Fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer: An Evidence Review Group perspective of a NICE Single Technology Appraisal

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**Abstract**

Clinical and cost-effectiveness evidence on fulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer evidence was submitted to the single technology appraisal (STA) process of the National Institute for Health and Care Excellence (NICE) by the manufacturer of fulvestrant. The Southampton Health Technology Assessments Centre (SHTAC) was commissioned by NICE as an independent Evidence Review Group (ERG) to critique the company’s submitted evidence. Fulvestrant is compared directly with anastrozole in two RCTs and is compared indirectly by means of a network meta-analysis with anastrozole, letrozole and tamoxifen. This paper is a summary of the ERG’s review of the company’s submission and a summary of the guidance the NICE Appraisal Committee issued in January 2018. The ERG had several concerns, the most important of which related to the degree to which fulvestrant might confer a benefit in overall survival (OS). This was because mature data were not available from the key phase III trial FALCON. The economic model was sensitive to changes in OS and the ERG considered the incremental cost-effectiveness ratio (ICER) was uncertain and likely to increase once mature results from FALCON become available. The NICE Appraisal Committee concluded that fulvestrant could not be recommended for treating locally advanced or metastatic estrogen-receptor positive breast cancer in postmenopausal women who have not had previous endocrine therapy.

**Key Points for Decision Makers**

Two randomised controlled trials, FALCON (phase III) and FIRST (phase II) provide direct head-to-head evidence comparing fulvestrant with one of the current treatment options, anastrozole. Fulvestrant treatment led to a gain in median time-to-progression of 10.3 months in FIRST [where time-to-progression had the same definition as progression-free survival (PFS)] but the median 2.8 month PFS in FALCON was modest in comparison to FIRST.

An overall survival (OS) benefit of 5.7 months has been shown in FIRST and this is much shorter than the gain in time-to-progression. OS data from FALCON are immature, and the ERG was concerned that the final OS benefit may be much lower than that observed in FIRST because PFS is much shorter in FALCON. The uncertainty about the potential OS benefit that could be obtained with fulvestrant caused uncertainty in the outcomes from cost-effectiveness modelling.

The NICE Appraisal Committee concluded that further survival data from FALCON are required to enable robust estimates of the cost-effectiveness of fulvestrant to be produced. The committee could not recommend fulvestrant as a cost-effective use of NHS resources at the present time for the treatment of postmenopausal women with untreated, locally advanced or metastatic estrogen-receptor positive breast cancer.

# Introduction

The National Institute for Health and Care Excellence (NICE) is a non-departmental public body that is independent of government. NICE provides guidance and advice to improve health and social care in England. One function of NICE is to assess whether health technologies (medicines, diagnostic tests and medical devices) are clinically effective and a cost-effective use of UK resources, such that they can be recommended for use within the English National Health Service (NHS).

NICE’s technology appraisals take one of two forms, either a single technology appraisal (STA) or a multiple technology appraisal (MTA). An STA is designed to evaluate a single health technology for a single indication whereas an MTA typically covers more than one technology or one technology for more than one indication. In an STA the company is invited to provide an evidence submission which includes the clinical effectiveness and cost-effectiveness evidence about their technology required by NICE for an STA. This evidence submission is critiqued by an independent research assessment team, the evidence review group (ERG).

The NICE Appraisal Committee meets in public to discuss the evidence presented by the company and the ERG’s critique of this. The committee also takes into account written submissions from other stakeholders (e.g. national bodies representing patients and carers, bodies representing health professionals, the Department of Health, NHS England and clinical commissioning groups) as well as hearing in person from any clinical, patient and commissioning representatives present at the meeting. The committee then makes provisional recommendations which enter a period of consultation before the final decision about the use of the technology in the NHS is made.

This article presents a summary of the ERG’s review and critique of the company submission (CS) to NICE, additional work conducted by the ERG, and the key issues that arose during the committee decision-making processes for the technology appraisal of fulvestrant for untreated hormone-receptor positive locally advanced or metastatic estrogen-receptor positive breast cancer.

In each section below, we summarise the evidence submitted by the company and then present our critique of this evidence. Full details of the appraisal documents; including, the company’s evidence submission, the ERG report, and appraisal committee decision documents are available on the NICE website (https://www.nice.org.uk/guidance/ta503).

# The Decision Problem

Breast cancer is a leading cause of cancer death worldwide among women and with 45,656 female cases registered in 2016 in England, it accounted for 9,613 of deaths in England in 2016 [1].

The majority of breast cancers express receptors for the female hormones estrogen and/or progesterone. Therefore these breast cancers are described as hormone-receptor positive (HR+). About 70% of breast cancers express estrogen receptors (ERs) [2] with approximately 96% of these being ER positive (ER+) and human epidermal growth factor receptor negative (HER-). The relative incidence of ER+ breast cancer increases with age [3], consequently breast cancers in post-menopausal women are mostly ER+ at diagnosis. The number of newly diagnosed breast cancer cases registered for post-menopausal women aged 50 to 59 and 60 to 69 in England in 2016 was 10,227 and 11,684 respectively [1]. Most breast cancer cases are diagnosed at an early stage, however between 6-10 % are diagnosed late, at metastatic stage [4].

The NICE treatment pathway for advanced breast cancer (ABC) [5] states that post-menopausal women with ER+ ABC who do not have life threatening disease should be treated with endocrine therapy. In the first instance the recommended endocrine therapy would be treatment with an aromatase inhibitor (AI) (either anastrozole or letrozole), but if AIs are not tolerated or are contra-indicated, tamoxifen is suggested. Where disease is life-threatening or requires early relief of symptoms, chemotherapy is recommended.

Fulvestrant (Faslodex®) is an ER antagonist that binds competitively to the ER, promoting receptor degradation and down regulation of ER protein levels in human breast cancer cells. As a result, the growth of tumour cells, which are stimulated by estrogen, is reduced. Fulvestrant can be described as a Selective Estrogen Receptor Degrader (SERD) [6].

Fulvestrant has marketing authorisation in the UK for treating locally advanced or metastatic ER+ breast cancer in postmenopausal women, whose disease has progressed during, or relapsed during or after, adjuvant anti-estrogen therapy. The recommended dose is 500 mg [administered as two intramuscular injections (IM) of 250 mg] every month, with an additional 500 mg dose given 2 weeks after the initial dose. InAug 2017,fulvestrant was also licensedfor first line treatment of locally advanced or metastatic ER+ breast cancer, with a recommended dosing regimen of two IM injections of 250 mg delivered over 1-2 minutes on days 1, 15, 29 and once monthly thereafter [6].

In 2011 NICE issued guidance not recommending fulvestrant as an alternative to aromatase inhibitors for the treatment of estrogen-receptor positive, locally advanced or metastatic breast cancer in postmenopausal women whose cancer had relapsed on or after adjuvant anti-estrogen therapy, or who had disease progression on anti-estrogen therapy [7].

In May 2017, AstraZeneca provided a submission to NICE regarding the clinical and cost effectiveness of fulvestrant for the treatment of ABC in post-menopausal women who had not been previously treated with endocrine therapy. The remit of this appraisal, specified by NICE’s final scope [8], was to evaluate the clinical and cost effectiveness of fulvestrant for the first line treatment of ABC in post-menopausal women who had not been treated with previous endocrine therapy.

# The Independent Evidence review group (ERG) Review

## Clinical effectiveness evidence provided by the company

The company set out to compare the clinical effectiveness, cost effectiveness and health related quality of life (HRQoL) of fulvestrant against two AIs (anastrozole and letrozole) or tamoxifen as defined by the NICE scope.

The company carried out a clinical systematic literature review (SLR), which identified two relevant randomised controlled trials (RCTs) comparing the licensed dose of fulvestrant against the standard care dose of anastrozole (oral, 1 mg).

The FIRST trial [9-11] was a phase II, open label, non-inferiority trial compared fulvestrant (500 mg) versus anastrozole (1 mg) in postmenopausal women with HR+ ABC who had either never received endocrine therapy for advanced disease or who had received previous adjuvant endocrine therapy, completed at least 12 months prior to randomisation into the trial. A subsequent phase III, double blind, superiority trial (FALCON) [12] compared fulvestrant (500 mg) versus anastrozole (1 mg) in postmenopausal women with ER+ and/or progesterone receptor positive (PgR+) ABC who had not previously been treated with any endocrine therapy.

Outcomes reported by the two trials included progression free survival (PFS), which was the primary outcome of the FALCON trial, and time to progression (TTP), a secondary outcome of the FIRST trial. The ERG noted that the definition of TTP in the FIRST trial included death as an event and therefore this was the same definition as PFS for the FALCON trial. Other outcomes included overall survival (OS), clinical benefit rate (CBR), objective response rate (ORR), adverse events (AEs) and health-related quality of life (HRQoL). These outcomes were consistent with those specified in the NICE scope [8].

In the phase III FALCON trial median PFS was 2.8 months longer with fulvestrant compared to anastrozole (a statistically significant difference, HR = 0.797, 95% CI 0.637 to 0.999, p = 0.0486) [12]. However, clinical experts consulted by the ERG did not believe that this was a clinically significant difference. In contrast, in the FIRST trial, median TTP was 10.3 months longer in the fulvestrant arm than the anastrozole arm, a difference that is both clinically and statistically significant (HR 0.66, 95% CI 0.47 to 0.92, p = 0.01) [10].

OS was a secondary outcome of the FALCON trial. However, at the time of the submission of evidence to NICE, it was not possible for the company to calculate a median OS due to the immaturity of these data. A slightly lower proportion of deaths was observed in the fulvestrant arm (29% vs 32% in the anastrozole arm), but this was not a statistically significant difference (HR 0.88, 95% CI 0.63 to 1.22, p = 0.4277) [12]. In the FIRST trial an analysis of OS was not originally specified, but an analysis was undertaken when approximately 65% of patients had died [11]. At the data cut-off, the proportion of patients who had died was lower in the fulvestrant arm than in the anastrozole arm (61.8% versus 71.8% respectively), which was a statistically significant improvement in median survival in favour of fulvestrant (54.1 months versus 48.4 months in the anastrozole arm, HR 0.70, 95% CI 0.50 to 0.98, p=0.04) [11].

The primary outcome for the FIRST trial was clinical benefit rate (CBR), but as a non-inferiority trial, FIRST was not powered to detect a difference in CBR. In the fulvestrant arm, 72.5% achieved clinical benefit versus 67% in the anastrozole arm (OR 1.30, 95% CI 0.72 to 2.38, p = 0.386) [9]. In the FALCON trial, CBR was secondary outcome and results were similar to those seen in the FIRST trial (78% in the fulvestrant arm versus 74% in the anastrozole arm, OR 1.25, 95% CI 0.82 to 1.93, p = 0.3045) [12].

Only the FALCON trial collected data on HRQoL using the EQ-5D-3L and the FACT-B questionnaires. Results from both measures indicated that HRQoL was typically maintained through to the 156 weeks visit and no difference was observed between the two treatment arms during this time.

Among the other secondary outcomes recorded (e.g. ORR and other response-related outcomes), results were either similar between treatment arms or favoured the fulvestrant arm.

### Network meta-analysis (NMA)

No direct comparisons of fulvestrant with letrozole or tamoxifen were available. However, the company’s SLR identified four additional RCTs that were considered for inclusion in a network meta-analysis (NMA). Two trials compared anastrozole (1 mg) versus tamoxifen (20 mg) [13, 14] and one compared anastrozole (1 mg) versus tamoxifen (40 mg) [15], a dose not recommended by the European Medicines Agency (EMA). This latter trial was subsequently excluded from the NMA, as it also only reported the outcomes of interest for a subset of participants. One further trial (the PO25 trial [16, 17]) compared letrozole (2.5 mg) versus tamoxifen (20 mg). The final network therefore included data from five trials: FIRST and FALCON (fulvestrant vs anastrozole); the North American and Target trials as a combined dataset termed NorthAmTARGET (anastrozole versus tamoxifen) and PO25 (letrozole versus tamoxifen). The studies included in the NMA are shown in Figure 1.

Figure 1. Studies included in the company’s NMA to compare fulvestrant, anastrozole, letrozole and tamoxifen

In all studies, the enrolled population was post-menopausal women with ER+ and/or PgR+ ABC. However, as HER status testing only became routine after the mid 2000’s, the only trial which fully excluded HER+ participants was the FALCON trial.

Individual patient data (IPD) were available for the two fulvestrant trials and for the pooled NorthAmTARGET data set. This enabled the company to match participants from the FIRST and NorthAmTARGET trials to the FALCON trial inclusion criteria that required participants to be ER+/ PgR+ and endocrine treatment naïve. The purpose of this matching process was to increase homogeneity between participants in the FALCON trial and those in the FIRST and NorthAmTARGET trials.

After the matching process described above, Kaplan-Meier (KM) plots of PFS and OS were produced for FALCON and the matched subgroups of participants from the FIRST, and NorthAmTARGET trials. It was not possible to match data from the PO25 trial comparing letrozole to tamoxifen because only aggregate data were available. PFS and OS plots were redrawn by digitising the published KM plots for the PO25 trial and reconstructing patient-level data using a published algorithm [18].

The KM plots and log cumulative hazard plots for OS and PFS for each trial were then examined visually and it was concluded that the assumption of proportional hazards did not hold for all studies. Therefore the company chose to use an NMA method developed by Ouwens et al. [19], in which the differences in the shape and scale parameters of the parametric survival function used to model PFS or OS between the intervention and each comparator over time are synthesised, and used both for the indirect comparison and to extrapolate the PFS and OS curves beyond the end of trial follow-up.

A fixed-effect NMA of PFS was conducted for five different parametric distributions (Weibull, Gompertz, log-logistic, lognormal and generalised gamma). For all distributions except the Gompertz, the difference in the scale parameter PFS with fulvestrant was statistically significantly better than anastrozole and PFS was tamoxifen was statistically significantly worse than anastrozole. For the shape parameter, the lognormal distribution results also indicated fulvestrant was better than anastrozole, whereas tamoxifen was worse than anastrozole. These were the only statistically significant results.

A fixed effect NMA of OS was also conducted for the five difference parametric distributions. No statistically significant differences were observed for the fulvestrant versus anastrozole comparisons in either the shape or scale parameters.

### ERG critique of the clinical effectiveness evidence

The company’s SLR identified all the relevant evidence for fulvestrant and the comparators anastrozole, letrozole and tamoxifen. The FIRST [9-11] and FALCON [12] trials comparing fulvestrant to anastrozole were of good methodological quality, but only interim OS results were available from FALCON at the time of the company’s submission to NICE. This meant median OS could not be calculated for this trial.

There was some heterogeneity between the FALCON trial (the key phase III trial for fulvestrant) and the other studies included in the NMA. In FALCON all participants had breast cancer that was ER+ and/or PgR+, HER2-, and all participants were endocrine therapy naïve. In the FIRST trial 25% of patients had received previous endocrine therapy at least 12 months prior to trial randomisation. Among the North American, TARGET and PO25 studies 11% to 20% of participants were not endocrine therapy naïve. All participants in the FIRST trial had HR+ breast cancer but this was not the case in the other studies (North American 89%, TARGET 45% and PO25 66% were HR+). Finally, because HER status was not routinely being tested until the mid-2000s [20], the FALCON trial was the only trial where participants were required to be HER-. Information for some participants was obtained retrospectively for the FIRST trial, but HER status remains unknown for the North American, TARGET and PO25 studies.

The matching process reported in the NMA to increase homogeneity between the FALCON trial and the FIRST and NorthAmTARGET trials, significantly reduced the numbers of patients contributing data to the NMA (Table 1). This reduction was most pronounced for the TARGET trial where only 39% of participants met the criteria. Whilst it was clear that the matching process allowed for the exclusion of participants who would not have met the criteria to enter the FALCON trial, which created a more homogeneous population in the NMA, the ERG was concerned about potential disadvantages. An example disadvantage is that matching creates scope for bias because randomisation has been broken. The ERG concluded that in this specific instance, the advantages of matching in reducing heterogeneity in the NMA (for the trials that could be matched) was likely to outweigh the potential disadvantages of reduced power. A similar conclusion was reached in a previous STA for fulvestrant (TA239 [7]), in which only a subgroup of one trial met the decision problem.

Table 1 Patient numbers in the NMA studies before and after matching to the FALCON trial.

## Cost-effectiveness evidence

To establish the cost-effectiveness of fulvestrant compared with two AIs (anastrozole and letrozole), the company submitted a de novo cohort-based partitioned survival economic model. In patients where AIs were contra-indicated or not tolerated, the model compared fulvestrant to tamoxifen. The analysis was conducted from the perspective of the NHS and Personal Social Services (PSS) over a 30-year (lifetime) horizon. A half-cycle correction was applied to the model and costs and effects were discounted at 3.5% per annum.

The company’s model consisted of three mutually exclusive health states that are commonly used in oncology modelling, i.e. PFS, progressed disease (PD) and death. All patients entered the model in PFS and over time moved to the PD health state. People who moved to the PD state could not return to the PFS health state. The ERG’s adapted diagram illustrating patient flow across the three health states is shown in Figure 2.

Figure 2 Model structure (adapted by the ERG)

All patients were modelled to receive treatment (fulvestrant or comparators) until disease progression. To account for the impact of AEs on costs and HRQoL these were included as a one-off event in the first treatment cycle. AE incidence rates for fulvestrant and anastrozole were obtained from the FALCON trial, whereas the AE incidence rates for letrozole and tamoxifen were sourced from the literature. After disease progression, the company’s model assumed that all patients received subsequent treatments and that subsequent treatments only impacted on costs and not on survival (as this was assumed to be captured in the overall survival estimate).

To inform HRQoL, the company conducted a SLR that identified two studies by Fukuda et al. [21] and Eyles at al. [22] alongside a review of the utility values used in NICE breast cancer appraisals. The economic model however was informed by the HRQoL data collected as part of the FALCON trial, which were adjusted using repeated measures mixed effects regression models. The economic model also included the costs of disease management, treatment acquisition, treatment administration, subsequent therapy and AEs. Costs were based on NHS Reference costs 2015/16 [23] and PSS Research Unit (PSSRU) costs [24].

The proportion of patients transitioning through the health states were predicted by estimating shape and scale parameters of the PFS and OS curves. These survival curves were obtained from the results of a fixed-effect NMA. The long-term data for these curves were extrapolated by fitting generalised gamma and Weibull distributions to the PFS and OS curves, respectively.

The company’s base case comparison of fulvestrant versus anastrozole produced an incremental cost effectiveness ratio (ICER) of £34,099; the ICER was £29,991 for fulvestrant versus letrozole and £22,498 for fulvestrant versus tamoxifen. The company presented a series of sensitivity and scenario analyses to test the structural assumptions of the model. Whilst changing the scale parameter for the OS curve had the most significant impact on the ICERs, the scenario analyses did not have any significant impact on the base case results.

### Critique of the cost-effectiveness evidence

The company’s model adequately reflected the clinical pathway of patients through the course of their treatment for advanced/metastatic breast cancer and conformed to the NICE reference case. However, it was noted that the economic evaluation had several significant limitations in relation to the literature search carried out, the NMA, extrapolation of the survival outcomes and the costs for disease management and resources used.

The ERG considered the company’s approach on the literature search for cost-effectiveness to be unusual as they only searched for previous Health Technology Assessments (HTAs). In addition, their strategy had the following limitations: (i) the company did not provide any information on the eligibility criteria for the search; (ii) there was a lack of discussion about the HTAs identified, especially their relevance to the current submission and (iii) the company did not search for published cost-effectiveness studies.

To inform treatment effectiveness outcomes of PFS and OS, the company conducted a fixed-effect NMA. The effect of treatment was estimated by the shape and scale parameters of parametric survival distributions

The ERG agreed with the company in excluding the Milla-Santos trial [15] from the NMA, as its inclusion led to heterogeneity in the NMA for both OS and PFS curves (due to higher dose of tamoxifen used compared to other pooled studies). The ERG also believed that the exclusion of the PO25 trial [17, 16] from the NMA analysis would be appropriate as, unlike other trials included in the NMA, i) patient level data were not available so PO25 data could not be matched to the FALCON trial; ii) results were compromised by approximately 50% cross-over after progression; and iii) it is widely accepted that letrozole and anastrozole have equivalent efficacy.

An important limitation of the cost-effectiveness analysis stems from the immature OS data of the FALCON trial. Therefore OS for fulvestrant versus anastrozole is largely based upon the FIRST trial data (where OS was not an originally specified outcome). The ERG was concerned that the OS benefit in FALCON will be lower than in the FIRST trial once data are mature, because the gain in PFS with fulvestrant is lower in the FALCON trial then in the FIRST trial. The model is sensitive to changes in OS and the ERG considered that the ICER was uncertain and likely to be higher once full results from FALCON are known.

Resource use for the PFS and PD health states in the model were obtained from descriptions in NICE clinical guideline 81 [5]. The ERG identified that these resources were for patients receiving chemotherapy, rather than endocrine therapy as in this STA. Consequently the resource use may not have been estimated appropriately.

The ERG had concerns about the proportion of patients receiving endocrine therapy as their second-line treatment. The company model assumed that approximately 54% of those at second-line therapy received endocrine therapy and approximately 38% chemotherapy, with the remainder receiving targeted therapy. Clinical advice to the ERG was that the proportion of patients receiving endocrine therapy second-line would be higher, in the region of 67-80% and with fewer receiving chemotherapy. One clinical expert considered that 20% of patients would have targeted therapy in combination with endocrine therapy or chemotherapy.

The final ERG concern regarding the economic model was the cost associated with fulvestrant administration. The company assumed that after administration of the first fulvestrant cycle, 32% of the subsequent cycles of treatment would be administered in primary care and 58% in the secondary care outpatient setting. One ERG clinical expert however believed that all patients in their locality would have fulvestrant administered in the secondary care setting.

### Additional analyses conducted by the ERG

The ERG undertook further exploratory analyses to test the robustness of the company’s base case economic analysis in relation to areas where the ERG considered the company’s base case to have limitations. These analyses were based on the company's assumptions relating to the OS curve, resource use for the PFS and PD health states, proportions of patients receiving different second-line treatments, the studies included in the NMA and the administration cost for fulvestrant. The findings of these analyses are discussed below.

Owing to the uncertainties associated with OS modelling, the ERG undertook two scenario analyses. The first ERG analysis involved extrapolating the OS curve using different distributions. On extrapolating the OS curve using the Gompertz distribution (instead of the Weibull distribution of the company base case), the direction of the company’s base case changed, showing that fulvestrant was dominated by letrozole (letrozole being less expensive and more effective, with higher QALYs). In addition the ICER increased significantly when fulvestrant was compared against anastrozole and tamoxifen in this scenario. However, the Gompertz distribution provided a poor fit to the observed data so it should be noted that the results are to be treated with caution. Assigning log-logistic and log-normal distributions had insignificant impacts on the base case results.

The second OS scenario analysis involved changing the OS scale parameter for fulvestrant. The ERG varied the OS scale parameter between its mean value and the lower 95% confidence interval to illustrate the effect of changes to the treatment benefit. The extent of survival benefit was uncertain due to the immaturity of the OS data from the FALCON trial. Example results for incremental changes in the scale parameter showed that a relatively small change had a significant impact on the ICER for fulvestrant vs anastrozole (Table 2).

Table 2 Effect of changes to the fulvestrant OS scale parameter, ERG scenario

To address the ERG’s concern that disease management costs for the PFS and PD health states may not have been estimated appropriately, the ERG estimated resource use from the study by Karnon et al. [25]. This ERG scenario resulted in a decrease in total costs for all the treatments in comparison to the company’s base case.

The clinical advice which indicated a higher proportion of people would receive endocrine therapy as a second line treatment was addressed by changing the proportions of patients receiving second-line treatment. Owing to limited information and different estimates of our clinical advisors the ERG pragmatically assumed the proportions shown in Table 3.

Table 3 ERG’s assumptions related to the proportion of patients receiving second-line treatments

Varying the proportion of patients receiving different therapy options as a second-line treatment did not influence the base-case results.

The ERG believed excluding the PO25 trial from the NMA was appropriate. This assumes that anastrozole and letrozole have similar efficacy. Using the PFS and OS estimates from a fixed effect NMA excluding the PO25 trial had almost no impact on the ICER.

In the last ERG scenario the administration cost for fulvestrant was based on all patients receiving fulvestrant in the outpatient setting. This change increased the ICER for fulvestrant versus anastrozole by £1,397 to £35,496 per QALY.

Finally, the ERG undertook an additional analysis to demonstrate its preferred base case scenario combining the following analyses: i) using PFS and PD data from the study by Karnon et al. [25]; ii) using alternative proportions of patients receiving 2nd line treatment based on expert clinical advice; iii) changing the proportion of patients receiving second line treatment and iv) by assuming a similar efficacy for both letrozole and anastrozole, the PO25 trial data for OS and PFS was excluded from the NMA.

The ERG’s base case produced an ICER of £33,455 per QALY for fulvestrant compared to anastrozole. Tamoxifen was dominated when compared with anastrozole because it is more expensive and less effective.

It is important to note that despite the ERG considering that the parametric distributions chosen by the company to model PFS and OS were appropriate and a reasonable fit to the observed data, uncertainty in the cost-effectiveness estimates remains. This is due to the immature OS data from the FALCON trial and the sensitivity of the model to changes in OS (Table 2). The ERG believes the ICERs for fulvestrant versus anastrozole are likely to be higher when the full results of the FALCON trial become available.

Conclusions of the ERG report

The lack of mature OS data from the FALCON trial was considered by the ERG to be a major issue in this trial. The absence of mature OS data means that it is not currently possible to accurately determine the cost effectiveness of fulvestrant compared with existing treatments. The additional exploratory analyses carried out by the ERG to test the robustness of the company’s base case economic analysis suggested that the cost is likely to be above that normally considered as cost-effective for NHS resources.

# National Institute for Health and Care Excellence Guidance

The NICE appraisal committee reviewed the clinical and cost-effectiveness evidence available through the company submission and the ERG report alongside testimony from clinical experts and patient representatives.

## NICE preliminary guidance

Following consideration of the evidence presented in the company submission and the critique of this provided by the ERG, alongside testimony from clinical experts and patient representatives, the NICE committee presented its preliminary guidance. The committee determined that fulvestrant could not be recommended within its marketing authorisation, for treating locally advanced or metastatic estrogen-receptor positive breast cancer in postmenopausal women who have not had previous endocrine therapy.

## Final NICE Guidance

After a period of public consultation, a second committee meeting was conducted in which the initial decision of the first appraisal committee was affirmed [26].

The committee considered that as the final results on overall survival from the FALCON trial were not yet available, it was unclear whether fulvestrant would extend OS compared with AIs. In addition, because of the uncertainty in the clinical evidence, the cost effectiveness of fulvestrant compared with existing treatments was also considered to be unclear. Furthermore, it was considered that the cost would be likely to be above the range normally considered a cost-effective use of NHS resources, as a result fulvestrant could not be recommended.

# conclusion

Two RCTs (one phase II and one phase III) provided evidence comparing fulvestrant to anastrozole for the treatment of HR+ locally advanced or metastatic breast cancer. The extent of the PFS benefit obtained with fulvestrant differed between the two trials and OS data for the key phase III trial were immature. The potential OS benefit was therefore unclear. The uncertainty in the OS data was reflected in uncertainty in the cost-effectiveness analyses.

Although patient and clinical expert opinion suggested that fulvestrant, administered as an intramuscular injection, has advantages over current oral treatments (e.g. potentially increasing compliance), the cost is likely to be above the range normally considered a cost-effective use of NHS resources and consequently NICE could not recommend fulvestrant for untreated HR+ locally advanced or metastatic cancer. The appraisal committee stated that the guidance executive will decide whether the technology should be reviewed when mature OS data from FALCON are available, which is expected at the end of 2019. A review of these data will be based on further information gathered by NICE, and in consultation with consultees and commentators.

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# Author contributions

All authors have commented on the submitted manuscript and have given their approval for the full version to be published.

Neelam Kalita, Keith Cooper and Olu Onyimadu summarised and critiqued the economic analysis submitted by the company. Petra Harris, Wendy Gaisford and Joanna Picot summarised and critiqued the clinical effectiveness evidence submitted by the company. Neelam Kalita and Wendy Gaisford drafted some parts of this manuscript, which were then edited and added to by Joanna Picot who completed the manuscript and responded to feedback from all other authors. All authors reviewed, critiqued, and approved this manuscript.

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# Compliance with Ethical Standards

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**Conflicts of interest**

All authors (JP, NK,WG, PH, OO, KC) declare no conflicts of interest.

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Table 4 Patient numbers in the NMA studies before and after matching to the FALCON trial.

|  |  |
| --- | --- |
|  | **Trial** |
| **FALCON** | **FIRST** | **North American** | **TARGET** | **NorthAm-Target** |
| Treatment arm | Ful | Ana | Ful | Ana | Ana | Tam | Ana | Tam | Ana | Tam |
| ITT population, n | 230 | 232 | 102 | 103 | 171 | 182 | 340 | 328 | 511 | 510 |
| Matched to FALCON, n (%) | 230(100) | 232(100) | 73(72) | 80(78) | 119(70) | 134(74) | 132(39) | 128(39) | 251(49) | 262(51) |

PO25 trial is not included because only aggregate data were available so no matching was undertaken.

Ana, anastrozole; Ful, fulvestrant; ITT, intention-to-treat; Let, letrozole; n, number; Tam, tamoxifen.

Table 5 Effect of changes to the fulvestrant OS scale parameter, ERG scenario

|  |  |  |
| --- | --- | --- |
| **Parameters** | **Base case ICER (OS: Weibull)** | **Scenario ICER** |
| ***Scenario 2: Fulvestrant Incremental scale parameter value Aa*** |
| Fulvestrant vs  | Letrozole | £29,991 | £33,475 |
| Anastrozole | £34,099 | £40,761 |
| Tamoxifen | £22,498 | £24,432 |
| ***Scenario 2: Fulvestrant Incremental scale parameter value Ba*** |
| Fulvestrant vs  | Letrozole | £29,991 | £38,326 |
| Anastrozole | £34,099 | £52,405 |
| Tamoxifen | £22,498 | £27,146 |
| ***Scenario 2: Fulvestrant Incremental scale parameter value Ca*** |
| Fulvestrant vs  | Letrozole | £29,991 | £45,842 |
| Anastrozole | £34,099 | £79,337 |
| Tamoxifen | £22,498 | £31,404 |
| ***Scenario 2: Fulvestrant Incremental scale parameter value Da*** |
| Fulvestrant vs | Letrozole | £29,991 | £59,000 |
| Anastrozole | £34,099 | £208,231 |
| Tamoxifen | £22,498 | £39,027 |

***a*** Values A, B, C and D differed by small increments. The actual values used remain confidential.

Table 6 ERG’s assumptions related to the proportion of patients receiving second-line treatments

|  |  |  |  |
| --- | --- | --- | --- |
| **Proportion of patients (%)** | **Endocrine therapy**  | **Chemotherapy** | **Targeted therapy** |
| **Baseline** | 54.35% | 37.57% | 8.08% |
| **Scenario** | 67.00% | 24.92% | 8.08% |

ANASTROZOLE

FULVESTRANT

TAMOXIFEN

20 mg

LETROZOLE

Figure 3. Studies included in the company’s NMA to compare fulvestrant, anastrozole, letrozole and tamoxifen

Figure 4 Model structure (adapted by the ERG)