abstract

Background: The phase III randomized FALCON trial (NCT01602380) demonstrated improved progression-free survival with fulvestrant 500 mg versus anastrozole 1 mg in endocrine therapy-naïve postmenopausal women with hormone receptor-positive (HR+) locally advanced or metastatic breast cancer (LA/MBC). Furthermore, overall health-related quality of life (HRQoL) was maintained and comparable for fulvestrant and anastrozole. Here, we present additional analyses of patient-reported HRQoL outcomes from FALCON.

Methods: Women with endocrine therapy-naïve HR+ LA/MBC were randomized 1:1 to fulvestrant (days 0, 14, 28, then every 28 days) or anastrozole (daily) until disease progression or discontinuation. HRQoL was assessed by FACT-B questionnaire (TOI and FACT-B total score) at randomization and every 12 weeks during treatment. HRQoL data post-treatment (with or without progression) were also collected.

Results: In total, 462 patients were randomized (fulvestrant, n = 230; anastrozole, n = 232). Compliance to FACT-B overall ranged from 60.0–97.4%. Mean change from baseline in TOI and FACT-B total score remained broadly stable (approximately ± 3 points to week 132) and was similar between arms during treatment. HRQoL was also maintained in FACT-B subscales. Approximately one-third of patients had improved TOI (≥+6 points) and FACT-B (≥+8 points) total scores from baseline up to week 120 and 132, respectively, of treatment with fulvestrant (ranges 26.4–45.0% and 22.4–35.8%, respectively) and anastrozole (ranges 18.6–32.9%, and 22.7–37.9%, respectively).

Conclusions: Mean change from baseline in TOI and FACT-B total score was maintained for fulvestrant and anastrozole; similar proportions of patients in both arms had improved TOI and FACT-B total scores.

ClinicalTrials.gov identifier: NCT01602380

KEYWORDS: Anastrozole; FALCON; Fulvestrant; Health-related quality of life;

Locally advanced or metastatic breast cancer

1. Introduction

Endocrine monotherapy is the recommended first-line treatment for the majority of postmenopausal patients with hormone receptor-positive (HR+), locally advanced or metastatic breast cancer (LA/MBC) [1–3]. First-line treatment options that are currently recommended include tamoxifen or an aromatase inhibitor (AI), such as anastrozole, letrozole, or exemestane, fulvestrant, and the cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with an AI [1–3]. Fulvestrant is a selective oestrogen-receptor degrader that blocks oestrogen-receptor function [4], and was originally approved by the European Medicines Agency for the treatment of postmenopausal patients with HR+ LA/MBC, and by the United States Food and Drug Administration for postmenopausal women with HR+ MBC, who have progressed on prior anti-oestrogen therapy [5,6]. Fulvestrant is also approved in the USA and Europe for the treatment of patients with HR+ human epidermal growth factor 2-negative advanced or MBC in combination with palbociclib, and in the USA with abemaciclib, following disease progression on prior endocrine therapy [6].

In the double-blind, randomized phase III Fulvestrant and Anastrozole Compared in Hormonal Therapy Naïve Advanced Breast Cancer (FALCON) trial (NCT01602380), fulvestrant 500 mg demonstrated significantly improved progression-free survival (PFS) versus anastrozole 1 mg in postmenopausal women with HR+ LA/MBC who had not received prior endocrine therapy (hazard ratio [HR] = 0.797; 95% confidence interval [CI]: 0.637–0.999; P = 0.0486) [7]. These data confirmed the results of the phase II, randomized, open-label FIRST (Fulvestrant First-Line Study Comparing Endocrine Treatments) study (NCT00274469), which reported that fulvestrant 500 mg improved time to disease progression and overall survival compared with anastrozole 1 mg for the first-line treatment of postmenopausal women with HR+ LA/MBC [8–10].

Following these findings, fulvestrant received regulatory approval in Europe, Russia, Japan and the USA for the first-line treatment of postmenopausal women with LA/MBC.

In addition to delaying progression and prolonging survival, a further aim of treatment for HR+ LA/MBC is to optimize health-related quality of life (HRQoL) [1,2]. HRQoL outcomes are now considered to be important endpoints in cancer clinical trials [11,12]. Indeed, consideration of HRQoL for patients with LA/MBC is recommended in treatment guidelines [1,2] and may support regulatory submissions [13,14]. This is particularly relevant considering the approval of fulvestrant as a combination therapy with palbociclib [6] and abemaciclib [15], as patients with MBC may receive multiple therapies, potentially affecting adverse-event (AE) profiles and HRQoL. Furthermore, given that HRQoL can be a prognostic indicator, it is important that clinicians consider HRQoL in clinical decision-making [16].

HRQoL with fulvestrant has previously been evaluated in the second-line setting. Results of the phase III, randomized, double-blind Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) study that compared fulvestrant 250 and 500 mg demonstrated that no significant difference in HRQoL was detected between the two study arms, as determined by the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B)-derived Trial Outcome Index (TOI) [17]. In the second-line PALOMA-3 study, global HRQoL scores and improvement from baseline in pain were significantly improved with fulvestrant plus palbociclib versus fulvestrant plus placebo. No significant differences were reported for the European Organisation for Research and Treatment of Cancer Quality-of-Life questionnaire breast cancer module (EORTC QLQ-BR23) functioning domains, breast or arm symptoms [18].

In the first-line setting, evaluation of HRQoL with fulvestrant was not included in the FIRST study; therefore, the FALCON study was the first to assess overall HRQoL with first-

line fulvestrant. Using the validated FACT-B questionnaire [19] total score and the TOI, results suggested that HRQoL was maintained and similar for fulvestrant and anastrozole [7]. There was no evidence of a detriment with fulvestrant versus anastrozole in time to deterioration (TTD) for both FACT-B total score (HR = 0.84; 95% CI: 0.66–1.07; *P* = 0.1594) and TOI (HR = 0.90; 95% CI: 0.70–1.15; *P* = 0.4008) [7].

Here, additional post-hoc analyses of patient-reported HRQoL outcomes from the FALCON study are presented.

2. Methods

2.1. Study design

The FALCON trial was a phase III, randomized, double-blind, double-dummy, multicentre study to assess the efficacy and tolerability of fulvestrant 500 mg versus anastrozole 1 mg in postmenopausal women with HR+ LA/MBC who had not received prior endocrine therapy.

The study design and results have been described previously [7]. Briefly, patients were randomized 1:1 to fulvestrant 500 mg (days 0, 14, 28, then every 28 days) or anastrozole 1 mg (once daily) until disease progression or discontinuation.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, the International Council on Harmonisation and Good Clinical Practice guidelines. The final protocol (NCT01602380) was approved by local ethics committees and institutional review boards at each study site, and all patients provided written informed consent.

2.2. HRQoL

HRQoL was assessed at randomization and every 12 weeks during treatment by FACT-B questionnaire, which assesses multidimensional QoL using physical, emotional, social and functional well-being domains, plus a breast cancer subscale that contains items specific to QoL in patients with breast cancer [19]. FACT-B total score is a sum of all FACT-B subscale scores, and assesses overall HRQoL, with a scale range of 0 (low HRQoL) to 144 (high HRQoL). TOI is a sum of physical and functional well-being and breast cancer subscale scores, and represents an index of overall physical and functional wellbeing [19], with a scale range of 0 (low HRQoL) to 92 (high HRQoL). HRQoL data post-treatment (in patients with or without disease progression) were collected at 3 months post-treatment discontinuation and every 6 months thereafter.

Compliance with FACT-B questionnaire completion (calculated as the number of patients with an evaluable baseline and at least one evaluable follow-up FACT-B form, divided by the number of patients expected to have completed at least the baseline form) was calculated over time, including data collected on treatment and post-treatment discontinuation.

Mean changes from baseline in FACT-B total score and TOI, and improvement rates during treatment with fulvestrant and anastrozole, were calculated. Based on recommendations by Eton et al [20], changes from baseline in FACT-B total score of ≥+8 points were classified as improved, ≤-8 points as deteriorated, and between -8 and +8 points as stable. Changes from baseline in TOI of ≥+6 points were classified as improved, ≤-6 points as deteriorated, and between -6 and +6 points as stable.

The TTD for HRQoL, based on FACT-B TOI or FACT-B total score, was defined as the interval from the date of randomization to the first assessment within the following

12 weeks of worsening without improvement in FACT-B TOI or FACT-B total score, or the date of death by any cause in the absence of deterioration.

2.3. Statistical analysis

A post-hoc mixed model repeated measures (MMRM) analysis (using baseline score as a covariate and study visit as a repeated measure) was performed to calculate the change from baseline in FACT-B total score and TOI in both treatment arms at every 12-week time point, and to estimate the overall treatment effect. The analysis included data collected after treatment discontinuation. The Kaplan-Meier method and the stratified log-rank test were performed to assess the TTD in FACT-B total score and TOI.

Post-hoc exploratory analyses of the TTD of FACT-B total score and TOI according to baseline visceral disease status (yes/no) were also performed. Visceral disease was defined as patients with adrenal, bladder, central nervous system, oesophagus, liver, lung, peritoneum, pleura, renal, small bowel, stomach, pancreas, thyroid, colon, rectal, ovary, biliary tract, ascites, pericardial effusion, spleen or pleural effusion disease sites at baseline.

3. Results

3.1. Patients

In total, 462 patients were randomized (fulvestrant, n = 230; anastrozole, n = 232). Of these, 460 patients received treatment (fulvestrant, n = 228; anastrozole, n = 232). Patient demographics were broadly similar between the treatment arms (Table 1). The time from diagnosis to randomization was ≤1 year for the majority of patients (fulvestrant, 160/230 [69.6%]; anastrozole, 165/232 [71.1%]) and most patients had metastatic disease (fulvestrant, 202/230 [87.8%]; anastrozole, 200/232 [86.2%]).

3.2. Compliance

Overall compliance to the FACT-B questionnaire was 91.3% with fulvestrant (range 66.7–94.3%) and 92.2% with anastrozole (range 60.0–97.4%) (Fig. 1). Decline in compliance was steady over time, with a similar rate of decline in both treatment arms.

3.3. Change from baseline in FACT-B total score and TOI

At baseline, the mean (standard deviation) FACT-B and TOI scores were high and similar in both fulvestrant and anastrozole treatment arms (FACT-B: 102.2 [16.93] and 101.1 [16.84], respectively; TOI: 63.9 [11.86] and 63.2 [11.89], respectively). Mean change from baseline in FACT-B total score and TOI remained broadly stable (approximately ± 3 points to week 132) and was similar between arms during treatment (Fig. 2). Mean change from baseline in FACT-B subscale data are presented in Supplementary Fig. 1, and are consistent with these findings.

Results of the post-hoc MMRM analysis of the change from baseline in FACT-B total score and TOI are shown in Fig. 3. Overall, the adjusted mean change from baseline in FACT-B total score was -0.57 with fulvestrant (95% CI: -2.32–1.18) and -3.53 (95% CI: -5.27, -1.78) with anastrozole ($P = 0.019$). For TOI, there was no overall adjusted mean change from baseline with fulvestrant (95% CI: -1.21–1.21); $P = 0.09$) versus a change of -1.47 (95% CI: -2.67, -0.27) with anastrozole. The results of the MMRM analysis of change from baseline in FACT-B subscale data are presented in Supplementary Fig. 2; the overall adjusted mean change from baseline was not significantly different for fulvestrant versus anastrozole for all subscales apart from functional well-being ($P = 0.007$) and social well-being ($P = 0.001$).

Approximately one-third of patients had improved FACT-B total score (from baseline up to week 120) and TOI (from baseline up to week 132) with fulvestrant (proportion of patients with improvement, ranges: 22.4–35.8% and 26.4–45.0%, respectively) and anastrozole (proportion of patients with improvement, ranges: 22.7–37.9% and 18.6–32.9%, respectively; Fig. 4).

3.4. TTD

Fig. 5 shows the Kaplan-Meier curves for the TTD in FACT-B total score and TOI with fulvestrant versus anastrozole. The median TTD in FACT-B total score was 13.8 months with fulvestrant compared with 11.1 months with anastrozole. There was no significant difference in TTD between the treatment arms (HR = 0.84; 95% CI: 0.66–1.07; $P = 0.1594$). The median TTD in TOI score was 13.8 months with fulvestrant compared with 11.1 months with anastrozole. There was no significant difference in TTD between the treatment arms (HR = 0.90; 95% CI: 0.70–1.15; $P = 0.4008$).

The TTD of FACT-B total score and TOI numerically favoured fulvestrant compared with anastrozole in patients with visceral disease (median TTD FACT-B 13.8 months versus 11.3 months, respectively; HR = 0.79; 95% CI: 0.56–1.11; median TTD TOI 16.1 months versus 13.3 months, respectively; HR = 0.85; 95% CI: 0.60–1.22) and non-visceral disease (median TTD 12.0 months versus 11.1 months, respectively; HR = 0.89; 95% CI: 0.62–1.27; median TTD TOI 13.7 months versus 11.1 months, respectively; HR = 0.98; 95% CI: 0.68–1.42).

4. Discussion

The phase III randomized FALCON trial demonstrated improved PFS with fulvestrant 500 mg versus anastrozole 1 mg in endocrine-naïve postmenopausal women with

HR+ LA/MBC (HR = 0.797; 95% CI: 0.637–0.999; *P* = 0.0486) [7]. The safety profile of fulvestrant and anastrozole was consistent with previous findings.

The post-hoc analyses reported here evaluated additional HRQoL data in the FALCON study. HRQoL, determined by the mean change from baseline in TOI and FACT-B total score, was maintained during treatment with fulvestrant and anastrozole. Fulvestrant had a numerically longer median TTD over anastrozole for both FACT-B total score and TOI, and this treatment effect was also observed in patients with visceral and non-visceral disease. Similar proportions of patients had improved FACT-B total score and TOI with fulvestrant versus anastrozole.

The results of the MMRM analysis suggest that, overall, there was a smaller decline in FACT-B total score from baseline (less of a reduction in HRQoL over time) with fulvestrant compared with anastrozole; however, the difference between the two treatments was small, and, as this was a post-hoc analysis, the results should be interpreted with caution.

The heterogeneous nature of LA/MBC, and timing of the HRQoL assessments during the study, may also have impacted the results, particularly in patients with early progression. The majority of patients in the FALCON study presented with metastatic disease, with the overall visceral component as high as 55%; factors that have been shown to compromise HRQoL [21–24]. In addition, patients with a greater disease burden may experience symptoms leading to discontinuation, or may lack interest in completing HRQoL questionnaires due to progressive disease or the worsening of psychological symptoms, such as depression [25]. Furthermore, differences in treatment-related toxicities and discontinuations due to AEs could have explained why a significant improvement with fulvestrant in terms of PFS compared with anastrozole was observed, while the findings of this post-hoc analysis suggest that there was no difference in HRQoL between the two

treatment arms. However, while the incidence of AEs leading to treatment discontinuation was slightly higher in the fulvestrant arm compared with the anastrozole arm, there were no relevant differences between the treatment arms when AEs leading to discontinuation were considered at the preferred term level. The lack of difference in HRQoL observed in this study could possibly reflect the fact that both drugs are known to be well tolerated. It should be noted that the FALCON study was not powered to demonstrate a difference in HRQoL over time.

Strengths of this study include the double-blind nature of study, which limits any bias in patient-reported outcome assessments. One limitation of this study, applicable to other studies of HRQoL [22], was the decline in completion of FACT-B questionnaires over time due to treatment discontinuation, which may have impacted the results if this was a consequence of disease severity or worsening HRQoL. However, overall compliance was high (>90%) and comparable in both treatment arms.

No information on comorbidities, including those of a psychological nature, or post-progression therapies after treatment discontinuation was collected; these factors may also have confounded the HRQoL findings. In addition, the post-hoc nature of this analysis limits the conclusions that can be made due to a lack of adjustment for multiplicity.

Overall, the results of these post-hoc analyses suggest that HRQoL is maintained and comparable with fulvestrant versus anastrozole in postmenopausal patients with HR+ LA/MBC who did not receive prior endocrine therapy.

Acknowledgements

The work was supported by AstraZeneca. The authors wish to thank Lynda M. Grinsted for her contribution to the statistical analysis of these data. Medical writing support, under the

direction of the authors, was provided by Laura Fullerton-Batten PhD of CMC CONNECT, a division of Complete Medical Communications Ltd, Macclesfield, UK, funded by AstraZeneca, Cambridge, UK, in accordance with Good Publication Practice (GPP3) guidelines.

Conflict of interest statement

JFRR has been a consultant for, and has received honoraria from, AstraZeneca and Bayer AG, has received research funding from AstraZeneca, Bayer AG and Novartis, has provided expert testimony for AstraZeneca, holds stocks or other ownership with Oncimmune, and holds stock options with Carrick Therapeutics.

KLC has received honoraria from Chugai and research funding from AstraZeneca, and has served as a member of an advisory board for Genomic Health.

SN has been an advisor for AstraZeneca, Novartis and Taiho, has received research funding from AstraZeneca, Chugai, Daiichi-Sankyo, Eisai, Nippon Kayaku, Novartis, Ono, Pfizer, Taiho and Takeda, and has received honoraria from AstraZeneca, Chugai, Nippon Kayaku, Novartis and Takeda.

ZS has nothing to disclose.

AD, JL and MF are employees of AstraZeneca. JL is also a shareholder of AstraZeneca.

JT is an employee of JMT Statistics Ltd, and is under contract to provide statistical support to AstraZeneca.

MJE holds stock and has a leadership position with Bioclassifier LLC, which derives royalties and other income from a sublicense to Nanostring LLC for PAM50-based diagnostics, including Prosigna; he has been an ad hoc consultant for, and received honoraria and research funding from, AstraZeneca, and has also been a consultant for Pfizer, Puma and Novartis.

Role of the funding source

The research and medical writing support were funded by AstraZeneca. AstraZeneca authors were involved in the data collection, analysis and interpretation, and writing of the manuscript, and the decision to submit the manuscript for publication.

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Table 1

Patient disposition and demographics.

	Fulvestrant 500 mg	Anastrozole 1 mg
Randomized, n (%)	230 (100.0)	232 (100.0)
Received treatment, n (%)	228 (99.1)	232 (100.0)
Discontinued treatment, n (%)	167 (73.2)	183 (78.9)
Disease progression	134 (58.8)	158 (68.1)
Adverse event	16 (7.0)	11 (4.7)
Patient decision	10 (4.4)	10 (4.3)
Severe non-compliance	3 (1.3)	1 (0.4)
Lost to follow-up	1 (0.4)	0 (0.0)
Other	3 (1.3)	3 (1.3)
Age, years; median (range)	64 (38–87)	62 (36–90)
Race		
White	175 (76.1)	174 (75.0)
Asian	36 (15.7)	34 (14.7)
Black or other	19 (8.3)	24 (10.3)

Figure legends

Fig. 1. FACT-B compliance.

FACT-B, Functional Assessment of Cancer Therapy for Breast Cancer.

[a]Number of patients still in the study at the specified time point.

Compliance rate at each time point was calculated as the number of evaluable forms divided by the number of expected forms, multiplied by 100. Includes patients on treatment and those who had discontinued treatment. Overall compliance includes patients with an evaluable form at baseline and at least one post-baseline time point.

Fig. 2. Mean (± SD) change from baseline in A) FACT-B total score and B) TOI (intention-to-treat population)

FACT-B, Functional Assessment of Cancer Therapy for Breast Cancer; SD, standard deviation; TOI, Trial Outcome Index.

Depicts patients on treatment only.

Fig. 3. MMRM analysis adjusted mean (± 95% CI) change from baseline in A) FACT-B total score and B) TOI.

CI, confidence interval; FACT-B, Functional Assessment of Cancer Therapy for Breast Cancer; MMRM, mixed model repeated measures; TOI, Trial Outcome Index.

Fig. 4. Percentage of patients with improved, stable or deteriorated A) FACT-B total score and B) TOI during treatment.

FACT-B, Functional Assessment of Cancer Therapy for Breast Cancer; TOI, Trial Outcome Index.

Time points with ≥20 patients in each arm are shown. The denominator in the percentage calculations includes the patients who were not evaluable at each visit.

Fig. 5. Kaplan-Meier curve of TTD of A) FACT-B total score and B) TOI.

FACT-B, Functional Assessment of Cancer Therapy for Breast Cancer; TOI, Trial Outcome Index, TTD, time to deterioration.

TTD was defined as the time from randomization to worsening in the FACT-B total score or TOI (without improvement in the following 12 weeks), or the date of death (any cause).

Supplementary Fig 1. Mean (± SD) change from baseline in A) physical well-being, B) functional well-being, C) social well-being, D) emotional well-being and E) breast cancer subscale FACT-B subscale scores.

FACT-B, Functional Assessment of Cancer Therapy for Breast Cancer;
SD, standard deviation.

Supplementary Fig. 2. MMRM analysis adjusted mean (± 95% CI) change from baseline in A) physical well-being, B) functional well-being, C) social well-being, D) emotional well-being and E) breast cancer subscale FACT-B subscale scores.

CI, confidence interval; FACT-B, Functional Assessment of Cancer Therapy for Breast Cancer; MMRM, mixed model repeated measures.