Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): a randomised, double-blind, Phase 3 trial

Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Royal Derby Hospital Centre, Derby, UK (Professor John FR Robertson MD*); Oncology Department, Dnipropetrovsk State Medical Academy, Dnipropetrovsk, Ukraine (Professor Igor M Bondarenko PhD); Leningrad Regional Oncology Dispensary, St Petersburg, Russia (Ekaterina Trishkina PhD); Clinical Oncology Dispensary, Omsk, Russia (Mikhail Dvorkin MD); Department of Oncology, Jewish General Hospital, Montreal, Canada (Professor Lawrence Panasci MD); City Clinical Oncology Dispensary, St Petersburg, Russia (Alexey Manikhas MD); Lviv State Oncology Regional Treatment and Diagnostic Centre, Lviv, Ukraine (Yaroslav Shparyk PhD); Breast Cancer Center, Tecnológico de Monterrey, Monterrey, Mexico (Servando Cardona-Huerta PhD); Division of Medical Sciences and Graduate Entry Medicine, School of Medicine, University of Nottingham, Royal Derby Hospital Centre, Derby, UK (Kwok-Leung Cheung MD); Unidad de Investigación, Instituto Oncológico de Lima, Lima, Peru (Manuel Jesus Philco-Salas MD); Hospital Universitario Virgen del Rocío, Seville, Spain (Manuel Ruiz-Borrego MD); Fudan University Shanghai Cancer Center, Shanghai, China (Professor Zhimin Shao MD); Department of Breast and Endocrine Surgery, Osaka University Graduate School of Medicine, Osaka, Japan (Professor Shinzaburo Noguchi PhD); AstraZeneca, Alderley Park, Macclesfield, UK (Jacqui Rowbottom MSc); AstraZeneca, Alderley Park, Macclesfield, UK (Mary Stuart MD); AstraZeneca, Cambridge, UK (Lynda M Grinsted MSc); AstraZeneca, Gaithersburg, MD, USA

(Mehdi Fazal MD); Lester and Sue Smith Breast Center, Baylor College of Medicine, Houston, Texas, USA (Professor Matthew J Ellis PhD*)

*Contributed equally to this article

Addresses for correspondence:

Professor John F.R. Robertson

Division of Medical Sciences and Graduate Entry Medicine

School of Medicine

Faculty of Medicine and Health Sciences

University of Nottingham

Royal Derby Hospital Centre

Uttoxeter Road

Derby

DE22 3DT

UK

Telephone: +44 (0)1332 724881

Fax: +44 (0)1332 724880

Email: john.robertson@nottingham.ac.uk

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SUMMARY

BACKGROUND: Aromatase inhibitors are a standard of care for hormone receptor-positive locally advanced or metastatic breast cancer (LA/MBC). We investigated whether the selective estrogen receptor degrader fulvestrant could improve progression-free survival versus anastrozole in postmenopausal patients who had not received prior endocrine therapy.

METHODS: In this Phase 3, randomised, double-blind trial (FALCON), eligible patients, from 113 centres in 20 countries, were endocrine therapy-naïve, had estrogen receptor and/or progesterone receptor-positive LA/MBC, WHO performance status 0–2, and ≥1 measurable/non-measurable lesion(s). Patients were randomised (1:1) to fulvestrant (500 mg IM; Days 0, 14, 28, then each 28 days) or anastrozole (1 mg orally daily) using a computer-generated randomisation scheme. The primary endpoint was progression-free survival (PFS), determined by RECIST 1·1, intervention by surgery or radiotherapy due to disease deterioration, or death (any cause). This trial is registered at ClinicalTrials.gov (NCT01602380).

FINDINGS: Between 17 October 2012 and 11 July 2014, 524 patients were enrolled and 462 patients were randomised (fulvestrant, n=230; anastrozole, n=232). Primary endpoint was met, as shown by a statistically significant improvement in PFS for fulvestrant *vs* anastrozole (hazard ratio [HR] 0·797; 95% confidence interval [CI] 0·637–0·999; p=0·0486). Median PFS was 16·6 (95% CI 13·83–20·99) *vs* 13·8 (95% CI 11·99–16·59) months for fulvestrant and anastrozole, respectively. Most common adverse events (AEs) were arthralgia (16·7% *vs* 10·3%) and hot flushes (11·4% *vs*

10·3%); 7·0% *vs* 4·7% discontinued due to AEs with fulvestrant and anastrozole, respectively.

INTERPRETATION: Results confirm the superior efficacy of fulvestrant over anastrozole in postmenopausal women with hormone receptor-positive LA/MBC who have not received prior endocrine therapy.

FUNDING: AstraZeneca

INTRODUCTION

First-line treatment recommendations for postmenopausal women with hormone receptor-positive (estrogen receptor [ER], and/or progesterone receptor [PgR]) locally advanced or metastatic breast cancer includes endocrine therapy with a third-generation aromatase inhibitor (AI; anastrozole, letrozole, exemestane) or tamoxifen.[1–3] In hormone receptor-positive disease, third-generation AIs have increased efficacy compared with tamoxifen in terms of time to progression.[4–8]

Fulvestrant, a selective ER degrader (SERD) that blocks ER function by inducing ER degradation,[9] is approved for postmenopausal women with hormone receptor-positive advanced breast cancer and disease progression following antiestrogen therapy.[10,11] The 500 mg dose of fulvestrant was approved based on data from the Phase 3, double-blind Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) study that compared fulvestrant 500 mg with fulvestrant 250 mg in patients with hormone receptor-positive advanced breast cancer who experienced progression after prior endocrine therapy.[12] In CONFIRM, progression-free survival (PFS; hazard ratio [HR] 0·80; 95% confidence interval [CI] 0·68–0·94; p=0·006)[12] and overall survival (OS; HR 0·81; 95% CI 0·69–0·96; p=0·02)[13] were increased with fulvestrant 500 mg *vs* fulvestrant 250 mg.

Improved efficacy of first-line treatment with fulvestrant *vs* anastrozole was demonstrated in a Phase 2, open-label Fulvestrant First-Line Study Comparing Endocrine Treatments (FIRST) study in postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer.[14] Fulvestrant was shown to be at least as effective as anastrozole in terms of clinical benefit rate (CBR;

72·5% [74/102] *vs* 67·0% [69/103], respectively; odds ratio, 1·30; 95% CI, 0·72–2·38; p=0·386).[14] In subsequent follow-up analyses, fulvestrant was associated with a longer PFS/time to progression (HR 0·66; 95% CI 0·47–0·92; p=0·01)[15] and improved OS (HR 0·70; 95% CI 0·50–0·98; p=0·04)[16] *vs* anastrozole.

The objective of the current study was to confirm the superior PFS advantage for fulvestrant versus anastrozole observed in the FIRST study, in a double-blind Phase 3 design. The population for FALCON were postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who had not received prior endocrine therapy, in order to avoid reducing efficacy of the control arm through exposure to adjuvant endocrine therapy.

METHODS

Study design

The Fulvestrant and AnastrozoLe COmpared in hormonal therapy Naïve advanced breast cancer (FALCON) trial (Clinicaltrials.gov: NCT01602380) is a Phase 3 randomised, double-blind, double-dummy, international, multicentre study that compared the efficacy and tolerability of fulvestrant with anastrozole in postmenopausal women with histologically confirmed ER+ and/or PgR+ locally advanced or metastatic breast cancer.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation/Good Clinical Practice guidelines. An

Ethics Committee or Institutional Review Board approved the final protocol at each study site. All patients provided written, informed consent.

Participants

Eligible patients were postmenopausal women who had a World Health Organization (WHO) performance status of 0–2, and ≥1 measurable and/or non-measurable lesion(s). Key exclusion criteria included prior hormonal treatment for breast cancer; presence of life-threatening, metastatic, visceral disease; prior systemic therapy for breast cancer, except one line of cytotoxic chemotherapy; radiation therapy if completed ≤28 days prior to randomisation (unless for bone pain control); human epidermal growth factor receptor (HER2) over-expression/gene amplification; concomitant anticancer treatment (except bisphosphonates/denosumab); systemic estrogen-containing hormone-replacement therapy (HRT) use ≤6 months prior to randomisation (see Supplementary Appendix for full inclusion and exclusion criteria).

Randomisation and masking

Patients were randomised sequentially (1:1) to fulvestrant 500 mg or anastrozole 1 mg using a computer-generated randomisation scheme and an integrated voice/web response system. Patients were stratified at randomisation according to locally advanced or metastatic breast cancer; prior or no prior treatment with chemotherapy for locally advanced or metastatic breast cancer; and measurable or non-measurable disease.

Study drugs were labelled using a unique identifier linked to the randomisation scheme. The active study drug and placebo for fulvestrant (pre-filled syringes) and anastrozole (tablets) were identically packaged to maintain blinding.

Procedures

Study treatment was initiated at randomisation (Day 0). Fulvestrant (plus daily anastrozole placebo) was administered on Days 0, 14 (±3), 28 (±3), and every 28 (±3) days thereafter as two 5 mL intramuscular injections at each visit. No fulvestrant dose reductions were permitted. Anastrozole (plus fulvestrant placebo on Days 0, 14, 28, and every 28 days thereafter) was administered once daily as a single tablet. Treatment continued until objective disease progression or other criteria for discontinuation were met in terms of adverse events (AEs), protocol non-adherence, or patient's decision to withdraw.

Study visits occurred at screening (Day -28 to -1), randomisation (Day 0), Day 14, every 4 weeks from Week 4 to 24 and every 12 weeks thereafter until disease progression. Safety and tolerability were assessed at each study visit, and for up to 8 weeks after the last fulvestrant/placebo injection. HRQoL questionnaires were administered at baseline and at 3-monthly intervals. Following disease progression or treatment discontinuation, HRQoL questionnaires will be administered at 6-monthly until a final OS analysis.

Outcomes

The primary endpoint of the study was to demonstrate the superior PFS of patients treated with fulvestrant *vs* anastrozole. A progression event was determined based on tumour assessments performed locally by each investigator, and was defined by Response Evaluation Criteria in Solid Tumours (RECIST) 1·1, or surgery/radiotherapy for worsening of disease, or death from any cause.

Secondary endpoints included objective response rate (ORR; best overall response of either complete response [CR] or partial response [PR] in patients with measurable disease at baseline), duration of response (DoR), and expected duration of response (EDoR), CBR (best overall response of CR, PR, or stable disease [SD] ≥24 weeks), duration of clinical benefit (DoCB), expected duration of clinical benefit (EDoCB), and OS (time from randomisation until death by any cause).

Health-related quality of life (HRQoL) was assessed using the Trial Outcome Index (TOI)[17] derived from the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) questionnaire, and FACT-B total score.

Safety and tolerability assessments included AEs (graded according to Common Terminology Criteria for Adverse Event [CTCAE], version 4·0), serious AEs (SAEs), discontinuations due to AEs, deaths due to AEs, and pre-defined AEs of special interest (joint disorders and back pain) were reported throughout the study. Laboratory parameters, electrocardiogram (ECG) recordings, physical examination, and vital signs were monitored at pre-specified time points throughout the study. The safety analysis population was used for all safety outcome variables and included all patients who received at least one dose of randomised treatment (including placebo) according to the actual treatment initially received.

Statistical analysis

For the primary outcome, PFS was evaluated at a single time point when approximately 306 progression events had occurred. Randomisation of approximately 450 patients was planned to achieve 306 progression events. It was calculated that if 0·69 is the true PFS HR for the comparison of fulvestrant *vs* anastrozole, this number

of events would provide 90% power for statistical significance at the 5% two-sided level. A PFS HR of 0·80 would deliver a statistically significant difference for the primary outcome. The primary analysis for this study was conducted in the intent-to-treat (ITT) population comprising all randomised patients.

Comparison of PFS for fulvestrant *vs* anastrozole was performed using a stratified log-rank test at the two-sided 5% significance level in the ITT population. Strata included were prior chemotherapy for locally advanced or metastatic disease and measurable disease; locally advanced *vs* metastatic disease was not included because only a small number of patients had locally advanced disease. Results are presented as an estimate of the HR, associated 95% CI, and p value. An interim analysis of OS was performed at the time of PFS analysis, and OS was analysed in the same way as PFS. OS and ORR were tested using a multiple testing procedure with an alpha-exhaustive recycling strategy to control type-I error at the overall alpha level.[18] CBR was analysed using a logistic regression model including the same stratification factors as for PFS and examination of odds ratio of the two treatment groups. ORR was analysed in the same way as CBR; however, measurable disease was not included in the model. Kaplan-Meier plots were produced for DoCB and DoR. EDoCB and EDoR are methodologies designed to provide an unbiased treatment comparison of DoCB and DoR by including all randomised patients (rather than just responding patients), and were calculated using the method of Ellis et al.[19] EDoR and EDoCB allow a statistical comparison to be made on the duration of response and clinical benefit between the two treatment arms. An analysis of time to deterioration of TOI and FACT-B total score was performed as described for PFS.

A subgroup analysis was performed on PFS data (ITT) for the following baseline covariates: ER+ and PgR+ (yes/no); metastatic disease (yes/no); concomitant use of bisphosphonates (yes/no); measurable disease (yes/no); prior chemotherapy for locally advanced or metastatic breast cancer (yes/no); geographic region; prior systemic estrogen containing HRT (yes/no); and visceral disease (yes/no). HRs and 95% CI were calculated, and a Kaplan-Meier was generated for each subgroup. A global interaction test was performed using a Cox-proportional hazard model to evaluate if the treatment effect was consistent across the covariates. A post hoc interaction test to assess for consistency of the treatment effects across the visceral and non-visceral subgroups was also performed.

All patients who received at least one dose of randomised treatment were included in the safety population. AEs were summarised descriptively using Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

This trial is registered at ClinicalTrials.gov, number NCT01602380.

Role of the funding source

This study was designed and funded by AstraZeneca, who was involved in the reviewing and interpretation of data, the writing of the manuscript, and in the decision to submit for publication.

All authors had access to all the data and were responsible for the decision to submit the manuscript.

RESULTS

Between 17 October 2012 and 11 July 2014, a total of 524 patients were enrolled. Of these, 462 patients were randomised (ITT; Figure 1): 230 received fulvestrant and 232 received anastrozole at 113 centres in 20 countries in Asia, Europe, North America, South America, and South Africa. Data cut-off was 11 April 2016.

Two patients in the fulvestrant group did not receive study treatment following randomisation (patient decision); therefore, the safety population comprised 228 and 232 patients in the fulvestrant and anastrozole groups, respectively.

In total, 14 and 13 protocol deviations related to eligibility criteria were observed in the fulvestrant and anastrozole arms, respectively. Three patients were reported to have received prior endocrine therapy. These protocol deviations were considered unlikely to affect the interpretation of study data.

Baseline demographic and disease characteristics were generally well balanced between groups (Table 1).

There were 309 progression events at data cut-off; of these, 143/230 (62·2%) and 166/232 (71·6%) occurred in the fulvestrant and anastrozole groups, respectively. Fulvestrant was associated with a statistically significant improvement in PFS compared with anastrozole (HR 0·797; 95% CI 0·637–0·999; p=0·0486; Figure 2). Median PFS was 16·6 months (95% CI 13·83–20·99) with fulvestrant and 13·8 months (95% CI 11·99–16·59) with anastrozole (difference in medians, 2·8 months).

Table 2 shows the proportions of patients with CR, PR, and SD. In patients with measurable disease, ORR was 46·1% (89/193) with fulvestrant and 44·9% (88/196) with anastrozole (odds ratio 1·07; 95% CI 0·72–1·61; p=0·7290). DoR in patients with measurable disease at baseline is shown in Supplementary Figure 1a. Median

DoR was longer in the fulvestrant arm than the anastrozole arm (20·0 [95% CI 15·90–27·63] and 13·2 [95% CI 10·64–16·72] months, respectively). EDoR was 11·4 and 7·5 months, respectively (EDoR ratio 1·52; 95% CI 1·03–2·26; p=0·0367).

CBR was 78·3% (180/230) and 74·1% (172/232) with fulvestrant and anastrozole, respectively (odds ratio 1·25; 95% CI 0·82–1·93; p=0·3045). DoCB in patients with clinical benefit is shown in Supplementary Figure 1b. Median DoCB was 22·1 (95% CI 18·46–24·87) and 19·1 (95% CI 16·53–20·47) months for fulvestrant and anastrozole, respectively. The EDoCB was 21·9 months in the fulvestrant arm and 17·5 months in the anastrozole arm (EDoCB ratio 1·26; 95% CI 0·99–1·59; p=0·0561).

Median OS could not be calculated as currently there is insufficient follow-up (31% maturity). At data cut-off, 67/230 (29·1%) and 75/232 (32·3%) patients in the fulvestrant and anastrozole groups, respectively, had died (HR 0·88; 95% CI 0·63–1·22; p=0·4277).

Treatment effects on PFS were largely consistent across the pre-specified patient subgroups (global interaction test, p=0·1061), with some exceptions noted: patients with prior chemotherapy for locally advanced or metastatic disease; patients with non-measurable disease; patients who were not ER+ and PgR+ at baseline; and patients with visceral disease (Figure 3a). For patients with non-visceral disease, the HR was 0·59 (95% CI 0·42–0·84), with median PFS of 22·3 (95% CI 16·62–32·79) *vs* 13·8 (95% CI 11·04–16·59) months for fulvestrant and anastrozole, respectively (Figure 3b). In the visceral disease subgroup, the HR was 0·99 (95% CI 0·74–1·33), with median PFS of 13·8 (95% CI 11·04–16·53) months for fulvestrant and 15·9

(95% CI 11·27–16·89) months for anastrozole. A post hoc interaction test to assess for consistency of the treatment effects across the visceral and non-visceral subgroups gave p=0·0092.

At data cut-off, median duration of actual exposure to fulvestrant was 14·7 months (range 0·9–37·7) and to anastrozole was 13·9 months (range 0·2–36·0). In total, 166/228 (72·8%) and 173/232 (74·6%) patients reported an AE in the fulvestrant and anastrozole groups, respectively. Table 3 presents AEs with an incidence >5% in either group. SAEs were reported by 30/228 (13·2%) *vs* 31/232 (13·4%) patients receiving fulvestrant or anastrozole, respectively (Supplementary Table 1 presents SAEs considered causally related to treatment). Overall, 16/228 (7·0%) and 11/232 (4·7%) patients in the fulvestrant and anastrozole groups, respectively, discontinued due to AEs (Supplementary Table 2). Grade 3 or worse AEs were reported by 51/228 (22·4%) and 41/232 (17·7%) patients receiving fulvestrant and anastrozole, respectively; none occurred in >5% of patients in either group. There were 6/228 (2·6%) and 7/232 (3·0%) deaths due to AEs in the fulvestrant and anastrozole groups, respectively. No deaths due to AEs were considered causally related to treatment.

AEs of special interest (joint disorders and back pain) were reported by 59/228 (25·9%) and 42/232 (18·1%) patients in the fulvestrant and anastrozole groups, respectively. All AEs of special interest were mild or moderate in severity (Grade 1 or 2), with the exception of one patient (1/228 [0·4%]) in the fulvestrant group who had Grade 3 back pain. No AEs of special interest led to treatment interruption, or had a fatal outcome. No SAEs of special interest were reported.

Overall, no clinically significant changes in laboratory parameters, ECG recordings, physical examination, or vital signs were observed in either group.

Mean FACT-B and TOI scores were maintained and similar in both treatment groups. Time to deterioration was not statistically significantly different between treatment arms for both TOI scores (HR 0·90; 95% CI 0·70–1·15; p=0·4008) and FACT-B total score (HR 0·84; 95% CI 0·66–1·07; p=0·1594).

DISCUSSION

The primary endpoint of this Phase 3 study was met, with patients receiving fulvestrant experiencing statistically significantly longer PFS than patients receiving anastrozole, confirming the hypothesis that fulvestrant is a more efficacious treatment than anastrozole in postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have not received prior treatment with endocrine therapy. This represents a meaningful and relevant finding for which clinical data are limited.[20] Strengths of this study are the inclusion of a diverse patient population, the double-dummy study design, and the use of a standard-of-care comparison arm. Unlike many other studies where patients were allowed to receive prior adjuvant endocrine therapy, patients in the FALCON study were completely endocrine therapy-naïve and were even limited in their use of HRT prior to randomisation to greater than 6 months, given the known effect of HRT withdrawal. Therefore, this study provides a direct comparison of the therapeutic efficacy between the SERD fulvestrant and a third-generation AI without the confounding effects of prior adjuvant endocrine therapy exposure of any type. The HR for PFS seen in this study (0·797) is similar to the improvement shown by third-generation AIs over

tamoxifen.[4–8] In addition to the primary endpoint results, pre-defined subgroup analyses were performed. The test for heterogeneity was not statistically significant across all the subgroups although it was noted that potential enhanced treatment effects with fulvestrant *vs* anastrozole were seen in some subgroups, including patients with non-visceral disease compared with visceral disease. This latter observation requires further study.

The FALCON data add to the extensive data on the efficacy of fulvestrant in patients with advanced breast cancer, and consolidate the evidence for superior efficacy for fulvestrant over a third-generation AI, initially raised by the results of the Phase 2 FIRST study, where the majority of patients were also endocrine-naïve.[14–16]

The superiority of fulvestrant over anastrozole in an endocrine therapy-naïve patient population warrants future clinical evaluation of fulvestrant in other endocrine therapy-naïve patient populations, such as the (neo)adjuvant setting, where a Phase 3 comparison with anastrozole for 6 months before surgery is currently underway (NCT01953588). The superior efficacy of fulvestrant was not associated with an enhanced response rate. The PFS advantage appears to be driven by the more durable responses associated with fulvestrant treatment as shown by the DoR and EDoR analyses. Since aromatase inhibition is prone to resistance generated by ESR1 mutation,[21] one possibility for the PFS advantage is that fulvestrant is less prone to this resistance mechanism. The recent advent of circulating tumour DNA analysis should allow this hypothesis to be further evaluated. In preliminary studies it does appear that fulvestrant retains activity against tumours that harbour an ESR1 mutation.[22]

346 The AE profile observed was generally consistent with the known safety profiles of
347 fulvestrant and anastrozole. The most common AE reported with fulvestrant in the
348 FALCON study was arthralgia, which occurred at a numerically higher frequency to
349 that noted in the FIRST study (16·7% [38/228] and 9·9%, respectively);[14] however, no
350 patients discontinued as a result. More patients in the fulvestrant group experienced
351 myalgia than in the anastrozole group. Less than 2% of patients in either treatment
352 group experienced SAEs causally related to treatment or discontinued treatment due to
353 AEs, and no treatment-related deaths occurred.

354 An alternative to first-line fulvestrant has been established by the results of the
355 Palbociclib Ongoing Trials in the Management of Breast Cancer (PALOMA-2) trial
356 (NCT01740427), which excluded patients resistant to AIs, and the Mammary
357 Oncology Assessment of LEE011's (ribociclib) Efficacy and Safety (MONALEESA-2
358 trial (NCT01958021). These studies investigated the efficacy of the cyclin-dependent
359 kinases 4 and 6 (CDK4/6) inhibitors palbociclib or ribociclib plus letrozole,
360 respectively, *vs* letrozole alone in postmenopausal women who had not received prior
361 systemic treatment for advanced breast cancer.[23,24] Statistically significant
362 improvements in PFS were shown for palbociclib plus letrozole (HR 0·58; 95% CI
363 0·46–0·72; p<0·0001) in PALOMA-2, and ribociclib plus letrozole (HR 0·56; 95% CI
364 0·43–0·72; $p=3{\cdot}29 \times 10^{-6}$) in MONALEESA-2 *vs* letrozole alone.[23] Both the
365 PALOMA-2 and MONALEESA-2 studies demonstrate that addition of a second agent
366 from a different class is associated with improved efficacy but additional toxicity, and
367 the potential for an increased financial burden.[25] As such, the incidence of Grade 3
368 and 4 SAEs, and permanent treatment discontinuation due to AEs (both
369 haematological and non-haematological AEs) was greater with palbociclib plus

letrozole and ribociclib plus letrozole than letrozole alone. Thus, when considered in the context of the results from FALCON, fulvestrant provides a lower toxicity option for first-line therapy that could be favoured for patients with low or intermediate risk disease with relatively good prognosis (e.g. non visceral disease), patients with high risk disease who have comorbidities restricting the use of combination targeted therapy, patients who cannot afford a CDK4/6 inhibitor, or in countries where CDK4/6 inhibitors are not been approved by regulatory authorities.

It is clearly important to identify patients likely to gain most benefit from treatment with endocrine monotherapy. Indeed, patients who achieved clinical response to fulvestrant experienced longer duration of response *vs* anastrozole. Thus, patients with endocrine-sensitive disease may not always require a combination treatment that is associated with greater toxicity. FALCON and PALOMA-2/MONALEESA-2 trials are not directly comparable and are immature from an OS perspective. OS results could provide additional evidence to support decisions between the use of a first-line CDK4/6 inhibitor with an AI *vs* fulvestrant monotherapy, particularly given the OS advantage already observed for fulvestrant over anastrozole in the FIRST study.

In conclusion, the FALCON study results support the conclusion that fulvestrant is more efficacious than anastrozole on the basis of a statistically significant improvement in PFS in postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer who have not received prior endocrine therapy. Both treatments were associated with an acceptable tolerability profile. Collectively, the efficacy and tolerability findings support the clinical effectiveness of fulvestrant in this setting.

RESEARCH IN CONTEXT PANEL

Evidence before this study

We performed a general search on PubMed and ClinicalTrials.gov (search terms 'fulvestrant 500 mg' and 'clinical trial') to identify clinical studies of fulvestrant 500 mg, a selective estrogen receptor degrader (SERD), versus any third-generation aromatase inhibitor. No date or language limitations were applied. From the results identified, we believe that the randomised, double-blind, multicentre FALCON trial (NCT01602380) is the first Phase 3 trial to evaluate the efficacy and safety of fulvestrant compared with anastrozole in hormone receptor-positive postmenopausal women with advanced breast cancer who have not received prior endocrine treatment, a clinically meaningful patient population.

Added value of the study

A previous open-label, Phase 2 study (the FIRST study) in postmenopausal women with hormone receptor-positive locally advanced or metastatic breast cancer, the majority of whom were endocrine-naïve, demonstrated that first-line fulvestrant was at least as effective as anastrozole in terms of clinical benefit rate and was superior in terms of time to progression and overall survival. Results from this randomised, double-blind, Phase 3 FALCON study therefore add to the extensive data on the efficacy and safety of fulvestrant in patients with advanced breast cancer, and consolidates evidence for superior efficacy for fulvestrant over anastrozole demonstrated earlier in the FIRST study.

Implications of all the available evidence

The results of the FALCON study confirm that a SERD is a more efficacious treatment than a third-generation AI, which is the standard-of-care in first-line endocrine therapy for patients with hormone receptor-positive advanced breast cancer. These findings consolidate the known clinical effectiveness of fulvestrant and support the use of fulvestrant monotherapy in endocrine-naïve patients with hormone receptor-positive advanced breast cancer. As such, the FALCON study results have important implications for clinical practice.

AUTHORS AND CONTRIBUTORS

John FR Robertson, Zhimin Shao, Shinzaburo Noguchi, Matthew J Ellis, and Mary Stuart were involved in the concept and design of the study.

John FR Robertson, Igor M Bondarenko, Ekaterina Trishkina, Mikhail Dvorkin, Lawrence Panasci, Alexey Manikhas,Yaroslav Shparyk, Servando Cardona-Huerta, Kwok-Leung Cheung, Manuel Jesus Philco-Salas, Manuel Ruiz-Borrego, Zhimin Shao, Shinzaburo Noguchi, and Matthew J Ellis were involved in the provision of study materials or patients, and Jacqui Rowbottom, Mary Stuart, Lynda M Grinsted, and Mehdi Fazal were involved in data collection.

All authors were involved in data analysis and interpretation, manuscript writing, and approved the final manuscript.

DECLARATION OF INTERESTS

John FR Robertson 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, and holds stocks or other ownership with Oncimmune, and stock options with Carrick Therapeutics.

Igor M Bondarenko, Ekaterina Trishkina, Mikhail Dvorkin, Lawrence Panasci, Alexey Manikhas, Yaroslav Shparyk, Servando Cardona-Huerta, Manuel Jesus Philco-Salas, Manuel Ruiz-Borrego, and Zhimin Shao have no conflicts of interest to declare.

Kwok-Leung Cheung has received honoraria from Chugai; and has received research funding from AstraZeneca.

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Mehdi Fazal is an employee of AstraZeneca. Lynda M. Grinsted is an employee and shareholder of AstraZeneca. Mary Stuart is a former employee of AstraZeneca, and is a current employee of Kingston Oncology Ltd, UK. Jacqui Rowbottom is a former employee of AstraZeneca, and is a current employee of JAR Statistics Ltd, UK.

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

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FIGURE LEGENDS

Figure 1. Patient disposition

[a]Two patients in the fulvestrant 500 mg arm did not receive treatment (patient decision)

[b]Includes patients with disease progression

AE=adverse event

Figure 2: **Kaplan-Meier curve for PFS (ITT population)**

A circle represents a censored observation

CI=confidence interval. HR=hazard ratio. ITT=intent-to-treat. PFS=progression-free survival

Figure 3: **a) Forest plot of PFS in patient subgroups defined by pre-specified baseline covariates and b) Kaplan-Meier curve for PFS in patients with and without visceral disease (ITT population)**

A circle represents a censored observation

CI=confidence interval. ER=estrogen receptor. HR=hazard ratio. HRT=hormone replacement therapy. ITT=intent-to-treat. NC=not calculable. PFS=progression-free survival. PgR=progesterone receptor

Table 1: **Patient baseline demographics and disease characteristics (ITT population)**

Characteristic	**Fulvestrant 500 mg (n=230) n (%)**	**Anastrozole 1 mg (n=232) n (%)**
Age		
Median, years	64·0	62·0
Range, years	38–87	36–90
≥65 years	108 (47·0)	91 (39·2)
Race		
White	175 (76·1)	174 (75·0)
Asian	36 (15·7)	34 (14·7)
Black or other	19 (8·3)	24 (10·3)
Time from diagnosis of breast cancer to randomisation		
≤2 months	102 (44·3)	99 (42·7)
>2 months to ≤1 year	58 (25·2)	66 (28·4)
>1 year	70 (30·4)	67 (28·9)
Receptor status		
ER+/PgR+	175 (76·1)	179 (77·2)
ER+/PgR-	44 (19·1)	43 (18·5)
ER+/PgR unknown	10 (4·3)	7 (3·0)

ER-/PgR+	1 (0·4)	3 (1·3)
ER-/PgR-	0	0
HER2 status		
Positive	0	1 (0·4)
Negative	230 (100)	231 (99·6)
WHO performance status[a]		
0	117 (50·9)	115 (49·6)
1	106 (46·1)	105 (45·3)
2	7 (3·0)	12 (5·2)
Disease stage		
Locally advanced	28 (12·2)	32 (13·8)
Metastatic	202 (87·8)	200 (86·2)
Visceral disease[b]	135 (58·7)	119 (51·3)
Bone/musculoskeletal only	24 (10·4)	24 (10·3)
Breast only	3 (1·3)	2 (0·9)
Skin/soft tissue only	8 (3·5)	6 (2·6)
Other/non-visceral	60 (26·1)	81 (34·9)
Measurable disease	193 (83·9)	196 (84·5)
Prior treatment[c]		
Chemotherapy		
LA/MBC[d]	36 (15·7)	43 (18·5)
Adjuvant	35 (15·2)	27 (11·6)

Neo-adjuvant	11 (4·8)	16 (6·9)
Radiotherapy	53 (23·0)	50 (21·6)
Immunotherapy	0	0
Hormonal therapy	2 (0·9)	1 (0·4)

[a]WHO performance status: 0=normal activity; 1=restricted activity; 2=in bed ≤50% of the time

[b]Includes patients with disease site at baseline of adrenal, bladder, CNS, oesophagus, liver, lung, peritoneum, pleura, renal, small bowel, stomach, pancreas, thyroid, colon, rectal, ovary, biliary tract, ascites, pericardial effusion, spleen, or pleural effusion

[c]Prior to enrolment; categories are not mutually exclusive

[d]Includes first-line, second-line, third-line, metastatic, and palliative chemotherapies (two patients were reported as deviations for having received second-line chemotherapy and one patient was reported in error to have received three prior lines of chemotherapy)

CNS=central nervous system. ER=estrogen receptor. HER2=human epidermal growth factor receptor. ITT=intent-to-treat. LA/MBC=locally advanced/metastatic breast cancer. PgR=progesterone receptor. WHO=World Health Organization

Table 2: **Clinical benefit (ITT population)**

Best objective response	**Fulvestrant 500 mg (n=230) n (%)**	**Anastrozole 1 mg (n=232) n (%)**
Clinical benefit		
Total	180 (78·3)	172 (74·1)
Complete response	7 (3·0)	8 (3·4)
Partial response	86 (37·4)	82 (35·3)
Stable disease ≥24 weeks	87 (37·8)	82 (35·3)
No clinical benefit		
Total	50 (21·7)	60 (25·9)
Stable disease ≥8 and <24 weeks	9 (3·9)	22 (9·5)
Progression	30 (13·0)	33 (14·2)
RECIST progression	27 (11·7)	28 (12·1)
Death	3 (1·3)	5 (2·2)
Not evaluable[a]	11 (4·8)	5 (2·2)

[a]Owing to incomplete post-baseline assessments for all non-evaluable patients

ITT=intent-to-treat. RECIST=Response Evaluation Criteria in Solid Tumours

Table 3: **Adverse events with a frequency of >5% in any treatment group regardless of causality (safety analysis population)**

Characteristic	**Fulvestrant 500 mg (n=228) n (%)**	**Anastrozole 1 mg (n=232) n (%)**
Patients with any AE	166 (72·8)	173 (74·6)
Arthralgia	38 (16·7)	24 (10·3)
Hot flush	26 (11·4)	24 (10·3)
Fatigue	26 (11·4)	16 (6·9)
Nausea	24 (10·5)	24 (10·3)
Back pain	21 (9·2)	14 (6·0)
ALT increased	16 (7·0)	7 (3·0)
Myalgia	16 (7·0)	8 (3·4)
Hypertension	15 (6·6)	21 (9·1)
Insomnia	15 (6·6)	13 (5·6)
Diarrhoea	14 (6·1)	13 (5·6)
Constipation	13 (5·7)	11 (4·7)
Pain in extremity	13 (5·7)	10 (4·3)

AST increased	12 (5·3)	8 (3·4)
Cough	12 (5·3)	8 (3·4)
Anaemia	9 (3·9)	20 (8·6)
Dyspnoea	9 (3·9)	13 (5·6)
Oedema peripheral	9 (3·9)	13 (5·6)

AEs were graded according to Common Terminology Criteria for Adverse Events version 4·0

AE=adverse event. ALT=alanine aminotransferase. AST=aspartate aminotransferase