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ORIGINAL RESEARCH ARTICLE

Cost-Effectiveness Analysis of Fulvestrant 500 mg in Endocrine Therapy-Naïve Postmenopausal Women with Hormone Receptor-Positive Advanced Breast Cancer in the UK

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Abstract

Introduction The selective estrogen receptor degrader fulvestrant is approved for the first-line treatment of postmenopausal patients with hormone receptor-positive (HR+), locally advanced or metastatic breast cancer who have not received prior endocrine therapy. We evaluated the cost-effectiveness of fulvestrant versus comparator treatments in endocrine therapy-naïve patients with locally advanced or metastatic breast cancer.

Methods A three-health-state (progression free, progressed disease, and death) partitioned survival model from the UK National Health Service and Personal Social Services perspective was developed to extrapolate study data for the cumulative probability of progression-free survival and overall survival to a lifetime (30-year) horizon. Relative comparator data were derived from a systematic literature review-informed network meta-analysis. Sensitivity analyses were applied to assess the impact of uncertainty in the parameter input values on the results.

Results Over a lifetime horizon (30 years), the incremental cost (British pounds sterling) per patient associated with fulvestrant treatment was £18,867 versus anastrozole, £23,097 versus letrozole, and £17,131 versus tamoxifen, with incremental quality-adjusted life-years of 0.55, 0.77, and 0.76, respectively, and incremental cost-effectiveness ratios of £34,109, £29,827, and £22,532, respectively. The largest difference in costs between fulvestrant and the comparators was related to treatment costs.

Conclusions Results suggest that fulvestrant could potentially be a cost-effective option compared with other endocrine monotherapies (anastrozole, letrozole, and tamoxifen) for treating endocrine therapy-naïve, postmenopausal women with HR+, locally advanced or metastatic breast cancer.

Key Points for Decision Makers

The results of this cost-effectiveness analysis suggest that fulvestrant 500 mg may be a cost-effective option compared with other endocrine monotherapies as a treatment for endocrine therapy-naïve, postmenopausal women with hormone receptor-positive, locally advanced or metastatic breast cancer.

Fulvestrant 500 mg is associated with progression-free survival and overall survival gains relative to the comparators.

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1 Introduction

Breast cancer is the most common cancer in women, and is the fifth leading cause of cancer deaths in women worldwide [1]. In 2015, 54,741 women were diagnosed with breast cancer in the UK [2]. The majority of patients diagnosed with breast cancer have hormone receptor-positive (HR+) disease [3], and standard treatment for these patients is endocrine therapy; however, a proportion of patients with HR+ advanced or metastatic breast cancer will not have received prior adjuvant endocrine therapy and are considered endocrine therapy-naïve. In the UK, approximately 13–21% of patients with breast cancer receive a late-stage diagnosis (stage III or IV), and 6–7% of patients have metastases at diagnosis [2]; a large proportion of these patients are likely to be endocrine therapy-naïve. However, one European observational study found that approximately one-quarter of postmenopausal patients with an initial diagnosis of HR+ locally advanced or metastatic disease did not receive subsequent endocrine therapy [4].

Recommended first-line treatment options for endocrine therapy-naïve postmenopausal patients include the selective estrogen receptor degrader fulvestrant, the selective estrogen receptor modulator tamoxifen, aromatase inhibitors (anastrozole, exemestane, or letrozole), or the cyclin-dependent kinase 4/6 (CDK4/6) inhibitor palbociclib in combination with an aromatase inhibitor [5–7]. In addition, the CDK4/6 inhibitor ribociclib in combination with an aromatase inhibitor is approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for the initial treatment of postmenopausal women with HR+ advanced or metastatic breast cancer [8, 9], but is not yet included in current treatment guidelines [5–7]. As of November 2017, both palbociclib and ribociclib, in combination with an aromatase inhibitor, have been recommended by the UK National Institute for Health and Care Excellence (NICE) for routine funding [10, 11].

Fulvestrant 500 mg has recently received approval from the EMA and the FDA, as well as in Japan and Russia, for the first-line treatment of postmenopausal patients with locally advanced or metastatic breast cancer who have not received prior endocrine therapy [12–14]. The approval of fulvestrant in the first-line setting was based on the findings of the international phase III, randomized, double-blind Fulvestrant and AnastrozoLe COmpared in hormonal therapy-Naïve advanced breast cancer (FALCON) study [15], which demonstrated that fulvestrant significantly improved progression-free survival (PFS; the primary endpoint) over anastrozole (median 16.6 vs 13.8 months; hazard ratio 0.797; 95% confidence interval 0.637–0.999; $p = 0.0486$) in endocrine therapy-naïve patients with HR+ locally advanced or metastatic breast cancer. The PFS findings from the FALCON study confirmed the improved time to progression with first-line fulvestrant over anastrozole reported in the phase II, open-label Fulvestrant fIRst-line Study comparing endocrine Treatments (FIRST) study [16, 17].

Given the recent regulatory approvals of fulvestrant 500 mg for the first-line treatment of endocrine therapy-naïve patients based on the clinical data in the FALCON study, the objective of this analysis was to evaluate the cost-effectiveness of fulvestrant 500 mg versus comparators in endocrine therapy-naïve patients with HR+ locally advanced or metastatic breast cancer.

2 Methods

2.1 Patient Population

The target population for this analysis was postmenopausal women with HR+, human epidermal growth factor (HER)2-negative, locally advanced or metastatic breast cancer who were endocrine therapy-naïve (i.e., had not received treatment with any hormone therapy).

2.2 Cost-Effectiveness Model Structure

A Microsoft Excel-based, three-health-state partitioned survival model, aligned with previous cost-effectiveness models in advanced breast cancer, was developed. The model used progression free, progressed disease, and death as health states (Online Resource 1: Supplementary Fig. 1, see electronic supplementary material [ESM]), with the assumption that events were progressive, mutually exclusive, and irreversible.

Survival data for fulvestrant and anastrozole were derived from two studies (based on the intention-to-treat populations): the phase III, randomized, double-blind FALCON study (NCT01602380) [15] and the phase II, open-label FIRST study (NCT00274469) [16–18]. Response and adverse event (AE) data were derived from the FALCON study only. The model included one cohort; further details regarding the patients included within this cohort are provided in Online Resource 1: Supplementary Table 1 (see ESM). Based on the FALCON study, the mean age at entry was 63.8 years.

In the partitioned survival model, the state occupancy of the simulated cohort was estimated by extrapolating study data for the cumulative probability of PFS and overall survival (OS) to a lifetime (30-year) horizon (i.e., a time point when < 0.01% of the population is alive). This model was validated by comparing predicted PFS and OS results with data from previous clinical studies, including FIRST [16–18], PO25 [19, 20], European Organisation for the Research and Treatment of Cancer (EORTC) [21],

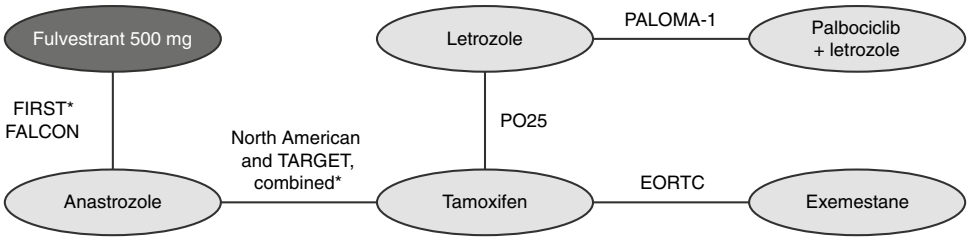

Fig. 1 Network diagram of the seven unique studies included in the analysis. *Studies in which patient-level data were available for the hormone receptor-positive, endocrine therapy-naïve population. *EORTC* European Organisation for the Research and Treatment of Cancer, *FALCON* Fulvestrant and AnastrozoLe COmpared in hormonal therapy-Naïve advanced breast cancer, *FIRST* Fulvestrant fIRst-line Study comparing endocrine Treatments, *PALOMA* PALbociclib: Ongoing trials in the MAnagement of breast cancer, *TARGET* Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability

Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) [22, 23], SWOG 0226 [24], and the retrospective study by Gamucci et al. [25].

Treatment cycles in the model were 4 weeks in duration; this was considered the shortest period in which a change in the disease course or symptoms would be observed in clinical practice, and corresponds to the dosing schedule of fulvestrant. Costs were considered from the UK National Health Service (NHS) and Personal Social Services perspective. Costs and outcomes were discounted at a rate of 3.5% per annum [26].

Results were expressed as total and incremental costs and quality-adjusted life-years (QALYs), and as incremental cost-effectiveness ratios (ICERs).

2.3 Clinical Data Inputs

2.3.1 Network Meta-Analysis

In the FIRST and FALCON studies, fulvestrant was compared with anastrozole. However, as neither study included all the relevant treatment comparators and the OS data in the FALCON study were relatively immature (31% maturity at data cut-off, at which point 67/230 [29%] patients in the fulvestrant group and 75/232 [32%] patients in the anastrozole group had died [15]), relative comparator data were derived from a systematic literature review-informed network meta-analysis (NMA) that enabled indirect comparisons with fulvestrant and long-term survival extrapolation. For the systematic literature review, English-language articles reporting results of randomized controlled trials in the target population were identified by searching the following databases: Embase®, MEDLINE®, MEDLINE® In-Process, and the Cochrane Central Register of Controlled Trials (from database inception to June 2017). Comparators evaluated in this analysis were anastrozole, letrozole, tamoxifen, exemestane, and palbociclib + letrozole. Eligible studies assessed endocrine therapy-naïve patients with HR+ and HER2-negative locally advanced or metastatic breast cancer, either in a population where at least 65% of patients met these inclusion criteria, or in a subgroup analysis; however, studies that did not report HR or HER2 status were also eligible for inclusion. Seven unique studies were identified for inclusion in the NMA (Fig. 1).

The NMA employed a 'network of parametric survival curves' approach [27]. This method was used as the proportional hazards assumption did not hold for PFS and OS across the included studies. In line with NICE guidance [28], standard parametric distributions were fitted to the PFS and OS Kaplan–Meier data (Weibull, Gompertz, log-logistic, log-normal, generalized gamma, and exponential). Relaxation of the proportional hazards assumption was enabled by modeling differences against a baseline treatment (fulvestrant) and study (FALCON), and using the treatment arm and study as parameters on the predictive scale. This allowed all parametric models, except exponential, to be estimated without assuming proportional hazard ratios, yet maintaining trial randomization. Based on Akaike's Information Criterion and Bayesian Information Criterion statistics (Online Resource 1: Supplementary Table 2, see ESM) and visual fit against observed Kaplan–Meier data, as well as the expert opinion of seven clinicians, the generalized gamma and Weibull distributions were chosen to extrapolate PFS and OS, respectively. The parametric curve fits for these distributions are reported in Online Resource 1: Supplementary Table 3 (see ESM).

The base case included a comparison of fulvestrant with anastrozole, letrozole, and tamoxifen (relevant to the UK setting) using data from the FALCON [15], FIRST [16–18], PO25 [19], and the combined North American and Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability (TARGET) studies [29]. Patient-level data were available for the intention-to-treat populations from the FIRST and the combined North American and TARGET studies. The HR+, endocrine therapy-naïve patient populations were extracted from the intention-to-treat populations for the FIRST and the combined North American

Table 1 Treatment dosing, administration, and drug acquisition costs[a]

	Fulvestrant (first 4 weeks)	Fulvestrant (after first 4 weeks)	Anastrozole	Letrozole	Tamoxifen
Label information					
Administration method	Intravenous	Intravenous	Oral	Oral	Oral
Dose per administration (mg)	500	500	1	2.5	20
Administration frequency	2 per 4 weeks	1 per 4 weeks	1 per day	1 per day	1 per day
Package information					
Formulation (mg)	250	250	1	2.5	20
Pack size	2	2	28	28	30
Cost per pack (£)	522.41	522.41	0.75	1.52	1.62

[a]Dosing information sourced from British National Formulary labels [44], acquisition costs (British pounds sterling; 2016) sourced from the National Health Service drugs and pharmaceutical electronic market information tool [45]

Table 2 Total 4-week treatment administration costs[a]

Cost item	Number per first cycle	Number per subsequent cycle	Percentage	Unit cost (£)	Total cost first cycle (£)	Total cost subsequent cycle (£)
Fulvestrant						
Oncologist visit	1	–	100	196.64	196.64	0.00
Oncologist visit follow-up	1	–	100	99.97	99.97	0.00
Community nurse specialist (15 min)	1	1	32	18.75	6.06	6.06
Oncologist visit follow-up	1	1	68	99.97	67.68	67.68
Total					370.35	73.74
Oral therapies (anastrozole, letrozole, and tamoxifen)						
Oncologist visit	1	–	100	196.64	196.64	0.00
General practitioner telephone consultation	–	1	100	27.93	0.00	27.93
Total					196.64	27.93

[a]Costs (British pounds sterling; 2016) calculated using National Health Service reference costs [35] and the Personal Social Services Research Unit pay and prices index [34, 59]

and TARGET studies to match the licensed population for fulvestrant, represented by the intention-to-treat population in the FALCON study. For the PO25 study, only published Kaplan–Meier curves were available; these were digitized using WebPlotDigitizer (version 3.6), and the algorithm presented in Guyot et al. (2012) [30] was run in the statistical package R to reconstruct patient-level data.

An additional scenario analysis was conducted, including exemestane data from the phase III EORTC study [21] and palbociclib + letrozole data from the phase II PALbociclib: Ongoing trials in the MAnagement of breast cancer (PALOMA-1) study [31]. These additional analyses were not perceived to be relevant to the UK at the time of the analysis, but could be considered relevant for additional markets. Although PALOMA-1 is a phase II study and phase III data for palbociclib + letrozole are available from the results of the PALOMA-2 study [32], the patient population in the PALOMA-2 study was not well matched to the FALCON patient population (only 44% were endocrine therapy-naïve and no Kaplan–Meier data relating to this subgroup were reported); additionally, no OS data were available at the time of this analysis.

2.3.2 Costs

Costs (British pounds sterling [UK£]; 2016) for fulvestrant and each comparator were calculated in the model, and included those relating to drug acquisition, treatment administration, disease management, AEs, and subsequent treatments.

Drug acquisition costs were calculated based on available formulations, pack sizes, unit costs, and price per mg for each treatment (Table 1). In the base case, treatment until progression was assumed, and drug acquisition costs were multiplied by overall rates of relative dose intensity. Treatment administration costs were calculated for the first 4-week cycle and subsequent cycles (Table 2). Disease management costs included in the model were calculated by

health state; progression free and progressed disease health states totaled £183.36 and £704.67, respectively, per 4 weeks of treatment, whilst the costs associated with terminal care totaled £4379.03, where the costs associated with terminal care were calculated by multiplying the cost of death in each setting (hospital, hospice, or home) by the likelihood of death in each setting [33, 34].

Costs for the management of grade ≥ 3 AEs experienced by at least 2% of patients in any treatment group were applied as one-off events at the start of treatment. NHS reference costs [35], with cost codes adopted from those reported in previous NICE submissions [36–42], were used to calculate the cost per event of increased alanine transaminase (£1757.79), increased aspartate transaminase (£1757.79), hypertension (£729.87), pleural effusion (£1830.68), pain (bone, £1038.08; other, £626.97), dyspnea (£718.76), and arthralgia (£63.60).

The costs of subsequent second- and third-line treatments post-progression—categorized into endocrine therapies, targeted therapies, and chemotherapies—were calculated, taking into account the percentage of patients who received each class of therapy [43], the mean duration of treatment [43], and the costs per 4-week cycle (based on drug acquisition and administration costs [34, 35, 44, 45]; Online Resource 1: Supplementary Tables 4-6 [see ESM]). The weighted average cost of subsequent treatments in the second- and third-line settings were £4558.56 for fulvestrant (£5378.16 including fulvestrant post-progression), and £5378.16 for anastrozole, letrozole, and tamoxifen.

2.3.3 Utility Values

Base-case health-state utility values were derived from the FALCON study (intention-to-treat population) using a mixed model repeated measures analysis that was based on EuroQol 5-Dimension 3-Level (EQ-5D-3L) data. In the FALCON study, the EQ-5D-3L questionnaire was administered at baseline, every 12 weeks thereafter until progression, and at treatment discontinuation. The EQ-5D-3L index was calculated based on data for the five EQ-5D-3L dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and the utility value set for the UK [46].

The utility values used in the scenario analysis were based on the FALCON study and a review of published literature, with search terms for health-related quality of life and locally advanced or metastatic breast cancer (time frame October 2013 to June 2016). In the first scenario, utility values were derived from summary statistics of the FALCON study (intention-to-treat-population), which included the mean EQ-5D-3L index values by health state for patients by treatment group [15]. In the second scenario, utility values from Lloyd et al. were used, as these were considered to be the best available data from the literature review [47]. In the third scenario, utility values were derived from the combined results of the FALCON study (using the aforementioned mixed model repeated measures analysis) and the study by Lloyd et al. [15, 47]. Utility decrements for AEs were based on published NICE submissions [48–51]. The disutility per event, applied once at the start of the model, was calculated based on the total utility decrement per event and based on an average duration applied to occurrence rates observed within the trials (Online Resource 1: Supplementary Tables 7 and 8, see ESM).

2.4 Probabilistic Sensitivity Analysis

A probabilistic sensitivity analysis (PSA) was conducted to provide an estimate of the uncertainty surrounding the cost-effectiveness of interventions; this used 10,000 Monte-Carlo simulations. In order to perform the PSA, parameters were assigned a probability distribution reflecting the central estimate (mean) of that parameter, its variance (standard error), and the anticipated shape of the data around its mean (Online Resource 1: Supplementary Table 9, see ESM). A cost-effectiveness plane and a cost-effectiveness acceptability curve were constructed from the PSA simulations for each comparator.

2.5 Scenario Analyses

Additional scenario analyses were conducted to explore the effect of varying OS extrapolations (Gompertz, log-logistic, log-normal, and generalized gamma), time horizon (3-, 10-, 15-, 20-, 25-, and 35-year time horizons), discount rate (1.5%), and the exclusion of AEs and subsequent treatments from the analysis.

3 Results

3.1 Base-Case Analysis

Over a lifetime horizon (30 years), the total cost per patient associated with fulvestrant treatment was calculated as £49,431, compared with £30,564 for anastrozole, £26,334 for letrozole, and £32,300 for tamoxifen, and total QALYs were 3.23, 2.68, 2.46, and 2.47, respectively. The incremental cost of fulvestrant per patient over a lifetime horizon versus each comparator ranged from £17,131 versus tamoxifen to £23,097 versus letrozole (Table 3), and incremental QALYs ranged from 0.55 versus anastrozole to 0.77 versus letrozole. The ICERs were £34,109, £29,827, and £22,532 versus anastrozole, letrozole, and tamoxifen, respectively. Tornado diagrams from the deterministic sensitivity analysis of the model results are shown in Online Resource 1: Supplementary Fig. 2 (see ESM).

Table 3 Results of the base-case analysis over a lifetime horizon[a]

	Total discounted costs (£)	Total discounted QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Fulvestrant	49,430.86	3.23			
Anastrozole	30,564.12	2.68	18,866.74	0.55	34,109.49
Letrozole	26,333.82	2.46	23,097.04	0.77	29,826.63
Tamoxifen	32,300.02	2.47	17,130.83	0.76	22,532.36

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

[a]Costs are in 2016 British pounds sterling

Table 4 Breakdown of total costs over the time horizon (base-case scenario)

Cost type (£)	Fulvestrant	Anastrozole	Letrozole	Tamoxifen
Disease management costs				
Progression free	5419.25	3736.94	4219.31	2576.71
Progressive disease	20,167.23	19,861.58	14,919.84	21,967.73
Terminal care	3773.58	3886.13	3937.51	3924.96
Treatment-related costs				
Acquisition	15,840.54	15.19	34.98	21.25
Administration	2457.65	732.76	811.00	560.71
Subsequent treatment[a]	1660.59	2287.40	2286.17	2968.04
AEs[b]	112.01	44.13	125.01	280.61
Relative dose intensity/compliance	1.00[c]/0.99[d]	0.99	1.00[e]	1.00[e]
Total costs	49,430.86	30,564.12	26,333.82	32,300.02

Costs are in 2016 British pounds sterling

AE adverse event

[a]Costs for subsequent second- and third-line treatments post-progression, categorized into endocrine therapies, targeted therapies, and chemotherapies, and taking into account duration of treatment

[b]Management of grade ≥ 3 AEs experienced by ≥ 2% of patients

[c]First 4 weeks

[d]After first 4 weeks

[e]Assumption (data not available)

Table 5 Survival outcomes: time (mean and median) spent in health states, undiscounted

Treatment	Time in PF (months)		Time in PD (months)		Time alive (months)	
	Mean	Median	Mean	Median	Mean	Median
Fulvestrant	29.58	16.56	30.51	31.28	60.08	47.84
Anastrozole	19.56	11.96	29.38	27.60	48.95	39.56
Letrozole	22.16	14.72	21.26	23.92	43.42	38.64
Tamoxifen	13.16	9.20	31.89	27.60	45.05	36.80

Means are estimated using an area-under-the-curve approach (restricted mean survival time) for the given time horizon; median durations represent the time point at which 50% of patients are still progression free (for progression-free survival) or alive (for overall survival)

PD progressed disease, *PF* progression free

The breakdown of total costs is presented in Table 4. The largest difference in costs between fulvestrant and the other comparators is related to treatment costs (including drug acquisition, administration, subsequent treatment, and management of grade ≥ 3 AEs). Drug acquisition and administration costs combined account for 37% of total costs for fulvestrant and < 3.5% of total costs for the comparators.

The breakdown of survival outcomes by time spent in each health state is presented in Table 5. In the base-case analysis results, fulvestrant was associated with longer mean

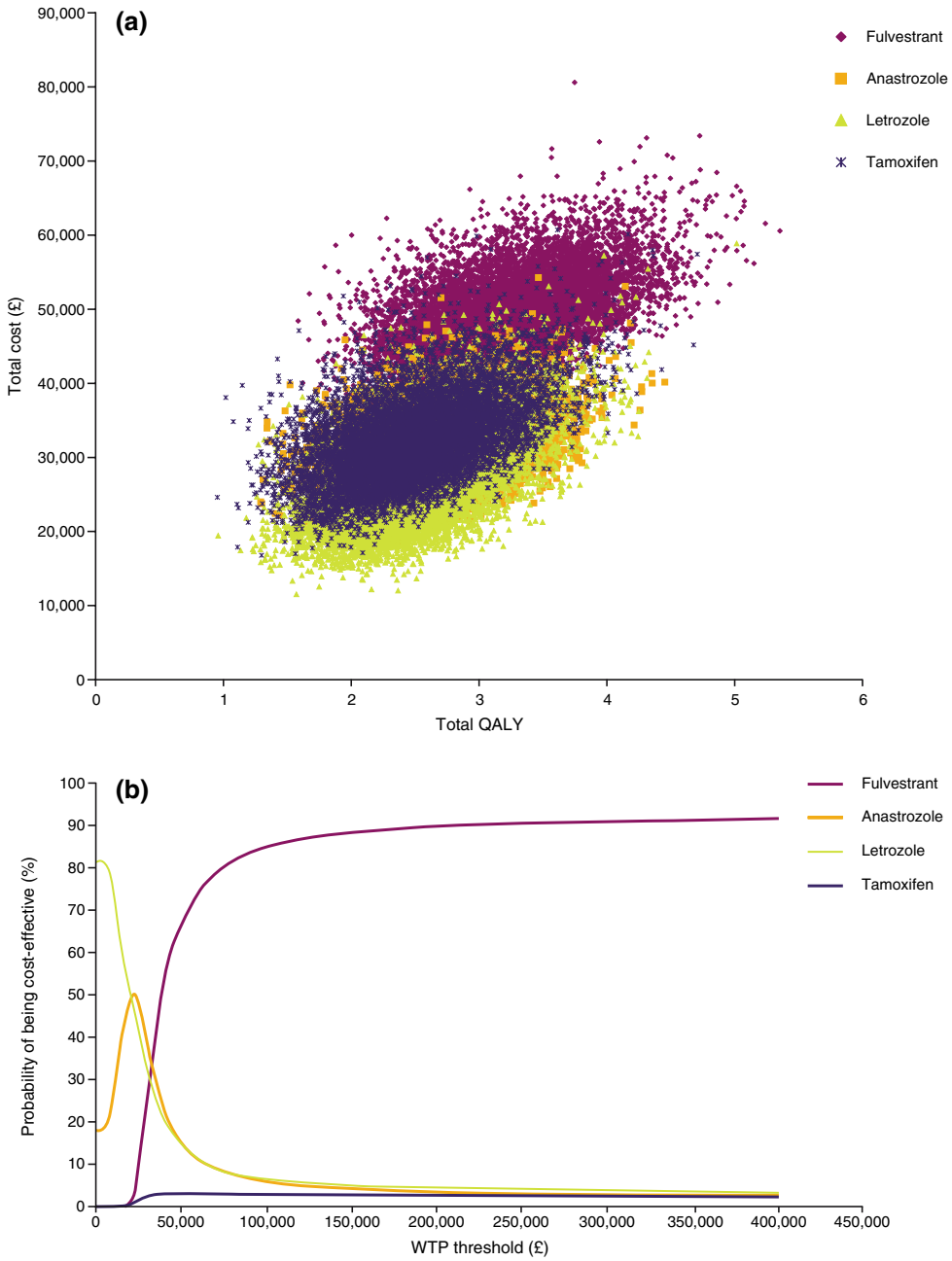

Fig. 2 Cost-effectiveness plane for the total results (**a**) and cost-effectiveness acceptability curves for all comparators (**b**). *QALY* quality-adjusted life-year, *WTP* willingness-to-pay

and median PFS (29.58 and 16.56 months, respectively) and time alive (60.08 and 47.84 months, respectively) than anastrozole, letrozole, and tamoxifen. In terms of PFS, the mean and median of the closest comparator, letrozole, were 22.16 months and 14.72 months, respectively; for time alive, anastrozole was the closest comparator, with a mean and median of 48.95 months and 39.56 months, respectively.

3.2 Probabilistic Sensitivity Analysis

The results from the PSA (10,000 Monte-Carlo simulations) showed that the average ICERs (£33,944, £30,943, and £22,813 versus anastrozole, letrozole, and tamoxifen, respectively) were similar (a ≤ 3% difference in total costs and QALYs) to the deterministic results shown in Table 3. Figure 2a shows the cost-effectiveness plane with the simulations from the PSA for each comparator. Similar levels of uncertainty were shown for all treatments. The cost-effectiveness acceptability curves showed that at a willingness-to-pay threshold of £30,000, the probability of being cost effective was 26.9% for fulvestrant, 38.7% for anastrozole, 31.9% for letrozole, and 2.5% for tamoxifen (Fig. 2b).

Table 6 Results of scenario analysis including exemestane and palbociclib + letrozole

	Total discounted costs (£)	Total discounted QALYs	Incremental costs (£)	Incremental QALYs	ICER (£/QALY)
Fulvestrant	49,523.48	3.23			
Anastrozole	30,484.59	2.68	19,038.88	0.56	34,189.91
Letrozole	26,206.13	2.46	23,317.34	0.77	30,138.59
Tamoxifen	32,317.52	2.47	17,205.96	0.76	22,492.06
Exemestane	28,291.37	2.37	21,232.10	0.87	24,470.03
Palbociclib + letrozole	169,332.18	3.08	− 119,808.71	0.15	Fulvestrant dominant

Costs are in 2016 British pounds sterling

ICER incremental cost-effectiveness ratio, *QALY* quality-adjusted life-year

3.3 Scenario Analysis

Results of the scenario analysis that included exemestane and palbociclib + letrozole as additional comparators are presented in Table 6. Across a 30-year time horizon, incremental costs were £19,039, £23,317, £17,206, £21,232, and − £119,809, respectively, and incremental QALYs were 0.56, 0.77, 0.76, 0.87, and 0.15, respectively, for fulvestrant versus anastrozole, letrozole, tamoxifen, exemestane, and palbociclib + letrozole. This led to ICERs of £34,190, £30,139, £22,492, and £24,470 per QALY versus anastrozole, letrozole, tamoxifen, and exemestane, respectively, and fulvestrant dominated palbociclib + letrozole.

A further scenario analysis was conducted (data not presented), whereby data from the PO25 study were removed because this study had crossover in approximately 50% of patients, which may have contributed to the finding of lack of difference in OS between tamoxifen and letrozole. Therefore, to include a comparison with palbociclib + letrozole in the scenario analysis, an assumption was required that letrozole was equivalent to anastrozole [52]. This did not impact on the overall cost-effectiveness result, and fulvestrant continued to dominate palbociclib + letrozole (incremental QALYs 0.16; incremental cost − £106,761.01).

Scenarios that varied the distribution used to extrapolate OS, whilst holding PFS constant, were analyzed. When OS extrapolations were varied from the base case (Weibull), the lowest and highest ICERs were observed for the generalized gamma and Gompertz extrapolations, respectively. ICERs ranged from approximately £33,300 to £60,000 per QALY for fulvestrant versus anastrozole, £22,100 to £75,400 per QALY for fulvestrant versus tamoxifen, and £28,500 per QALY to fulvestrant being dominated by letrozole.

A time horizon of 35 years had little impact on the ICERs (£34,078, £29,809, and £22,522 versus anastrozole, letrozole, and tamoxifen, respectively) and corresponded to a difference of approximately £10–£30 from the base-case analysis. ICERs stabilized after 15 years, and a lifetime horizon of 30 years was deemed appropriate.

A discount rate of 1.5% for both costs and outcomes reduced the base-case ICER for fulvestrant by approximately £2000 per QALY versus anastrozole, £1700 per QALY versus letrozole, and £900 per QALY versus tamoxifen.

Exclusion of AE costs and disutilities had little impact on the cost-effectiveness results (no AE costs and disutilities: ICERs of £33,984, £29,854, and £22,767 per QALY versus anastrozole, letrozole, and tamoxifen, respectively).

4 Discussion

The efficacy of fulvestrant 500 mg over anastrozole in the treatment of endocrine therapy-naïve patients with HR+ locally advanced or metastatic breast cancer was demonstrated in the phase II, randomized FIRST study and the phase III, randomized FALCON study [15–18]. This three-health-state partitioned survival model evaluated the cost-effectiveness of fulvestrant 500 mg in this treatment setting.

The modeled PFS and OS data for fulvestrant within this analysis reflects trial results, such as the phase II FIRST and phase III FALCON studies. These studies suggest that fulvestrant is associated with a greater median PFS and OS when directly compared with anastrozole; this is consistent with the results of the NMA, which suggested that fulvestrant improved PFS versus other endocrine monotherapies and improved OS versus both endocrine monotherapies and palbociclib + letrozole. Despite improving PFS versus letrozole, the combination of palbociclib + letrozole failed to deliver a significant OS difference in the PALOMA-1 study [31, 53]. This is noteworthy, as OS is often regarded as the gold-standard outcome [54, 55]; therefore, the OS benefit observed in the FIRST study and versus all other comparators in this analysis suggests that fulvestrant 500 mg is an efficacious first-line endocrine therapy.

The current analysis suggests that fulvestrant 500 mg could potentially be a cost-effective option in the UK compared with other endocrine monotherapies (anastrozole, letrozole, tamoxifen, and exemestane) based on UK values

and calculated ICERs. The base-case incremental cost of fulvestrant versus each comparator ranged from £17,131 to £23,097, which was associated with an increase in QALYs gained of 0.55–0.77. In addition, the findings of this analysis suggest that fulvestrant dominates palbociclib + letrozole.

Although this analysis provides the most robust estimate of the health benefit and cost-effectiveness of fulvestrant given the current evidence, the results should be considered in the context of several key limitations. In the absence of direct head-to-head studies, an NMA was conducted to estimate relative PFS and OS data, which may increase uncertainty of the results. However, this methodology, which is increasingly being utilized, provides a controlled comparison in situations where the proportional hazards assumption does not hold [27]. In addition, patient-level data were not available for PALOMA-1, PO25, or the phase III EORTC study; therefore, these comparisons may have contained patients who were not HR+ and/or endocrine therapy-naïve, which may have increased the comparative uncertainty. However, these studies were included as they met the required threshold of patients fulfilling the inclusion criteria (HR+, endocrine therapy-naïve). Furthermore, OS data from FALCON were immature at the time of this analysis, although this was mitigated by the inclusion of data from the FIRST study, and by conducting a sensitivity analysis to demonstrate how different assumptions regarding extrapolation and resulting OS estimates may impact on the results. Treatment efficacy could also have been impacted by treatment adherence rates, which in turn could have impacted the reported cost-effectiveness estimates, as it has not been possible to adjust the findings of this analysis to reflect the differing rates of treatment adherence in the real-life setting. It should also be noted that costs were averaged for the progressed disease health state, and the model was therefore unable to distinguish between the costs of managing life-threatening versus non-life-threatening disease progression, which may have added uncertainty in the ICERs. Furthermore, in the current analysis, the results are based on 2016 prices and small differences may be apparent if the costs are adjusted to 2019 prices; however, any differences are unlikely to substantially impact the conclusions from the model.

NICE currently recommends palbociclib with an aromatase inhibitor [10] for routine funding as a first-line treatment for patients with locally advanced or metastatic breast cancer. Despite positive PFS findings in PALOMA-1 and PALOMA-2 [32], final OS results from the PALOMA-1 study suggest there was not a statistically significant survival benefit with palbociclib + letrozole compared with letrozole alone in the first-line setting [31]. While OS was a key driver for cost-effectiveness, the committee concluded that the PFS gain is likely to result in an OS gain, and that further OS data from PALOMA-2 will reduce the OS uncertainty [10]. NICE has also recommended ribociclib with an aromatase inhibitor for previously untreated, HR+, HER2-negative, locally advanced or metastatic breast cancer [11]; this decision was also made on the basis of positive PFS data as the OS data from the MONALEESA-2 study were not mature at the time of this analysis [56].

However, NICE has recently released guidance stating that fulvestrant is not a cost-effective resource [57]. Despite noting statistically significant OS gains in the phase II FIRST study, NICE concluded that OS is uncertain, citing the immaturity of OS data from the phase III FALCON study [57]. This decision was inconsistent with NICE's evaluation of palbociclib and ribociclib; unlike fulvestrant, these were not able to demonstrate an OS benefit in phase II studies, and mature OS data from phase III studies were also unavailable to support these recommendations. On the basis of this decision, NHS patients cannot receive fulvestrant. Mature OS data from FALCON are awaited to confirm the analysis presented here.

A recent cost-effectiveness analysis of fulvestrant compared with anastrozole as first-line treatment of patients with HR+ advanced breast cancer was conducted from a Chinese societal perspective [58]. While the results suggested that the ICER exceeded the willingness-to-pay threshold, there were methodological shortcomings in the analysis. For example, constant rates of progression and death were assumed (which is not relevant to fulvestrant), and the treatment setting explored did not reflect the licensed population for first-line fulvestrant, which stipulates that patients should be specifically endocrine therapy-naïve, postmenopausal, HR+, HER2-negative and with locally advanced or metastatic breast cancer.

5 Conclusion

Despite its limitations, the results of the present cost-effectiveness analysis suggest that fulvestrant 500 mg could potentially be a cost-effective option in the UK compared with other endocrine monotherapies (anastrozole, letrozole, tamoxifen, and exemestane) as a treatment for endocrine therapy-naïve, postmenopausal women with HR-positive, locally advanced or metastatic breast cancer, and is associated with PFS and OS gains relative to the comparators.

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Compliance with Ethical Standards

This study was funded by AstraZeneca. Informed consent was given in all the studies included in the analysis. Formal consent was not required for this type of study. All authors contributed to the design of the study, were involved in drafting the outline, first, and second drafts, and approved the final version of the manuscript. CT is guarantor of this manuscript. ME and CT are employees and stock holders of AstraZeneca. CL is an employee of AstraZeneca. EB, SL, and HP are employees of PAREXEL Access, which received payment to develop the cost-effectiveness model.

Data-sharing statement Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data-sharing policy, described at: https://urldefense.proofpoint.com/v2/url?u=https-3A__clicktime.symantec.com_3LnH9m1H1SgLoyUr5foT2w37Vc-3Fu-3Dhttps-253A-252F-252Fastrazenecagrouptrials.pharmacm.com-252FST-252FSubmission-252FDisclosure&d=DwIFAw&c=Ftw_YSVcGmqQBvrGwAZugGylNRkk-uER0-5bY94tjsc&r=yLg47-8Q1HiWYj5iF19JhiORJzzcsz8xrlrSS6VvSZw&m=ijcbsVUwn5UnHtJ3VEY6XDecwwJTREaiISMNqUbvVj4&s=dLGBVIXBzwnt5KAph1narBmwVSoyu-7d3NuYqBRoTPo&e=.

References

1. World Cancer Research Fund International. Breast cancer statistics. 2017. http://www.wcrf.org/int/cancer-facts-figures/data-specific-cancers/breast-cancer-statistics. Accessed 1 Mar 2018.
2. Cancer Research UK. Breast cancer incidence (invasive) statistics. 2018. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer/incidence-invasive. Accessed 4 Oct 2018.
3. Lim E, Metzger-Filho O, Winer EP. The natural history of hormone receptor-positive breast cancer. Oncology (Williston Park). 2012;26(688–94):96.
4. Bastiaannet E, Charman J, Johannesen TB, et al. A European, observational study of endocrine therapy administration in patients with an initial diagnosis of hormone receptor-positive advanced breast cancer. Clin Breast Cancer. 2017;18:e613–9.
5. Rugo HS, Rumble RB, Macrae E, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology guideline. J Clin Oncol. 2016;34:3069–103.
6. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). Ann Oncol. 2017;28:16–33.
7. Cardoso F, Costa A, Senkus E, et al. 3rd ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 3). Breast. 2017;31:244–59.
8. European Medicines Agency. Kisqali summary of product characteristics. 2017. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/004213/WC500233997.pdf. Accessed 1 Mar 2018.
9. US Food and Drug Administration. Approved drugs: ribociclib (Kisqali). 2017. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm546438.htm. Accessed 1 Mar 2018.
10. National Institute for Health and Care Excellence (NICE). Palbociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. 2017. https://www.nice.org.uk/guidance/ta495/chapter/1-Recommendation. Accessed 1 Mar 2018.
11. National Institute for Health and Care Excellence (NICE). Ribociclib with an aromatase inhibitor for previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer. 2017. https://www.nice.org.uk/guidance/ta496/chapter/1-Recommendation. Accessed 1 Mar 2018.
12. AstraZeneca. 2017-05-11 ru HA approval letter Faslodex Doc ID-003626426 v 1.02017.
13. European Medicines Agency. Fulvestrant summary of product characteristics. 2015. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000540/WC500021174.pdf. Accessed 15 Oct 2018.
14. US Food and Drug Administration. Fulvestrant highlights of prescribing information. 2017. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021344s035lbl.pdf. Accessed 01 May 2018.
15. Robertson JFR, Bondarenko IM, Trishkina E, et al. Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. Lancet. 2016;388:2997–3005.
16. Robertson JF, Llombart-Cussac A, Rolski J, et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: results from the FIRST study. J Clin Oncol. 2009;27:4530–5.
17. Robertson JFR, Lindemann JPO, Llombart-Cussac A, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study. Breast Cancer Res Treat. 2012;136:503–11.
18. Ellis MJ, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: overall survival analysis from the Phase II FIRST study. J Clin Oncol. 2015;33:3781–7.
19. Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the International Letrozole Breast Cancer Group. J Clin Oncol. 2001;19:2596–606.
20. Mouridsen H, Gershanovich M, Sun Y, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. J Clin Oncol. 2003;21:2101–9.
21. Paridaens RJ, Dirix LY, Beex LV, et al. Phase III study comparing exemestane with tamoxifen as first-line hormonal treatment of metastatic breast cancer in postmenopausal women: the European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group. J Clin Oncol. 2008;26:4883–90.
22. Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol. 2010;28:4594–600.
23. Di Leo A, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. J Natl Cancer Inst. 2014;106:djt337.

24. Mehta RS, Barlow WE, Albain KS, et al. Combination anastrozole and fulvestrant in metastatic breast cancer. N Engl J Med. 2012;367:435–44.
25. Gamucci T, Mentuccia L, Natoli C, et al. A real-world multicentre retrospective study of paclitaxel-bevacizumab and maintenance therapy as first-line for HER2-negative metastatic breast cancer. J Cell Physiol. 2017;232:1571–8.
26. National Institute for Health and Care Excellence (NICE). Guide to the methods of technology appraisal 2013. 2013. https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed 1 Mar 2018.
27. Ouwens MJ, Philips Z, Jansen JP. Network meta-analysis of parametric survival curves. Res Synth Methods. 2010;1:258–71.
28. Latimer N. NICE DSU technical support document 14: Survival analysis for economic evaluations alongside clinical trials—extrapolation with patient-level data. 2013. http://nicedsu.org.uk/wp-content/uploads/2016/03/NICE-DSU-TSD-Survival-analysis.updated-March-2013.v2.pdf. Accessed 1 Mar 2018.
29. Nabholtz JM, Bonneterre J, Buzdar A, Robertson JF, Thürlimann B. Anastrozole (Arimidex™) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: survival analysis and updated safety results. Eur J Cancer. 2003;39:1684–9.
30. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Med Res Methodol. 2012;12:9.
31. Finn RS, Crown J, Lang I, et al. Overall survival results from the randomized phase II study of palbociclib (P) in combination with letrozole (L) vs letrozole alone for frontline treatment of ER +/HER2– advanced breast cancer (PALOMA-1; TRIO-18) [abstract]. J Clin Oncol. 2017;35(15 Suppl):1001.
32. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. N Engl J Med. 2016;375:1925–36.
33. National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment. 2009. https://www.nice.org.uk/guidance/cg81/update/CG81/documents/full-version2. Accessed 21 May 2018.
34. Curtis L, Burns A. Unit Costs of Health and Social Care 2016. 2016. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2016/. Accessed 21 May 2018.
35. Department of Health. NHS Reference Costs. 2016. https://www.gov.uk/government/collections/nhs-reference-costs. Accessed 21 May 2018.
36. National Institute for Health and Care Excellence (NICE). Bortezomib for induction therapy in multiple myeloma before high-dose chemotherapy and autologous stem cell transplantation. 2014. https://www.nice.org.uk/guidance/ta311. Accessed 21 May 2018.
37. National Institute for Health and Care Excellence (NICE). Nintedanib for previously treated locally advanced, metastatic, or locally recurrent non-small-cell lung cancer. 2015. https://www.nice.org.uk/guidance/ta347. Accessed 21 May 2018.
38. National Institute for Health and Care Excellence (NICE). Paclitaxel as albumin-bound nanoparticles in combination with gemcitabine for previously untreated metastatic pancreatic cancer. 2015. https://www.nice.org.uk/guidance/ta360. Accessed 21 May 2018.
39. National Institute for Health and Care Excellence (NICE). Cabazitaxel for hormone-relapsed metastatic prostate cancer treated with docetaxel. 2016. https://www.nice.org.uk/guidance/ta391. Accessed 21 May 2018.
40. National Institute for Health and Care Excellence (NICE). Enzalutamide for treating metastatic hormone-relapsed prostate cancer before chemotherapy is indicated. 2016. https://www.nice.org.uk/guidance/ta377. Accessed 21 May 2018.
41. National Institute for Health and Care Excellence (NICE). Ramucirumab for treating advanced gastric cancer or gastro–oesophageal junction adenocarcinoma previously treated with chemotherapy. 2016. https://www.nice.org.uk/guidance/ta378. Accessed 21 May 2018.
42. National Institute for Health and Care Excellence (NICE). Ticagrelor for preventing atherothrombotic events after myocardial infarction. 2016. https://www.nice.org.uk/guidance/ta420. Accessed 21 May 2018.
43. Kurosky S, Mitra D, Zanotti G, Kaye JA. Patient characteristics and treatment patterns in Er+/Her2− metastatic breast cancer in the UK: results from a retrospective medical record review. Value Health. 2015;18:A492.
44. British National Formulary. British National Formulary. 2016. https://www.bnf.org/products/bnf-online/. Accessed 21 May 2018.
45. Department of Health. Drugs and pharmaceutical electronic market information (eMit). 2016. https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit. Accessed 21 May 2018.
46. Szende A, Oppe M, Devlin N, editors. EQ-5D value sets: inventory, comparative review and user guide. 1st ed. Dordrecht: Springer; 2007.
47. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95:683–90.
48. Doyle S, Lloyd A, Walker M. Health state utility scores in advanced non-small cell lung cancer. Lung Cancer. 2008;62:374–80.
49. Sullivan PW, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Med Decis Making. 2006;26:410–20.
50. Swinburn P, Lloyd A, Nathan P, Choueiri TK, Cella D, Neary MP. Elicitation of health state utilities in metastatic renal cell carcinoma. Curr Med Res Opin. 2010;26:1091–6.
51. National Institute for Health and Care Excellence (NICE). Lung cancer (non-small cell)—nintedanib: committee papers. 2014. https://www.nice.org.uk/guidance/ta347/documents/lung-cancer-nonsmall-cell-nintedanib-committee-papers4. Accessed 21 May 2018.
52. Smith I, Yardley D, Burris H, et al. Comparative efficacy and safety of adjuvant letrozole versus anastrozole in postmenopausal patients with hormone receptor-positive, node-positive early breast cancer: final results of the randomized phase III femara versus anastrozole clinical evaluation (FACE) trial. J Clin Oncol. 2017;35:1041–8.
53. Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. Lancet Oncol. 2015;16:25–35.
54. Driscoll JJ, Rixe O. Overall survival: still the gold standard: why overall survival remains the definitive end point in cancer clinical trials. Cancer J. 2009;15:401–5.
55. Saad ED, Buyse M. Overall survival: patient outcome, therapeutic objective, clinical trial end point, or public health measure? J Clin Oncol. 2012;30:1750–4.
56. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med. 2016;375:1738–48.
57. National Institute for Health and Care Excellence (NICE). Appraisal consultation document: Fulvestrant for untreated locally advanced or metastatic oestrogen-receptor positive breast cancer. 2017. https://www.nice.org.uk/guidance/

gid-ta10106/documents/appraisal-consultation-document-2. Accessed 1 Mar 2018.
58. Ding H, Fang L, Xin W, Tong Y, Zhou Q, Huang P. Cost-effectiveness analysis of fulvestrant versus anastrozole as first-line treatment for hormone receptor-positive advanced breast cancer. Eur J Cancer Care (Engl). 2017;26:e12733.
59. Curtis L, Burns A. Unit Costs of Health and Social Care 2015. 2015. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2015/. Accessed 21 May 2018.