ALPELISIB PLUS FULVESTRANT FOR PIK3CA-MUTATED, HORMONE RECEPTOR-POSITIVE, HUMAN EPIDERMAL GROWTH RECEPTOR-2-NEGATIVE ADVANCED BREAST CANCER

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Abstract

Objectives

Breast cancer is a leading cause of death worldwide, and the most prevalent cancer death in the United Kingdom. Treatment with alpelisib and fulvestrant showed significant increase in progression-free and overall survival in patients with hormone receptor-positive, (HER2)-negative advanced breast cancer, after progression on or during treatment with an aromatase inhibitor. The objective of this analysis was to evaluate the cost-effectiveness of alpelisib plus fulvestrant as compared to monotherapy fulvestrant in second line breast cancer treatment, from a United Kingdom perspective.

Methods

The lifetime cost-effectiveness of alpelisib plus fulvestrant as compared to monotherapy fulvestrant in second line treatment, was estimated using a Markov model with 3 health states; stable disease, progressed disease and death. Using clinical data from the SOLAR-1 trail, a simulation was performed to model the course of the disease, over a lifetime horizon. Data on costs linked to the treatment acquisition, treatment administration, adverse events, disease monitoring, disease management, and palliative care were obtained from the literature. The analysis was performed following the guidelines of the reference case of the National Institute of Health and Care Excellence.

Results

Based on this analysis, the addition of alpelisib to a fulvestrant treatment regimen resulted in a mean increase of 0.13 quality adjusted life years per patient. The costs of the additional treatment were £168,880 per patient. Resulting in an incremental cost-effectiveness ratio of £1,294,907 per gained quality-adjusted life year, of alpelisib plus fulvestrant as compared to monotherapy fulvestrant.

Conclusions

Despite the significant increase in progression-free and overall survival of alpelisib and fulvestrant, the incremental cost effectiveness ratio is extensively higher than the threshold of £20,000-£30,000 in the United Kingdom.

Table of Contents

Tables and figures

Introduction

Breast cancer is a leading cause of cancer deaths among women worldwide (Globocan, 2021), and the most common cancer in the United Kingdom (UK), with over 55.000 new cases every year. Advanced breast cancer (ABC) is largely incurable and has a severe impact on the quality of life (QoL) due to the poor prognosis, experienced discomfort from the disease and side-effects of the treatment (Caissie, 2012). Besides the tremendous impact on the patient, caregivers report adverse impact on their work, perceived burden and an increased incidence of depression (Grunfeld, 2004). Thus, breast cancer has a huge impact on the patient and their environment, and it is of great importance to optimise treatment.

Treatment of ABC aims to relieve symptoms, prevent spread of the disease and increase QoL (Breast Cancer expert Advisory Group, 2018). Treatment is mainly palliative, however optimal treatment might increase survival as well. The last decade the overall death rate of cancer has continued to decline, due to major advances in prevention, diagnosis and treatment (McDowell, 2019). The amount of treatment options for ABC increases rapidly, due to constantly new approved interventions by the Food and Drug Administration (FDA). On May 24th, 2019 alpelisib in combination with fulvestrant was approved by the FDA, for ABC in men and postmenopausal woman with ABC (Food and Drug Administraion, 2019). The FDA based their approval on the safety and efficiency as found in the SOLAR-1 trial, carried out by Novartis Pharmaceuticals: a triple blind, phase III trial in men and postmenopausal woman with hormone receptor-positive (HR+), human epidermal growth factor-2-negative (HER2-), advanced breast cancer, who had progressed on or after treatment with an aromatase inhibitor (AI). In the alpelisib treatment arm prolonged progression free survival (PFS) and overall survival (OS) was found as compared to the placebo treatment arm (André, et al., 2021).

Addition of alpelisib to routine treatment might increase the PFS and OS, however, because resources for health care funding are scarce, the National Health Services (NHS) should only offer interventions which are most cost-effective. For each approved drug the cost-effectiveness should be determined to distribute the scarce resources as efficiently as possible. In the United Kingdom, decisions on which interventions are provided by the NHS are made by the National Institute for Health and Care Excellence (NICE). These decisions are based on evidence submissions on the cost-effectiveness of the treatment.

The aim of this analysis was to appraise the cost effectiveness of alpelisib plus fulvestrant as compared to monotherapy fulvestrant, for HR+, HER2- advanced breast cancer in patients previously treated with an aromatase inhibitor. This analysis was carried out using a Markov model and a NICE perspective.

The background session elaborates on breast cancer in a UK setting, the current treatment and alpelisib as new intervention. In the methods the used theories, techniques and input values are discussed. Following, the results of the analysis are shown. Finally, the main strengths and weaknesses are reviewed in the discussion.

Background

Breast cancer causes around 11.500 deaths per year in the UK. Breast cancer is even the most prevalent cause of cancer-related deaths among women (Cancer research UK, 2017). Breast cancer can be divided into four stages based on size, lymph node involvement and metastases. Stage 4 is considered advanced, meaning the cancer has metastasised to other tissue like the lungs, liver or bones. Regional lymph node involvement is not considered advanced (Cancer research UK, 2021). At diagnosis at least 13% of all breast cancers is 'advanced', an additional 20% to 40% of women develops ABC at some point following diagnosis (Vera-Llonch M, 2011). ABC is treated systematically, but has a poor prognosis, the 5-year survival rate is around 25% (American Cancer Society, 2021; Cancer research UK, 2017).

The choice of treatment is guided by the receptors expressed in the tumour tissue, patient characteristics and whether the patient received previous treatment (National Institute for Health Research , 2017). When hormone sensitive receptors are present, chemotherapy in combination with endocrine therapy is preferred for breast cancer with significant visceral spread (Northern cancer alliance, 2017). Eighty percent of the breast tumours in postmenopausal women express hormone receptors. 67% of breast tumours express estrogen receptors (ER), the other HR+ tumours express progesterone receptors (PR) (National Institute for Health Research , 2017). Human epidermal growth factor is overexpressed in 15-25% in women with breast cancer. Phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA) mutations are present in 15.8% of the primary breast cancers (Markham, 2019).

Alpelisib is a form of oral medication which inhibits the PIK3CA-pathway, PIK3CA is a growth factor involved in the proliferation, survival and growth of tumour cells (Arsenic & Ruza, 2014). In HR+, HER2- breast cancer this mutation is seen more frequently, about 40% instead of the earlier mentioned 15.8%. Patients with a mutation in the PIK3CA-gene have worse prognosis than patients with the wild type disease. Alpelisib is a form of a targeted therapy, a type of cancer treatment that specifically acts on certain mutations present in the tumour (Rugo L. C.-B., 2021). Alpelisib is approved in combination with fulvestrant, an endocrine therapy. Fulvestrant acts as an estrogen receptor antagonist. When fulvestrant is bound, it downregulates the production and expression of estrogen receptors in human breast cancer cells (AstraZeneca, 2016).

Every year around 55,000 women and 370 men receive the diagnosis breast cancer in the UK (Breast cancer now, 2021). There are four main types of breast cancer, most prevalent the HR+/HER2- subtype, also known as the 'luminal A' subtype. The luminal A subtype comprises around 68% of all breast cancers (National cancer institute, 2021). The PIK3CA mutation occurs in around 40% of the luminal A subtype, resulting in around 15,000 patients who could possibly benefit from treatment with alpelisib (Rugo L. C.-B., 2021).

Approval was based on the SOLAR-1 trial, which evaluated the safety and efficiency of alpelisib plus fulvestrant in men and postmenopausal women with HR+, HER2- ABC after treatment with an AI. 572 patients were randomized to receive either alpelisib plus fulvestrant or placebo plus fulvestrant (Novartis Pharmaceuticals , 2020). Patients received

500 mg fulvestrant, every 28 days and once on day 15 of the treatment. Additionally patients received either 300 mg alpelisib, or placebo. PFS was assessed by investigators using the Response Evaluation Criteria In Solid Tumors (RECIST). Median PFS in the alpelisib plus fulvestrant group was 11.0 months (95% confidence interval (CI) 7.5-14.5), as compared to 5.7 months (95% CI 3.7-7.4) in the placebo plus fulvestrant group. The median OS was 39.3 months (95% CI 34.1-44.9) in the alpelisib treatment arm, as to 31.4 months (95% CI 26.8-41.3). Beside of the key endpoint PFS and OS, safety of alpelisib and fulvestrant was constantly assessed with the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Information on adverse events (AE) was collected until 30 days after the last dose of study treatment. The most common AEs were hyperglycaemia, rash and diarrhoea (André, et al., 2021; André C. R., 2019).

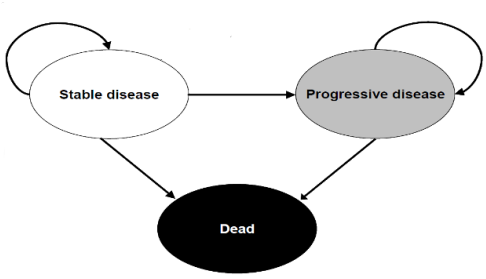
Methods

Model structure

A Markov model was used to perform this cost-effectiveness analysis (CEA). Markov models are used for solving problems involving sequential, stochastic decision making (Komorowski & Raffa, 2016). In medical decision making, this model uses states to represent different stages of the disease. In the oncology setting a Markov model typically has three health states: Stable disease (SD), progressed disease (PD) and death (see Figure 1).

A trademark of the Markov model is that it is not possible to track the history of a patient, meaning that the probability of a patient to move to a different health state solely depends on the current health state of the patient. These probabilities are called transition probabilities (Sonnenberg & Beck, 1993).

Figure 1 Stages Markov Model oncology setting



Source (Al, Advanced Health Economic Modelling, 2020)

The model used for this analysis was built in Microsoft excel, version 16, and contained three stages; stable disease, progressed disease and death. Each cycle had a duration of 28 days, what corresponded with the treatment cycle of fulvestrant. Patients could transition between health states. In the model patients could only transition at the end of a cycle, following the direction of the arrows. However, in reality patients can transition between health states at any moment during the cycle. When estimating the amount of utilities and costs that occur during the cycle, there was adjusted for the moment of transition. This adjustment is called the half cycle correction (HCC). The corrected value was the mean number of patients at the beginning and at the end of each cycle. (Al, Advanced Health Economic Modelling, 2020).

Population

The patients in this CEA were men or postmenopausal woman with HR+, HER2-, PIK3CA-mutated advanced breast cancer, who progressed on or after treatment with an aromatase inhibitor. The model simulated two thousand patients, one thousand in the alpelisib plus fulvestrant group and one thousand in the placebo plus fulvestrant group. Information on clinical effectiveness and safety was obtained from the SOLAR-1 trial, using the same cancer characteristics and treatment regimen. In the Markov model no information on patient characteristic, i.e. age, sex, demographics, was included.

Intervention and comparator

Patients in de alpelisib plus fulvestrant group received 300 mg alpelisib daily, and 500 mg fulvestrant intramuscular (i.m.) on day 1 and 15 of the first cycle, and the first day of each

subsequent cycle. In the SOLAR trial the other group received placebo plus fulvestrant. Because the model aimed to simulate the course of the disease as realistic as possible, no information for placebo was included. In the Markov model alpelisib plus fulvestrant was compared with monotherapy fulvestrant. The monotherapy fulvestrant treatment arm did receive the same treatment regimen for fulvestrant as the alpelisib treatment arm.

Perspective, time horizon and discounting

This technology appraisal (TA) was performed following the reference case of NICE. A guideline that ensures that all evidence submissions on cost-effectiveness align with the appraisal committee's purpose, and are consistent with the NHS objective to maximize health gain with scarce resources. In line with the reference case, a CEA with a full increment analysis was performed. The health effects are expressed in quality-adjusted life years (QALYs). QALYs combine the length and the quality of life into an index number to value health outcomes. QoL can be measured using direct measures, for example time trade-off or standard gamble, where the patient values the quality of life. QoL can also be measured using an indirect valuation, patients experiencing the disease report on health outcomes, after which these outcomes are valued by an independent party. Questionnaires for the health outcomes can be generic or disease specific (Penton, 2021; Prieto & Sacristán, 2003). In this analysis QALYs were valued using the EQ-5D questionnaire, in line with the NICE reference case. An indirect generic valuation descriptive system including five dimensions; mobility, self-care, usual activities, pain and discomfort, and anxiety and depression (NICE, 2013).

For the monetary effects, all costs relevant from a NHS and personal social service (PSS) perspective were included. Both costs and effects were discounted with a rate of 3.5% (NICE, 2013).

The time horizon of this analysis was lifetime, i.e. until all patients have died. The model ran for 260 cycles of four weeks each, corresponding with twenty years of simulation. It can be assumed that all patients have died by then, since the 5-year survival of ABC is approximately 25% (Cancer research UK, 2021).

Clinical effectiveness

Data on clinical effectiveness of alpelisib plus fulvestrant was obtained from the SOLAR-1 trial, the primary outcomes of this study were PFS and OS. A summary of the data was provided in Kaplan Meier curves (KM-curves) on PFS and OS (André, et al., 2021). At the moment of data cut-off not all patients had died, nevertheless, the time horizon for this analysis was lifetime. Estimates for the PFS and OS are ideally obtained from individual patient data, however this data was not available for this analysis. Therefore, the method as described by Hoyle and Henley was used to fit survival curves to the published data. This method used the patients at risk and KM-curves as published, and fits survival curves by the maximum likelihood estimation or other suitable approaches. The method by Hoyle and Henley was chosen because it gives more accurate curve fits than traditional methods, like regression or least squares, under realistic scenarios (Hoyle, 2011).

First the curves were uploaded to webplotdigitizer version 4.4 and per two months the survival probabilities were determined for the alpelisib plus fulvestrant and placebo plus

fulvestrant treatment arms. The KM-curves as sourced from the SOLAR-1 trial and the extracted survival probabilities are included in appendix 2. This data was extrapolated to estimate the course of the disease over a life time horizon, using the software of R studio version 1.4.17. The library 'survival' was used as available in R studio. Four potential curves were considered; exponential, Weibull, lognormal and loglogistic. The code as used in R, per data set, is provided in appendix 3. Running the code in R studio provided an AIC, intercept and log(scale) for all four data sets, the output data is included in appendix 4. Using this data four distributions of PFS and OS were extrapolated for both treatment arms. The survival curves and the extrapolated distributions are shown in appendix 5. Distributions as used for the base case were chosen based on clinical plausibility and the AIC value. AIC stands for Akaike information criterion, it is a mathematical method to determine the fit of the model to the data it is extracted from. The distribution with the lowest AIC value has the best statistical fit, based on the number of independent variables and the maximum likelihood estimate of the model (Bevans, 2020). For OS the AIC-values of the Weibull distribution were lowest, for PFS the lognormal distribution had the lowest AIC values. These distributions were assumed to be clinically realistic. As noted earlier is the 5-year survival of ABC around 25% (Cancer research UK, 2021), the OS after 60 months was around 20% in the placebo group, and approximately 22% in the alpelisib group. The extrapolation lies a little below the average of 25% for ABC, however, patients with a PIK3CA mutation are known to have a slightly worse prognosis (Rugo L. C.-B., 2021). Thus, for the base case (BC) of this analysis a Weibull distribution was used for OS and a lognormal distribution for PFS.

In the model the survival probabilities per four weeks were multiplied with the 1,000 patients per treatment arm to determine the amount of patients for each health state per cycle. For the costs and effects which could occur at any moment during the cycle, a HCC amount of patients was determined per cycle.

In reality PFS could never exceed OS, however the model used survival probabilities which are estimates. It could thus occur that the PFS was overestimated, while OS was underestimated. This would result in a negative amount of patients in the progressed state in the model. When this occurred in the model, was assumed that PFS was equal to OS.

Adverse events

Information on adverse events was obtained from an article by Rugo, et al. on the incidence, time course and management of AEs in the SOLAR-1 trial (Rugo, 2020). Only adverse events considered grade 3 and 4, with an incidence higher than 5% were considered relevant. It was assumed that AEs with lower incidence and disease burden did not have a relevant impact on the cost-effectiveness of the intervention. Adverse events of grade 3/4 with an incidence higher than five percent were hyperglycaemia, diarrhoea and rash, and only occurred in the alpelisib plus fulvestrant treatment arm. The table on incidences of adverse events, as published by Rugo, et al. is included in appendix 6.

Management was described in the article by Rugo, et al. The doses and frequencies were obtained from the website with evidence based information on medicine for developed for doctors (Zorginstituut Nederland, 2021). The costs were obtained from the eMIT, NHS reference case and the PSSRU (GOV.uk, 2020) (NHS , 2019) (PSSRU, 2019). The mean duration of the adverse events was calculated using the provided median (m), and the low

end (a) and the high end (b) of the range, using the formulae $x = \frac{a+2m+b}{4}$. The variance of the mean was estimated by taking the square root of the range divided by 6, a method for estimating the standard error (SE) for random distributions (Pudar Hozo, 2005). The calculated mean and standard errors for durations were; hyperglycaemia 5.75 days (SE 0.70), diarrhoea 22.5 days (SE 2.45), rash 13.25 days (SE 1.58) (Rugo, 2020). The elaborated equations are provided in appendix 7.

Hyperglycaemia was assessed using the laboratory markers fasting plasma glucose (FPG) and glycosylated haemoglobin (Hb1Ac). Grade 3 hyperglycaemia occurred in 32.7% of the alpelisib treatment arm, grade 4 occurred in 3.9%. For treatment of grade 3 hyperglycaemia an oral antidiabetic (metformin 500 mg orally, daily) and insulin sensitizer (pioglitazone 15 mg orally, daily) were needed. For treatment of grade 3 hyperglycaemia was assumed that two general practitioner (GP) consultations were needed, the first for diagnosis and the second as follow-up. Two times prescription charges were assumed, for metformin and pioglitazone. For grade 4 hyperglycaemia the same cost were assumed, plus the consultation of an endocrinologist. The costs included are shown in Table 1.

Table 1 Cost of treating hyperglycaemia

	Amount	Unit cost	Total cost	source
Metformin 500 mg	1 pack (28 tablets)	£ 0.18	£ 0.18	(GOV.uk, 2020)
Pioglitazone 15 mg	1 pack (28 tablets)	£ 0.83	£ 0.83	(GOV.uk, 2020)
Prescription charges	2	£ 9.35	£ 18.7	(NHS, 2021)
GP consultation (10m)	2 x 10 min	£ 43	£ 86	(PSSRU, 2020, p. 120)
Endocrinologist	1 consult	£ 90	£ 90	(NHS , 2019)
Costs of treating grade 3 hyperglycaemia			£ 105.71	
Costs of treating grade 4 hyperglycaemia			£ 195.71	

Abbreviates: GP, General Practitioner.

Diarrhoea was considered grade 3 when the frequency of stool increased with seven or more stools per day, as compared to baseline. For treatment hospitalization was indicated and patients were treated according to local guidelines for diarrhoea treatment. Grade 3 diarrhoea occurred in 6.7% of the patients treated with alpelisib. Hospitalization was needed, to prevent dehydration and severe complications. The calculated mean duration was 22.5 days, however, it was assumed that patients were hospitalised for 3 days. Thereafter, twice daily treatment with oral rehydration salts (ORS) and a weekly follow up with their GP (West Midlands Cancer alliance, 2018). The costs included are shown in Table 2.

Table 2 Cost of treating diarrhoea

	Amount	Unit cost	Total cost	source
Hospitalisation	3 days	£ 296	£ 296	(NHS , 2019)
ORS	2 packs (20 sachets)	£ 5.90	£ 11.80	(GOV.uk, 2020)
Prescription charges	2	£ 9.35	£ 18.70	(NHS, 2021)
GP consultation (10m)	3 x 10 min	£ 43	£ 129	(PSSRU, 2020, p. 120)
Costs of treating grade 3 diarrhoea			£ 455.5	

Abbreviates: GP, General Practitioner; ORS, oral rehydration salts.

Grade 3 rash was defined as skin toxicity with coverage over 30% of body surface area, and occurred in 9.9% of the alpelisib treatment arm. For the treatment of grade 3 rash an

antihistamine (loratadine 10 mg oral daily) and a dermal topical steroid (hydrocortisone/Vaseline crème 10%, up to four times a day) were needed. Considering the affected body surface, apply frequency, size of the tube (30 mg) and the duration of 13.25 days, was assumed that a total of 4 tubes was needed. For treatment of grade 3 rash two additional GP consultations and two times prescription charges were assumed. The costs included are shown in Table 3.

Table 3 Cost of treating rash

	Amount	Unit cost	Total cost	source
Loratadine 10 mg	1 pack (30 tablets)	£ 0.26	£ 0.26	(GOV.uk, 2020)
Hydrocortisone/ Vaseline 10%	4 tubes (30 mg)	£ 1.00	£ 4.00	(GOV.uk, 2020)
Prescription charges	2	£ 9.35	£ 18.7	(NHS, 2021)
GP consultation (10m)	2 x 10 min	£ 43	£ 86	(PSSRU, 2020, p. 120)
		Costs of treating grade 3 rash	£ 108.96	

Abbreviates: GP, General Practitioner

The development of severe adverse events, thus grade 3 or higher, decreased the QoL. No disutility values for the occurrence of AEs were available from the SOLAR-1 trial. Thus, a literature search was conducted to determine the total effect of the AEs on the experienced utility. The utility decrements used for this analysis were sourced from NICE TA449 on treatment with everolimus for unresectable or metastatic neuroendocrine tumours. When patients experienced hyperglycaemia a utility value of 0.771 (SE 0.020) was found, when diarrhoea occurred a utility value of 0.600 (SE 0.025) was found. The TA did not include a decrement in utility for rash, however, a utility decrement for hand-foot syndrome was provided. Hand-foot syndrome occurs with some cancer treatments, and causes redness, swelling and pain on the palms of the hands and feet. Since hand-foot syndrome is also a side effect to anti-tumour medication with infectious features of the skin, the utility decrements were assumed to be similar to rash. The adjusted utility as found was 0.583 (SE 0.007), this is an extensive decrement (Varley-Campbell, 2016). However, in a study in breast cancer patients in Sweden in the Netherlands, a utility of 0.58 was found when rash occurred as compared to 0.81 in stable disease without AEs (Frederix, 2013). Thus this disutility was assumed to be reasonable.

The adjusted utility values for AEs were decreased from the reference point of 0.771, as used in TA449 for stable disease without any adverse events (Varley-Campbell, 2016). For the CEA of alpelisib plus fulvestrant the difference in utility was subtracted from the utility for stable disease. Because the utility value for hyperglycaemia was equal to stable disease in NICE TA 449, no disutility for hyperglycaemia was assumed for the model.

Table 4 Utility decrements of adverse events

	Decrement	Source
Hyperglycaemia	0.000 (SE 0.000)	(Varley-Campbell, 2016)
Diarrhoea	-0.171 (SE 0.025)	(Varley-Campbell, 2016)
Rash	-0.188 (SE 0.007)	(Varley-Campbell, 2016)

Abbreviates: SE, standard error.

Because no information on the timing of occurrence of adverse events was provided, the costs and effects associated with adverse events were included at the start of the model.

Health-related quality of life

There was no information published on patient reported utility in the SOLAR-1 trial. Therefore, utility values were sourced from the FALCON trial, a phase 3, randomised, double-blind trial comparing fulvestrant with anastrozole in patients with HR+, HER2- locally advanced or metastatic breast cancer patients. The study valued utility using the EQ-5D questionnaire. The found utilities were 0.75 (SE 0.01) for progression free disease and 0.69 (SE 0.03) for progressed disease (Robertson, 2016). No difference in QoL was found between the treatment groups. These values were used in NICE TA503 on treatment with fulvestrant 500 mg for ABC, which was reviewed by an Evidence Review Group (ERG) on behalf of NICE. The ERG agreed with the company's use of the QoL as found in the FALCON trial, and considered the values to be an improvement on the data used in previous TAs because of the use of EQ-5D data collected in a patient population as specified in the decision problem, was in line with the NICE reference case (Cooper, 2017). The QoL found in this study can be assumed to match with the patients in this model, because both the patient populations had HR+, HER2- ABC and both trials compared treatment with fulvestrant with another treatment. In the FALCON trial Progression was evaluated using RECIST, similar to the SOLAR-1 trial. Patient characteristics at baseline, i.e. age, demographics and performance status were similar. However, there was one notable difference, patients in the FALCON trial were endocrine therapy (ET) naïve while patients in the SOLAR-1 trial received an AI as previous treatment. Nevertheless, QoL is assumed to be similar among the FALCON and SOLAR-1 trial.

The utility values are shown in Table 5. Utility is assumed to be equal among both treatment arms. Because AEs have a negative effect on the experienced QoL, utility decrements were assumed during the occurance of adverse events. The utility decrements are shown in Table 4.

Table 5 Utility values of health states

	Value	Source
Utility progression-free disease	0.75 (SE 0.01)	(Robertson, 2016)
Utility progressed disease	0.69 (SE 0.03)	(Robertson, 2016)

Abbreviates: SE, standard error.

Health care resource use and costs

The model use 2019 prices in UK sterling (£), form a NHS and PSS perspective. Costs relating to previous years were inflated using the 'Personal Social Services Research Unit' (PSSRU) Hospital and community health services (HCHS) pay and price index. The model included the following costs

- Drug acquisition
- Drug administration
- Diagnostics
- Disease monitoring
- Health state costs
- Subsequent therapy

Drug acquisition

Patients in the alpelisib treatment arm received 300 mg alpelisib orally once a day. Additionally, all patients received an intramuscular injection of 500 mg fulvestrant on day 1 and 14 of treatment, and every first day of the subsequent treatment cycles (André, et al., 2021).

Alpelisib was launched in the UK at a list price of £4,082 for a box of 56 tablets of 150 mg (NHS, 2016). Patients in the SOLAR-1 trial would receive two 150 mg tablets a day. In a cycle of 28 days, patients would use exactly one box of 56 alpelisib tablets. Additional premedication or concomitant medication was not needed alongside alpelisib treatment. Patients may benefit from anti-nausea medication, however because use was not common, no costs for anti-nausea medication were included (Butler, 2020).

As previously described, no additional costs for placebo were included in the model.

The list price used for fulvestrant was £522.41 for two 5 ml prefilled syringes, both containing 250 mg of fulvestrant (NICE, 2011). In the first month of treatment an additional loading dose of 500 mg is required (André, et al., 2021). A summary of the acquisition costs was provided in Table 6.

Table 6 Acquisition cost per cycle per treatment arm

	Use per cycle	Unit cost	Total cost per cycle	Source
Alpelisib (56 x 150mg)	1	£4,082.14	£4,082.14	(NHS, 2016)
Fulvestrant first cycle	2	£ 522.41	£1,044.82	(NICE, 2011)
Drug acquisition first cycle alpelisib plus fulvestrant				£5,126.96
Alpelisib (56 x 150mg)	1	£4,082.14	£4,082.14	(NHS, 2016)
Fulvestrant subsequent cycles	1	£ 522.41	£ 522.41	(NICE, 2011)
Drug acquisition subsequent cycles alpelisib plus fulvestrant				£4,604.55
Fulvestrant first cycle	2	£ 522.41	£1,044.82	(NICE, 2011)
Drug acquisition first cycle monotherapy fulvestrant				£1,044.82
Fulvestrant subsequent cycles	1	£ 522.41	£ 522.41	(NICE, 2011)
Drug acquisition subsequent cycles monotherapy fulvestrant				£ 522.41

Drug administration

The cost associated with prescribing the drug and dispensing by the pharmacy were assumed to be £9.35 (NHS, 2021). In the model this prescription charge is added to each package of medication as used by the patients. An exception is the hydrocortisone/Vaseline crème, because it is certain patients will use over one tube, the tubes are dispensed per two. It was assumed that packages could not be shared between patients. For alpelisib the prescription charge was included once per cycle. For fulvestrant the prescription charge was included twice in the first cycle, and once in subsequent cycles.

The data on administration was assumed to be equal to the NICE TA503. This TA seems applicable because the same treatment regimen for fulvestrant was evaluated, patients had similar tumour characteristics and both analysis were performed in a UK setting (Robertson, 2016). The first cycle fulvestrant was administered during an oncologist visit and the loading dose was administered during an follow up appointment with the oncologist. Subsequent doses of fulvestrant were assumed to be delivered either in the primary care setting (32.3%)

or in the outpatient setting (67.7%). In the primary care setting a community nurse administered the injections in a 15-minute appointment. In the outpatient setting, a follow-up appointment with an oncologist was required. The administration costs of fulvestrant are provided in Table 7.

Table 7 Cost administration fulvestrant

	Cost item	Percentage of administrations	Unit cost	Mean total cost per cycle	Source
Fulvestrant first cycle	Oncologist visit	100%	£ 195.00	£ 195.00	(NHS , 2019)
	Oncologist visit follow-up	100%	£ 143.00	£ 143.00	(NHS , 2019)
Fulvestrant subsequent cycles	Community nurse specialist (15 minutes)	32.3%	£ 21	£ 6.78	(PSSRU, 2019, p. 117)
	Oncologist appointment follow-up	67.7%	£ 143.00	£ 96.81	(NHS , 2019)
			Administration costs fulvestrant first cycle	£ 338.00	
			Administration costs fulvestrant subsequent cycles	£ 103.59	

The fulvestrant injections can cause injection site pain, but pain medication was not commonly required and was therefore not included in the analysis (Lohr, 2017).
The costs for drug administration and acquisition were not HCC, because they occurred at the start of the cycle. With the exception of the loading dose fulvestrant in the first cycle, which was HCC because it occurred on day 15 of the cycle.

Diagnostic costs

Only patients with a PIK3CA mutation were eligible for therapy with alpelisib. For the alpelisib treatment arm, costs for genetic testing were included to determine the PIK3CA mutation in the tumour tissue. This mutation is present in approximately 40% of the HR+, HER2- ABC (NEO genomics, 2021). For the identification of this mutation, histopathology and histology services were needed. The average unit cost of this pathology service was £40 (NHS , 2019). Because PIK3CA is not overexpressed by all patients, the costs are divided by the prevalence of the mutation in HR+, HER2- ABC patients. For identification of the mutation, a costs of £100 was once included at the start of the treatment.

Disease monitoring

During treatment patients should be monitored for increased adverse reactions. For treatment with alpelisib, patients were monitored to prevent hyperglycaemia because glucose increase is expected by PIK3CA inhibition. Before treatment is initiated FPG and HbA1c should be evaluated. After which FPG is measured weekly for two weeks, then at least once every four weeks (Novartis Pharmaceuticals Corporation, 2019). The costs for determination of FPG and HbA1c were assumed to be £2, as described by the national schedule of NHS costs as integrated blood services (NHS , 2019).

Abnormalities in haematological and biochemical laboratory parameters occurred frequently in patients in the SOLAR trial. Therefor was assumed that every four weeks laboratory research was performed. The haematological parameters were tested for abnormalities in

lymphocyte and platelet count, haemoglobin and activated partial thromboplastin time (aPTT). The biochemical parameters were tested for abnormalities in: creatinine, calcium, sodium, potassium, albumin, magnesium, lipase, gamma glutamyl transferase (GGT) and alanine aminotransferase (ALT) (Novartis Pharmaceuticals Corporation, 2019). The unit costs were sourced from the national schedule of NHS costs (NHS , 2019). The cost for monitoring the disease are summarized in Table 8.

Table 8 Cost of disease monitoring

Laboratory marker	Unit cost	Total cost	Source
HbA1c	£2	£2	(NHS , 2019), DAPS, integrated blood services
FPG	£2	£2	(NHS , 2019), DAPS, integrated blood services
Cost disease monitoring before initiating treatment			£4
FPG	£2	First cycle £6 Subsequent cycles £2	(NHS , 2019), DAPS, integrated blood services
Lymphocyte count	£3	£3	(NHS , 2019), DAPS, haematology
Platelet count	£3	£3	(NHS , 2019), DAPS, haematology
haemoglobin	£3	£3	(NHS , 2019), DAPS, haematology
aPTT	£3	£3	(NHS , 2019), DAPS, haematology
Creatinine	£1	£1	(NHS , 2019), DAPS, clinical biochemistry
Calcium	£1	£1	(NHS , 2019), DAPS, clinical biochemistry
Sodium	£1	£1	(NHS , 2019), DAPS, clinical biochemistry
Potassium	£1	£1	(NHS , 2019), DAPS, clinical biochemistry
Albumin	£1	£1	(NHS , 2019), DAPS, clinical biochemistry
Magnesium	£1	£1	(NHS , 2019), DAPS, clinical biochemistry
Lipase	£1	£1	(NHS , 2019), DAPS, clinical biochemistry
GGT	£1	£1	(NHS , 2019), DAPS, clinical biochemistry
ALT	£1	£1	(NHS , 2019), DAPS, clinical biochemistry
Cost disease monitoring first cycle			£25
Cost disease monitoring subsequent cycles			£21

Abbreviates: FPG, Fasting plasma glucose; aPTT, Activated partial thromboplastin time; GGT, Gamma glutamyl transferase; ALT, Alanine aminotransferase; DAPS, Directly accessed pathology services.

It was assumed that beside the health state depended healthcare use, e.g. consultations with the oncologist, no additional monitoring was needed in the fulvestrant treatment arm (Food and Drug administration, 2017).

Health state costs

Due to lack of data on resource utilization from the SOLAR-1 trial, the use of healthcare resources for disease management was assumed to be equal to the FALCON trial, as described in NICE TA503. The FALCON trial evaluated the effectiveness of fulvestrant as compared to anastrozole in postmenopausal women, with HR+, HER2- ABC. 60% of patients in the FALCON trial received previous therapy, however they were excluded when endocrine therapy was previously received, while in the SOLAR-1 trial patients were included after progression on an AI (an endocrine treatment). The mean age in the SOLAR-1 and FALCON treatment arms are similar, respectively 63 and 64 as compared to 62 and 64. In the FALCON trial was 100% female, as compared to 99.4% in the SOLAR-1 trial. Both studies were multicentre trials with countries participating all over the world. The SOLAR-1 trial gathered information in 34 countries, while the FALCON trial obtained their results from 20 countries in Asia, Europe, North and South America and Africa (Robertson, 2016; André, et al., 2021).

Based on the similarities between these trials, was assumed that health state dependent resource utilisation was equal.

The health state costs were divided into three groups; stable disease, progressed disease and palliative care. Costs were calculated per cycle. The unit costs were sourced from the PSSRU from 2019 (PSSRU, 2019), matching NICE TA503 (Robertson, 2016). An overview of healthcare use, unit costs, and the corresponding sources are provided per health state in Tables 9-11.

Table 9 Costs stable disease

	Resource use per 4 weeks	Source	Unit cost (2018/19)	Costs per 4 weeks	Source
Community nurse (home visit – 20 min.)	2	(Robertson, 2016)	£ 20.00	£ 40.00	(PSSRU, 2019, p. 117)
GP contact (surgery visit – 11.7 min.)	1		£ 50.31	£ 50.31	(PSSRU, 2019, p. 120)
Clinical nurse specialist (1 hour)	1		£ 47.00	£ 47.00	(PSSRU, 2019, pp. 147, 147)
			Total costs stable disease per 4 weeks	£ 137.31	

Abbreviates: GP, General Practitioner.

Table 10 Costs progressed disease

	Resource use per 4 weeks	Source	Unit cost (2018/19)	Costs per 4 weeks	Source
Community nurse (home visit – 20 min.)	4	(Robertson, 2016)	£ 20.00	£ 80.00	(PSSRU, 2019, p. 117)
Consultation with a GP (home visit)	2		£ 255.00	£ 510.00	(PSSRU, 2019, p. 120)
Clinical nurse specialist (1 hour)	4		£ 47.00	£ 188.00	(PSSRU, 2019, pp. 145, 147)
NHS community occupational therapist	2		£ 44.00	£ 88.00	(PSSRU, 2019, p. 133)
			Total costs progressed disease per 4 weeks	£ 866.00	

Abbreviates: GP, General Practitioner; NHS, National Health Service.

For terminal care was assumed that 40% of patients received palliative care in the hospital, 10% in a hospice and 50% at home, in line with the clinical guidance (CG) 81 as provided by NICE for the diagnosis and treatment of advanced breast cancer (NICE, 2017). The unit costs in CG81 were reported for the cost year 2015/16, and were inflated to 2018/2019 using the NHS cost inflation index (NHSCII) from PSSRU (NHS, 2019).

Table 11 Costs palliative care

Setting	% of patients	Source	Unit cost (2018/19)	Total cost	Source
Hospital	40%	(NICE, 2017)	£ 5,866.89	£ 2,346.76	(Robertson, 2016); (NHS, 2019)
Hospice	10%		£ 7,314.30	£ 713.43	(Robertson, 2016); (NHS, 2019)
Home	50%		£ 3,023.95	£ 1,511.975	(Robertson, 2016); (NHS, 2019)
	Mean costs palliative care cycle per patient			£ 4,590.16	

Subsequent therapy

If patients progressed on treatment with fulvestrant with alpelisib or placebo, or if the adverse events of the therapy were intolerable, treatment was discontinued in the model. In the SOLAR-1 trial not all patients had discontinued study treatment at data cut-off. In the alpelisib treatment arm 148 out of 169 patient discontinued treatment, compared to 164 out of 172 in the placebo group. Respectively, 78.4% and 81.7% received additional antineoplastic medication after discontinuation. Subsequent therapy consisted of chemotherapy (CT), ET, targeted therapy (TT) or other treatment. CT-based regimens were most common in both treatment arms, respectively 50.0% and 56.0%. Hormone-based regimens were given as subsequent therapy to 49.1% in the alpelisib treatment arm, and 41.8 in the placebo treatment arm. TT alone was given to respectively 0.9% and 1.5%. In the fulvestrant treatment arm one patient (0.7%) received other treatment (André, et al., 2021). The elaborated table on new antineoplastic medication after discontinuation of study treatment as published by André, et al. is provided in appendix 8.

Because TT and other treatment were rare as subsequent therapy, these patients were distributed among the other groups receiving ST. The proportions were reweighted and patients receiving solely TT or other therapy were distributed among the treatment groups; CT, CT plus other treatment, ET, and ET plus TT. It was assumed that distribution of the patients over the other ST groups would not have a relevant impact on the incremental cost-effectiveness ratio (ICER), because the proportions of patients were very small. A summary of the percentages of observed received ST, and their assumed value in the Markov model are shown in Table 12.

Table 12 Subsequent therapy after progression

	Alpelisib plus fulvestrant n(%)	*Assumption model probability*	*Placebo plus fulvestrant n(%)*	*Assumption model probability*
No additional treatment	*32 (21.6)*	*0.216*	*30 (18.3)*	*0.183*
CT	*38 (25.7)*	*0.260*	*49 (29.9)*	*0.306*
CT + other	*20 (13.5)*	*0.136*	*26 (15.8)*	*0.162*
ET	*20 (13.5)*	*0.136*	*21 (12.8)*	*0.131*
ET + TT	*37 (25.0)*	*0.252*	*35 (21.3)*	*0.218*
TT	*1 (0.7)*	*0*	*2 (1.2)*	*0*
Other	*0 (0)*	*0*	*1 (0.6)*	*0*

Abbreviates: CT, chemotherapy; ET, endocrine therapy; TT, targeted therapy.

In the study by André, et al., not all subsequent therapies were specified. In the model was assumed that each treatment subgroup received the most frequently prescribed regimen of that form of therapy, for simplicity. For chemotherapy this was capecitabine, for CT in combination with other treatment was everolimus plus exemestane assumed (Jing, 2019) (Xie, 2019). For the ET subgroup was exemestane assumed (NICE, 2017), and for ET plus TT additional therapy with palbociclib plus fulvestrant was assumed (Sayed, 2019). Regardless

that patients would have progressed on a fulvestrant based regimen by then, this seemed an acceptable treatment option. Whether patients had progressed on treatment with alpelisib or placebo with fulvestrant they might benefit from an similar treatment regimen with the addition of palbociclib.

The costs for ST with chemotherapy were obtained from NICE TA263, bevacizumab or placebo plus capecitabine for treating metastatic breast cancer (NICE, 2012). The cost for treatment acquisition and administration as provided in the TA, were corrected for cycle length and inflated to cost year 2018/2019 (NHS, 2019) (PSSRU, 2020). The corrected cost, as used in this CEA, of additional treatment with capecitabine was £580.05 per cycle. In the monotherapy capecitabine treatment arm, only diarrhoea occurred with an incidence of 2.47%. Because this incidence was below the 5% incidence threshold as handled in this CEA, no additional costs for adverse events were included (Roche, 2011).

The additional treatment costs for CT plus other treatment were obtained from NICE TA421 on everolimus with exemestane for treating ABC after endocrine therapy (NICE, 2016). The costs as found in this TA for treatment acquisition and administration were corrected for cycle length and cost year. This resulted in a cost of £2280.95 per cycle. For adverse events the TA provided a mean cost per patient, this cost was inflated and an additional cost of £189.20 for of AEs was included at the start of the simulation (Novartis, 2016).

For ST with exemestane no relevant TA was found, however a final appraisal determination on ET for ER+ breast cancer did provide information on costs. Exemestane tablets were taken once daily. Exemestane is licensed in the UK with acquisition price of £88.80 for a pack with thirty 25 mg tablets (NICE, 2006). Because this acquisition cost might be outdated, an acquisition price of £65.00 was assumed (Mistrys, 2021). Besides prescription charges, no additional administration costs were included. For adverse events no additional cost were assumed, because in the treatment arm with fulvestrant, another of ET, also no relevant AEs occurred. Correcting the for cycle length resulted in a cost of subsequent ET of £70.02 per cycle.

The cost for the combination of ET and TT were obtained from NICE TA619 (NICE, 2020). The found post-progression therapy cost was £734.06 per cycle for treatment with palbociclib plus fulvestrant. The cycle length was 28 days, thus no correction was applied for cycle length. The model of NICE TA619 was not sensitive to the inclusion of AEs, thus no additional costs were included for managing AEs (Pfizer, 2019).

Healthcare resource use was assumed to be equal among all subgroups during progressed disease. For simplicity, one line of subsequent therapy (ST) was assumed. This is a realistic assumption, since the patients would have received three lines of therapy by then. No disutility for adverse events was included, because the expected influence was very small, due to short duration and low incidence. Finally, in the model was assumed that all patients which received subsequent therapy, received it for the entire length the patient resided in the PD state.

Calculating the deterministic ICER

Using the total calculated effects and costs associated with alpelisib plus fulvestrant and fulvestrant treatment, the ICER was determined. The ICER is calculated by dividing the difference in costs (incremental costs) by the difference in effects (incremental effect), see formula.

$$\text{ICER} = \frac{cost_A - cost_B}{effect_A - effect_B}$$

Whether an intervention is cost-effective depends on the threshold ICER. This threshold represents the maximum willingness to pay (WTP) per QALY gained. The used ICER threshold by NICE has been between £20,000 and £30,000 (McCabe, 2008).

The mean total costs and effects were determined per patient. LYs were determined by multiplying the HCC number of patients per cycle with the cycle length. QALYs were determined by multiplying the LYs per state with the corresponding utility value. To correct for the occurrence of adverse events, the duration of AEs was multiplied with the corresponding disutility. QALYs lost due to AEs were subtracted of the total amount of QALYs. The total costs and benefits were discounted using an annual discount rate of 3.5%, in line with the NICE reference case (NICE, 2013).

Sensitivity analysis

Most input values are informed by empirical estimates that are subject to sampling variation i.e., PFS, OS, utilities, healthcare utilisation and costs. When no or limited information was available assumptions were made, aimed to simulate reality. Nevertheless, all input values are surrounded by a range of uncertainty. In consideration of this uncertainty, a probabilistic sensitivity analysis (PSA) and sensitivity analysis (SA) were performed.

Probabilistic sensitivity analysis

A PSA was conducted to assess the parametric uncertainty associated with the base case results. The input parameters where estimates of uncertainty and they were assigned probability distributions. For utilities and probabilities a beta distribution was chosen, because the interval ranged between 0-1 (Picot, 2011). For costs, healthcare use and duration of events a gamma distribution was chosen, because both costs and durations cannot reach a negative value. Inflation indices, dosages and the cost of alpelisib were assumed to be fixed values, thus no distribution was included for these input values.

When a standard error was not available in the literature, fixed percentages of the mean were assumed. For probabilities a standard error of 10% of the mean value was used, for costs and healthcare use was 20% deviation of the mean value assumed. The parameters to which there was uncertainty, and what distribution and SE were used in the PSA, is shown in Table 13. For input parameters with value 0, an deterministic value of 0.0001 with SE 0.0001 was assumed. Also, a gamma distribution was chosen without regard to the parameter, to prevent mathematical errors caused by division through 0.

Table 13 PSA distributions according to parameter

	Distribution	SE (when not provided in literature)
Utilities	Beta	n/a
AE disutilities	Beta	n/a
Duration	Gamma	Calculation
Cost	Gamma	20% of the mean
Probabilities	Beta	10% of the mean
Healthcare use	Gamma	20% of the mean

Abbreviates: SE, standard error; AE, adverse events.

The PSA entailed 1,000 simulations. Each simulation consisted of a set of input values, randomly drawn from the distributions surrounding the input parameters. With these sets of input parameters 1,000 iterations of the base case were generated. Al 1,000 simulations were placed on a cost-effectiveness plane (CE-plane). A CE-plane has the incremental effects on the x-axis and the incremental costs on the y-axis. This plane illustrates the uncertainty surrounding the ICER.

Based on the results of the PSA, the percentage of simulations which is 'cost-effective' was determined given multiple WTP-thresholds. A cost-effective acceptability curve (CEAC) was drawn with on the x-axis the WTP threshold, and on the y-axis the percentage of simulations which is cost-effective. The curve starts at the point of the percentage of simulations which is cost saving, the limit of the curve is the percentage of curves which is more effective (Fenwick & Byford, 2018; Al, Probabilistic Sensitivity Analysis, 2021)

Scenario analysis

A SA was performed to evaluate the effect of assumptions made in the model. For the SA alternative input values were considered, and the effect on the ICER was determined. The alternative values chosen are extreme values, thus the expected high or low end of the deviation range from the BC. The assumptions and adjusted values are elaborated on, and a summary is provided in Table 14.

Clinical efficiency

The BC analysis employs a lognormal distribution for the extrapolation of the PFS curve and a Weibull distribution for OS. For the SA, the ICERs of scenarios were both OS and PFS were extrapolated using different distributions were determined.

Utility

For both treatment arms equal utility was assumed. In the FALCON study equal utility was found in both treatment arms. However, the FALCON trial compared fulvestrant with anastrozole, two endocrine therapies. In this analysis, ET is compared with ET plus TT. An systematic literature review was performed to assess the impact of endocrine therapies, including monotherapy and ET plus TT, on the QoL in woman with HR+, HER2- ABC. The review showed that patients receiving combination therapy experienced similar or even better QoL, as compared to patients receiving mono ET (Zhou, 2016). For the SA the experienced utility when receiving combination therapy was increased. The new value for utility under alpelisib plus fulvestrant therapy was assumed to be 0.80, instead of 0.75.

Adverse events

The article by Rugo, et al. described the incidence, management and timeline of adverse events in the SOLAR-1 trial. However, no information on the effect on the QoL was provided. The disutility as found by another TA was assumed, this assumption seemed accurate since the burden of adverse events is equal despite of the perceived treatment. However, there are three assumptions worth noting. For hyperglycaemia a disutility of 0 was assumed, a scenario was performed with an extreme value of 0.2 for the occurrence of hyperglycaemia. The disutility for rash was assumed to be equal to hand-food syndrome, however this disutility of 0.188 seems quite high for an adverse events. Therefore, the disutility was divided by two, and a scenario was performed with 0.094 as decrement for rash occurrance. Lastly, the disutility decrements were from a reference utility of 0.771 instead of the 0.75 used in this CEA. For all disutilities adjusted values were assumed and their effect on the ICER was determined.

List price alpelisib

The list price of alpelisib as assumed in this analysis was £4082 per 4 weeks, this price was provided by a specialist pharmacy service in the UK (NHS, 2016). However, the list price of drugs is usually open to negotiation. The true acquisition cost of alpelisib as provided by the British National Formulary (BNF) could not be accessed from the Netherlands, and thus not be included. To adjust for this, discounts of 25%, 50% and 75% for the list price of alpelisib were included in the SA.

Health care resource use

Healthcare recourse utilization in SD and PD, was assumed to be equal to the healthcare use in the FALCON trial. However, the FALCON trial investigated patients who had not perceived previous endocrine therapy. In contrast to the patients in this CEA, who progressed on or after treatment with an aromatase inhibitor. Health care resource use might increase, when patients have progressed on previous treatment, because patients have been sick for a longer time. Therefor an adjusted input value for healthcare resource use was included in the SA. Recourse use in SD and PD was multiplied with factor 1.5. No adjusted values for palliative care or disease monitoring were assumed.

Subsequent therapy

For treatment after progression on the alpelisib plus fulvestrant or monotherapy fulvestrant, was assumed that all subsequent therapy subgroups received the same treatment. For instance, all patients with subsequent chemotherapy received a capecitabine regimen. The costs of these subsequent therapies were obtained NICE TA's. To adjust for the same assumption of the same treatment in each subgroup, the costs of all additional treatments were increased and decreased with 50%.

It was assumed that patients received a maximum of one additional line of therapy. At that point patients already progressed on an aromatase inhibitor, fulvestrant with or without alpelisib, and ST. A fourth line of therapy is rare (around 5%) in breast cancer treatment (Palumbo, 2013), and was thereforconsidered in this SA.

Finally was assumed that patients received additional therapy during the entire length of PD, the impact of this assumption could be evaluated by dividing the mean costs of ST per cycle by two, thus simulating that patients would receive additional therapy for half as long. No

additional SA was performed, because the impact of was already determined by decreasing the costs of additional treatment with 50%.

Table 14 List of scenario analyses conducted

	Adjusted parameter	Value BC	Value SA
Clinical efficiency	Distribution extrapolation PSF	Lognormal	Exponential
			Weibull
			Loglogistic
	Distribution extrapolation OS	Weibull	Exponential
			Lognormal
			Loglogistic
Equal utility for both treatment arms	Utility value stable disease ET + TT	0.75	0.80
Disutility of adverse events	Disutility hyperglycaemia	0.000	0.200
	Disutility rash	0.188	0.094
	Disutility hyperglycaemia	0.000	0.000
	Disutility diarrhoea	0.171	0.150
	Disutility rash	0.188	0.167
Healthcare use stable disease	Use SD community nurse	2	3
	Use SD GP contact	1	1.5
	Use SD clinical nurse	1	1.5
	Use PD community nurse	4	6
	Use PD GP visit	2	3
	Use PD clinical nurse	4	6
	Use PD NHS community occupational therapist	2	3
Cost subsequent therapy	Chemotherapy	£ 580.05	£ 870.08
			£ 290.03
	Chemotherapy plus other	£ 2,280.96	£ 3,421.44
			£ 1,140.48
	Endocrine therapy	£ 70.02	£ 105.03
			£ 35.01
	Endocrine plus targeted therapy	£ 734.06	£ 1,101.09
			£ 367.03
List price alpelisib	Acquisition price alpelisib	£ 4082	£ 3,061.50
			£ 2041.00
			£ 1,020.50

Abbreviates: BC, base case; SA, scenario analysis; OS, overall survival; PFS, progression-free survival; ET, endocrine therapy; TT, targeted therapy; SD, stable disease; PD, progressed disease; GP, general practitioner; NHS, National Health Service.

Results

Deterministic ICER

The total discounted costs of treatment with alpelisib plus fulvestrant were £220,406,390 as compared to £51,526,728 in the monotherapy fulvestrant group. 4065.02 LYs were gained in the alpelisib plus fulvestrant group, as compared to 3846.42 in the monotherapy fulvestrant group. When LYs were adjusted for experienced QoL, respectively 2968.85 QALYs versus 2838.43 QALYs were gained. The discounted incremental cost-effectiveness ratio of alpelisib plus fulvestrant for treating HR+, HER2-, PIK3Ca-mutated ABC was £1,294,908 per QALY gained, and £772,559 per LY gained. A summary of the results is shown in Table 15.

Table 15 Incremental costs and effects and ICER of alpelisib plus fulvestrant versus placebo plus fulvestrant

	Total costs (discounted)	QALYs (discounted)	LYs (discounted)
Alpelisib plus fulvestrant	£ 220,406,390	2968.85	4065.02
Placebo plus fulvestrant	£ 51,526,728	2838.43	3846.42
Increment	£ 168,879,662	130.42	218.60
		Incremental cost/QALY	Incremental cost/
ICER		£ 1,294,908	£ 772,559

Abbreviates: QALY, quality adjusted life year; LY, life year.

The cost and benefits of the treatment were disaggregated into subgroups. For stable disease the aggregated costs were divided into the subgroups: costs of alpelisib treatment, costs of fulvestrant treatment, costs for disease management and costs associated with adverse events. For progressed disease costs were divided into the subgroups: subsequent therapy, adverse events of ST, disease management and palliative care. The effects of the intervention were disaggregated into LYs or QALYs gained in stable and progressed disease, for QALYs also a decrement for QALYs lost due to AEs was included. The undiscounted disaggregated results are provided in Table 16.

Table 16 Undiscounted disaggregated costs, QALYs and LYs

	Alpelisib plus fulvestrant	Placebo plus fulvestrant	Increment
	Costs stable disease		
Cost alpelisib	£ 180,710,336	£ -	£ 180,710,336
Cost fulvestrant	£ 28,827,622	£ 28,825,206	£ 2,415
Disease management	£ 7,021,216	£ 6,093,642	£ 927,574
Cost adverse events	£ 85,014	£ 87	£ 84,927
	Costs progressed disease		
Subsequent therapy	£ 9,945,671	£ 8,308,997	£ 1,636,674
Adverse events ST	£ 17,645	£ 15,264	£ 2,381
Disease management	£ 13,138,954	£ 10,046,808	£ 3,092,147
Palliative care	£ 4,576,112	£ 4,570,387	£ 5,725
	LYs accrued		
In SD state	3359.14	3413.75	-54.60
In PD state	1167.08	892.41	274.66
	QALYs accrued		
In SD state	2519.36	2560.31	-40.95
In PD state	805.28	615.77	189.52
Loss due to AEs	-18.49	-0.02	-18.46

Abbreviates: ST, subsequent therapy; LY, life year; QALY, quality adjusted life year; SD, stable disease, PD, progressed disease.

Probabilistic ICER

The ran PSA provided 1,000 iterations for the base case analysis, the average results of the PSA are presented in Table 17. The mean probabilistic discounted ICER for alpelisib plus fulvestrant vs. monotherapy fulvestrant is £1,277,584 per QALY gained, compares to £1,294,908 in the deterministic analysis, results in a difference of 1.34%.

Table 17 Average results based on the probabilistic sensitivity analysis (1,000 simulations); alpelisib plus fulvestrant versus monotherapy fulvestrant

	Costs	LYs	QALYs	
Alpelisib + fulvestrant	£ 221,639,165	4,075.13	2,976.81	
Monotherapy fulvestrant	£ 53,383,026	3,856.41	2,844.90	**ICER**
Increment	£ 168,256,139	218.72	131.91	£ 1,277,584

Abbreviates: LY, life year; QALY, quality adjusted life year; ICER, incremental cost-effectiveness ratio.

The CE-plane for alpelisib plus fulvestrant compared with monotherapy fulvestrant is presented in Figure 2.

Figure 2 Cost effectiveness plane alpelisib plus fulvestrant vs. monotherapy fulvestrant

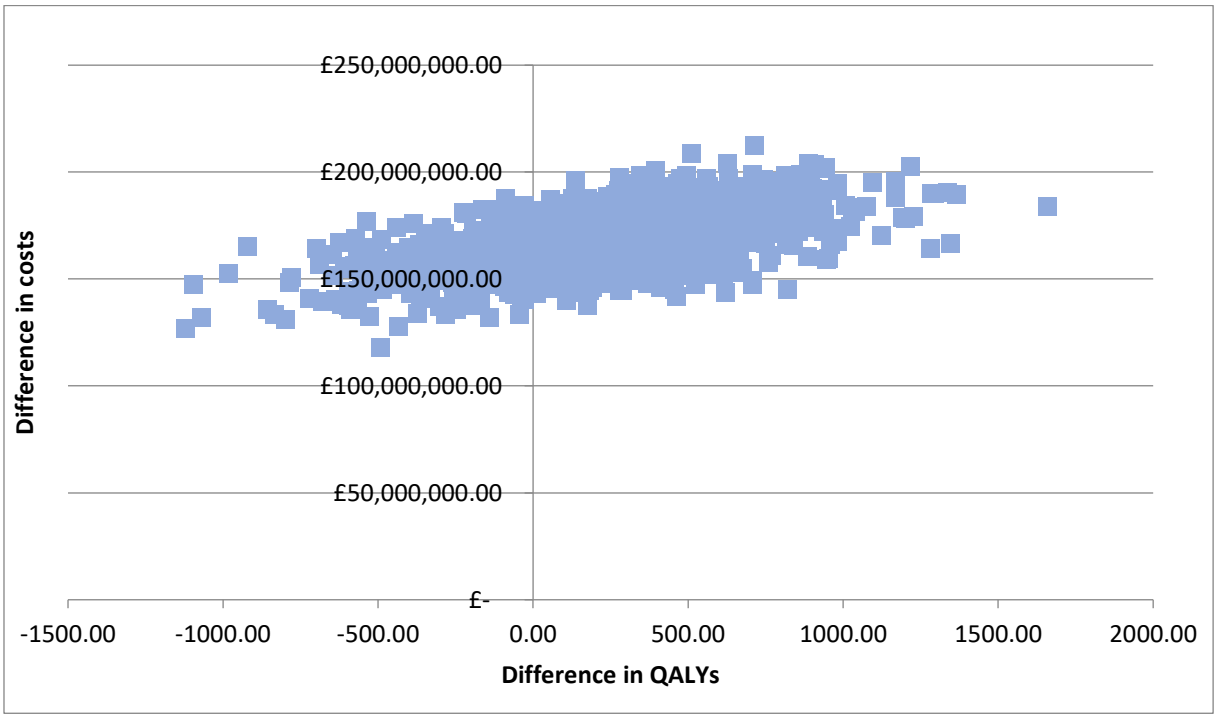


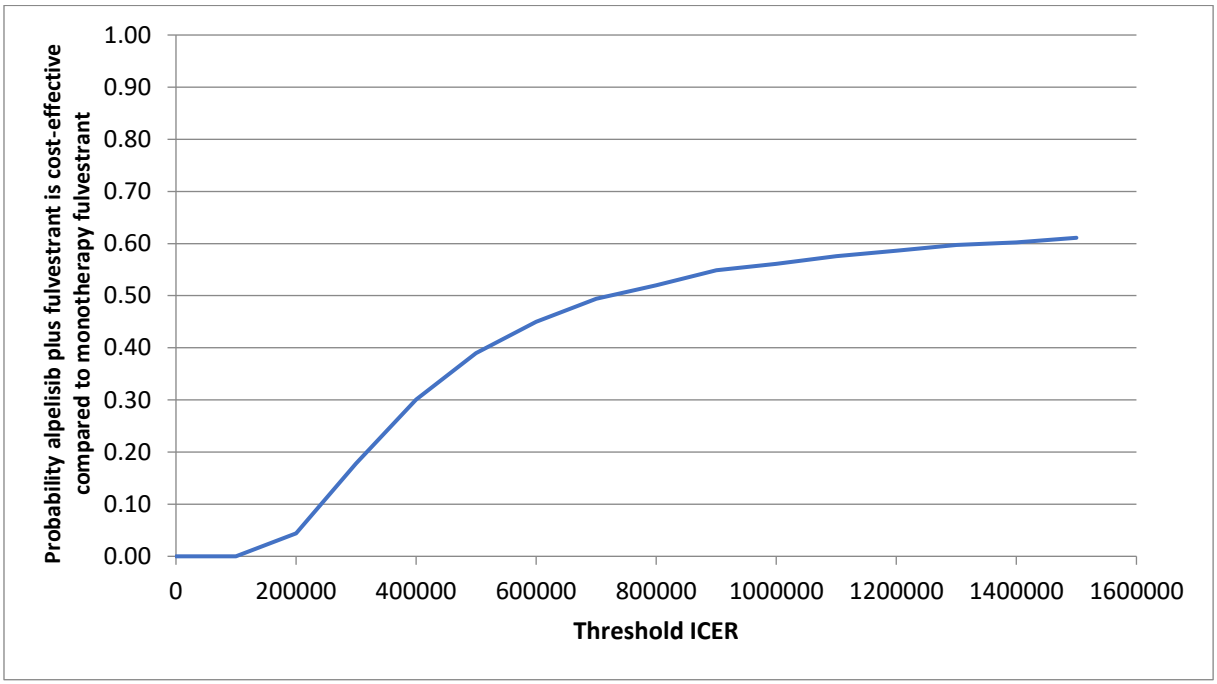
Table 18 and Figure 3 represent the probability of alpelisib flus fulvestrant being cost-effective, as compared to monotherapy fulvestrant. Based on the PSA the chance of addition of alpelisib to the fulvestrant treatment regimen being cost effective with a WTP threshold of £20.000 to £30.000 is 0%.

Table 18 Probability of alpelisib plus fulvestrant compared to monotherapy fulvestrant is cost-effective

WTP threshold	probability cost-effective
£ 20,000	0.00
£ 30,000	0.00
£ 50,000	0.00
£ 200,000	0.04
£ 300,000	0.18

Abbreviates: WTP, willingness to pay.

Figure 3 Cost-effectiveness acceptability curve alpelisib plus fulvestrant versus monotherapy fulvestrant



Abbreviates: ICER, incremental cost-effectiveness ratio.

Scenario analysis

The scenarios as described in Table 14, were performed on the model and the results on the discounted incremental costs and QALYs and the discounted ICERs are provided in Table 19, 20 and 21. Table 19 presents the results of the SA when using alternative distributions for the extrapolation of PFS.

Table 19 Results of scenario analysis alternatives distributions for PFS

	Incremental costs	Incremental QALYs	ICER
PSF exponential, OS Weibull	£ 166,607,175	130.93	£ 1,272,480
PSF Weibull, OS Weibull	£ 155,196,362	132.37	£ 1,172,454
PSF Loglogistic, OS Weibull	£ 169,221,862	129.96	£ 1,302,113

Abbreviates: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; OS, overall survival.

Table 20 presents the results of the SA when using different alternatives distribution for extrapolating OS.

Table 20 Results of scenario analysis alternatives distributions for OS

	Incremental costs	Incremental QALYs	ICER
PSF lognormal, OS exponential	£ 177,133,543	334.24	£ 529,955
PSF lognormal, OS lognormal	£ 172,647,749	146.27	£ 1,180,370
PSF lognormal, OS loglogistic	£ 172,921,088	153.53	£ 1,126,307

Abbreviates: QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; PFS, progression-free survival; OS, overall survival.

Table 21 presents the SA for the alternatives of assumed input parameters, as discussed in the method section.

Table 21 Impact of the scenario analysis on incremental costs, effects and ICERs

	Value BC	Value SA	Incremental cost	Incremental QALYs	ICER
Base case			£ 168,879,662	130.42	£ 1,294,908
Equal utility for both treatment arms					
Utility value stable disease alpelisib	0.75	0.80	£ 168,879,662	282.47	£ 597,858
Disutility of adverse events					
Disutility hyperglycaemia	0.000	0.200	£ 168,879,662	115.27	£ 1,465,062
Disutility rash	0.188	0.094	£ 168,879,662	134.82	£ 1,252,594
Disutility hyperglycaemia	0.000	0.000	£ 168,879,662	130.43	£ 1,294.832
Disutility diarrhoea	0.171	0.150	£ 168,879,662	131.60	£ 1,283,234
Disutility rash	0.188	0.167	£ 168,879,662	131.40	£ 1,285,225
Healthcare use stable disease					
Use SD community nurse	2	3	£ 168,871,210	130.42	£ 1,294,842
Use SD GP contact	1	1.5	£ 168,869,031	130.42	£ 1,294,826
Use SD clinical nurse	1	1.5	£ 168,869,730	130.42	£ 1,294,831
Use PD community nurse	4	6	£ 169,010,236	130.42	£ 1,295,909
Use PD GP visit	2	3	£ 169,712,076	130.42	£ 1,301,290
Use PD clinical nurse	4	6	£ 169,186,513	130.42	£ 1,297,260
Use PD NHS community occupational therapist	2	3	£ 169,023,294	130.42	£ 1,296,009
Cost subsequent therapy					
Chemotherapy	£ 580.05	£ 870.08	£ 168,991,789	130.42	£ 1,295,767
		£ 290.03	£ 168,767,540	130.42	£ 1,294,047
Chemotherapy plus other	£ 2,280.96	£ 3,421.44	£ 169,088,083	130.42	£ 1,296,505
		£ 1,140.48	£ 168,671,242	130.42	£ 1.293,309
Endocrine therapy	£ 70.02	£ 105.03	£ 168,898,154	130.42	£ 1,295,049
		£ 35.01	£ 168,861,163	130.42	£ 1,294,766
Endocrine plus targeted therapy	£ 734.06	£ 1,101.09	£ 169,306,958	130.42	£ 1,298,184
		£ 367.03	£ 168,452,365	130.42	£ 1.291,631
List price alpelisib					
Acquisition price alpelisib	£ 4082	£ 3,061.50	£ 128,077,127	130.42	£ 982,046
		£ 2,041.00	£ 87,274,593	130.42	£ 669,190
		£ 1,020.50	£ 46,472,059	130.42	£ 356,331

Abbreviates: BC, base case; SA, scenario analysis; QALYs, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; SD, stable disease; PD, progressed disease; GP, general practitioner; NHS, National Health Service.

Discussion

In this analysis, the cost-effectiveness alpelisib plus fulvestrant as compared to monotherapy fulvestrant was assessed for treating HR+, HER2- advanced breast cancer, from a NICE perspective. Based on the results from this CEA, the addition of alpelisib had an ICER of £1,294,908 per QALY gained. In the context of the current £20,000-£30,000 range for cost-effectiveness in the UK, addition of alpelisib is not cost-effective.

A PSA was performed, and the mean of 1,000 simulations had a 1.34% difference with the found deterministic ICER. As could be assumed, was the probability of this intervention being cost-effective 0.00 for both thresholds of £20,000 and £30,000.

In the SA multiple alternatives for single input parameters were explored, and their effect on the discounted incremental costs and QALYs, and ICER was determined. Choosing alternatives of disutilities for adverse events, healthcare resource use and cost of ST, did not have an significant impact on the ICER. Contrarily, alternatives for QoL under alpelisib plus fulvestrant treatment, discounts for the list price of alpelisib and another distribution for OS did have significant impact on the ICER. However, even with the alternatives for input values, addition of alpelisib to an fulvestrant treatment regimen remains far from cost effective, given the NICE threshold.

At moment of writing, no evidence submission has been published on the cost-effectiveness of alpelisib plus fulvestrant from a NICE perspective. A project team lead by Thomas Feist started a CEA in October 2018, however the project was suspended per September 7th, 2020. The research team informed NICE that it would not provide an evidence submission for the appraisal (NICE, 2020). This CEA is thus the first study to assess the cost-effectiveness of alpelisib plus fulvestrant following the NICE reference case. Accordingly, could this analysis serve as a reference point for other evidence submissions on alpelisib in Western Europe.

In the USA, a similar economic evaluation was conducted comparing alpelisib plus fulvestrant with fulvestrant with either palbociclib or everolimus. This study found ICERs of $641,303 and $648,000 respectively, and concluded that the alpelisib plus fulvestrant regimen was clearly not cost effective (Delevry, 2020). Despite the other perspective and comparators used in this analysis, the conclusion is similar, addition of alpelisib is certainly not cost-effective. Notwithstanding the similar conclusion, the ICER as found in this analysis is over 2 times higher than the ICER as found by Delevry, et al. A substantial part of the difference in ICER can be explained by the different perspective, comparators and the difference in routine treatment and costs in the USA. However, the skewed results are most likely due to choices made in the analysis.

The clinical effectiveness of alpelisib plus fulvestrant is sourced from the SOLAR-1 trial. The trial is a double-blind, placebo-controlled, trial in 34 countries and enrolled 572 patients, both with and without PIK3CA mutations. In regard of the trial being funded by Novartis, the manufacturer of the drug, the results seem trustworthy (National Health Care Institute, 2019). The clinical effectiveness was sourced from the published KM-curves, which were extrapolated to estimate the course of the event. After consideration of different distributions for the BC, a Weibull and lognormal distribution were employed for

respectively OS and PFS. A SA was performed with different distributions for both OS and PFS. Exploring other alternatives for PFS did not have a substantial effect on the ICER. In contrast, when for OS an exponential distribution was chosen, the ICER decreased with 59.1%. However the impact of choosing a loglogistic or lognormal distribution for OS is not that extensive, the ICER does decrease significantly with an loglogistic or lognormal distribution for OS. The large deviations in ICER when the OS is extrapolated by another distribution can be explained by the sudden steep decrease in OS in the alpelisib treatment arm at the end of the observed data (André, et al., 2021).

Another notable aspect on the published KM curves by André et al. on the PFS an OS of the SOLAR-1 trial cross at approximately 49 months (André, et al., 2021). Meaning that patients with monotherapy fulvestrant have a higher progression-free or overall survival rate from that moment on. Whether the crossing of the curves is coincidental or due to long term toxic effects of alpelisib is not certain, because data cut-off was relatively soon after that the 49 months. No explanation for the fall in survival data was provided in the literature. Additionally, the model used transition probabilities based on extrapolations which fitted the data. However, when combining the estimated extrapolations the model had a negative amount of patients in some cycles. Because, this is not realistic PFS was assumed to be equal to, or higher than OS. For monotherapy fulvestrant the cost do not differ much between SD and PD per patient per cycle, thus the effect of this assumption was limited for this treatment arm. However, for the alpelisib treatment arm the total costs per patient per cycle in stable disease are over three times higher than in progressed disease. This assumption might thus have caused an overestimation of the ICER.

Furthermore, the list price of alpelisib is assumed. It is customarily that pharmaceutical companies negotiate over the price with the payers of healthcare, i.e. the NHS for the UK. Large discounts (up to 76%) are given on list prices (Hermandez, 2020). In the SA the alternatives for the list price were provided; discounts of 25%, 50% and 75%. The effect on the ICER was extensive, as could be expected. However, lowering the discount price, did not push the drug below the cost-effectiveness threshold of £20,000-£30,000 per QALY.

Finally, Novartis announced in September 2020 not to make an evidence submission on the cost-effectiveness of alpelisib plus fulvestrant. No reason for suspension of the project was provided. No sudden deaths or extreme adverse events due to drug toxicity during or after the trial, were reported in the literature. Thus, a reasonable assumption might be that the company realised that the drug was not cost-effective during the trial, and chose to terminate the analysis to save valuable time and monetary resources.

Conclusion

The current cost-effectiveness threshold of the National Institute of Health and Care Excellence lies between the £20,000 and £30,000 per QALY gained, for reimbursement by the NHS (Gandjour, 2020). The found deterministic ICER was over 1.2 million, thus addition of alpelisib to a fulvestrant treatment regimen is not cost-effective for treating HR+, HER2-, PIK3Ca- mutated ABC patients who progressed on treatment with an AI. Some assumptions were made which potentially overestimated the ICER, however adjusting these assumptions did not reduce the ICER enough to come close to the £20,000-£30,000 cost-effectiveness threshold.

References

Al. (2020). Advanced Health Economic Modelling. *Introduction advanced modelling.* Rotterdam: Erasmus University.

Al. (2021). Probabilistic Sensitivity Analysis. *Advanced Health Economic Modelling.* Rotterdam: Erasmus University.

American Cancer Society. (2021, January 27). *Understanding a breast cancer diagnosis*. Retrieved from Survival Rates for Breast Cancer: https://www.cancer.org/cancer/breast-cancer/understanding-a-breast-cancer-diagnosis/breast-cancer-survival-rates.html

André, C. R. (2019). Alpelisib for PIK3CA-Mutated, Hormone Receptor–Positive Advanced Breast Cancer. *New England journal of medicine*, 1929-1940.

André, Ciruelos, Juric, Loibl, Campone, Mayer, . . . Rugo. (2021). Alpelisib plus fulvestrant for PIK3CA-mutated, hormone receptor-positive, human epidermal growth factor receptor-2–negative advanced breast cancer: final overall survival results from SOLAR-1. *Annals of Oncology*, 127-284.

Arsenic, & Ruza. (2014). Analysis of PIK3CA mutations in breast cancer subtypes. *Applied Immunohistochemistry and molecular morphology*.

AstraZeneca. (2016). *FASLODEX Prescribing information.* AstraZeneca, editor .

Bevans, R. (2020, March 26). *An introduction to the Akaike information criterion*. Retrieved from Scribbr: https://www.scribbr.com/statistics/akaike-information-criterion/

Blommestein. (2020). Introduction in economic evaluation . *Health Technology assesment.*

Breast Cancer expert Advisory Group. (2018). *Clinical Guidelines for the Management of Breast Cancer.* NHS England.

Breast cancer now. (2021). *The research and care charity*. Retrieved from Facts and statistics 2021: https://breastcancernow.org/about-us/media/facts-statistics

Butler. (2020). Alpelisib (Piqray®). *Oncology Times*, 19.

Caissie, N. C. (2012). Quality of life in patients with brain metastases using EORTC QLQ-BN20+2 and QLQ-C15-PAL. *Int JRadiatOncolBiolPhys*, 1238-45.

Cancer research UK. (2017). *Breast cancer statistics*. Retrieved from statistics by cancer type: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Zero

Cancer research UK. (2021, February 10). *Cancer research UK*. Retrieved from About advanced cancer: https://www.cancerresearchuk.org/about-cancer/breast-cancer/stages-types-grades/advanced/about

Cooper, K. H. (2017). *ulvestrant for untreated hormone-receptor positive locally advanced or metastatic breast cancer: A Single Technology.* Southampton: Southampton Health Technology Assessments Centre (SHTAC).

Covance. (2019). *Pricing and reimbursement in England.* New Jersey: Cavance Inc.

Delevry, L. (2020). PCN55 ECONOMIC ANALYSIS OF COMBINATION THERAPY WITH ALPELISIB AND FULVESTRANT FOR TREATMENT OF HORMONE RECEPTOR-POSITIVE (HR+) AND HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2-NEGATIVE (HER2-) ADVANCED BREAST CANCER. *Elsevier*, S32-33.

Fenwick, & Byford. (2018). A guide to cost-effectiveness acceptability curves. *The Britisch Journal of Psychiatry*.

Food and Drug Administraion. (2019, May 28). *FDA approves alpelisib for metastatic breast cancer* . Retrieved from Approved drugs: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-alpelisib-metastatic-breast-cancer

Food and Drug administration. (2017, August). FASLODEX safely and effectively.

Frederiks, W. (2021, June 7). General Practitioner. (M. Walraven, Interviewer)

Frederix, Q. H. (2013). Utility and Work Productivity Data for Economic Evaluation of Breast Cancer Therapies in the Netherlands and Sweden. *Clinical Therapeutics*, e1-e7.

Gandjour, A. (2020). Willingness to pay for new medicines: a step towards narrowing the gap between NICE and IQWiG. *BMC Health Services Research*.

Globocan. (2021, June 3). *Estimated cancer incidence, mortality and prevance wordwide*. Retrieved from http://globocaniarcfr/Pages/fact_sheets_canceraspx: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

GOV.uk. (2020). *Drugs and pharaceutical electronic market information tool (eMIT).* Department of health and social care.

Grunfeld, C. W. (2004). Family caregiver burden: results from a longitudinal study of breast cancer in patients and their principal caregivers. *CMAj.*, 1798-1801.

Hermandez, S.-J.-R. G. (2020). Changes in List Prices, Net Prices, and Discounts for Branded Drugs in the US, 2007-2018. *Original investigation - JAMA*, 854-862.

Hoyle, H. (2011). Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Medical Research Methodology*, 139.

Jing, O. T.-A. (2019). Retrospective Analysis of Treatment Patterns and the Effectiveness of Palbociclib and Subsequent Regimens in Metastatic Breast Cancer. *Journal of the National Comprehensive Cancer Network*, 141-147.

Komorowski, & Raffa. (2016). Markov Models and Cost Effectiveness Analysis: Applications in Medical Research. In Komorowski, & Raffa, *Secondary Analysis of Electronic Health Records* (pp. 351-367). Springer.

Kurosky, M. Z. (2018). Treatment Patterns and Outcomes of Patients With Metastatic ER+/HER-2− Breast Cancer: A Multicountry Retrospective Medical Record Review. *Clinical breast cancer*, 529-538.

Lohr. (2017). Palbociclib & Fulvestrant. *Oncology times*, 18.

Markham. (2019). Alpelisib: First Global Approval. *Drugs*, 1249-1253.

McCabe, C. C. (2008). The NICE cost-effectiveness threshold: what it is and what that means. *Pharmacoeconomics*, 733-744.

McDowell, L. R. (2019, December 30). *Cancer.org*. Retrieved from Cancer Research Insights from the Latest Decade, 2010 to 2020: https://www.cancer.org/latest-news/cancer-research-insights-from-the-latest-decade-2010-to-2020.html

Mistrys. (2021, June 20). *https://www.mistrys.co.uk*. Retrieved from Exemestane tablets f/c 25 mg 30: https://www.mistrys.co.uk/exemestane-tablets-f-c-25mg-351.html

National cancer institute. (2021, June 23). *Surveillance, epidemiology, and End Results Program*. Retrieved from Cancer stat facts: Female Breast cancer subtypes: https://seer.cancer.gov/statfacts/html/breast-subtypes.html

National Health Care Institute. (2019, June 12). *Horizonscan geneesmiddelen > Medicines* . Retrieved from Oncology and Hematology; Alpelisib.

National Institute for Health Research . (2017). *Alpelisib in combination with fulvestrant for advanced HR positive, HER2-negative breast cancer in men and post menopausal women.*

NEO genomics. (2021). *https://neogenomics.com/*. Retrieved from PIK3CA Mutation CDx: https://neogenomics.com/pik3ca

NHS . (2019). *National schedule of NHS costs.*

NHS. (2016, August 15). *Specialist Pharmacy service*. Retrieved from Alpelisib: https://www.sps.nhs.uk/medicines/alpelisib/

NHS. (2019). *Cost inflation index.*

NHS. (2021, March 31). *www.nhs.uk*. Retrieved from Prescriptions and pharmacies : https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/nhs-prescription-charges/

NICE. (2006). *Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer .*

NICE. (2011). *Fulvestrant for the treatment of locally advanced or metastatic breast cancer - Final appraisal determination.*

NICE. (2012, August 22). *nice.org.uk*. Retrieved from Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer: https://www.nice.org.uk/guidance/ta263

NICE. (2013). *Assessing cost effectiveness.* NICE.

NICE. (2016). *Everolimus in combination with exemestane for treating advanced HER2-negative hormone-receptor-positive breast cancer after endocrine therapy (Cancer Drugs Fund reconsideration of TA295).* National Institute for Health and Care Excellence.

NICE. (2016, December 21). *nice.org.uk*. Retrieved from Everolimus with exemestane for treating advanced breast cancer after endocrine therapy: https://www.nice.org.uk/guidance/ta421

NICE. (2017, August 16). *Advanced breast cancer: diagnosis and treatment*. Retrieved from Clinical guideline [CG81]: https://www.nice.org.uk/guidance/cg81

NICE. (2020, September 7). Alpelisib in combination with fulvestrant for treating advanced hormone-receptor positive, HER2-negative, PIK3CA-positive breast cancer [ID1412]. London, United Kingdom.

NICE. (2020, January 15). *nice.org.uk*. Retrieved from Palbociclib with fulvestrant for treating hormone receptor-positive, HER2-negative, advanced breast cancer: https://www.nice.org.uk/guidance/ta619/history

Northern cancer alliance. (2017, December 20). *Breast Cancer* . Retrieved from Chemotherapy Protocols & Prescriptions: http://www.northerncanceralliance.nhs.uk/advisory_group/breast-expert-advisory-group/breast-cancer-chemotherapy-protocols-prescriptions/

Novartis. (2016). *Submission template for the reconsideration of current CDF technologies under the new proposed CDF criteria.* NICE.

Novartis Pharmaceuticals . (2020). *Study Assessing the Efficacy and Safety of Alpelisib Plus Fulvestrant in Men and Postmenopausal Women With Advanced Breast Cancer Which Progressed on or After Aromatase Inhibitor Treatment. (SOLAR-1).* ClinicalTrials.gov.

Novartis Pharmaceuticals Corporation. (2019). PIQRAY® (alpelisib) tablets, for oral use. East Hanover, New Jersey, USA.

Palumbo, S. R. (2013). Which patients with metastatic breast cancer benefit from subsequent lines of treatment? An update for clinicians. *Therapy Advanced medical oncology*, 334-350.

Penton. (2021). Valuing health states. *Advanced Heath Economic modelling.* Erasmus University .

Pfizer. (2019). *Palbociclib (PD-0332991) in combination with fulvestrant for the treatment of hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer that has become resistant to previous endocrine therapy.* NICE.

Picot, C. B. (2011). The Clinical Effectiveness and Cost-Effectiveness of Bortezomib and Thalidomide in Combination Regimens with an Alkylating Agent and a Corticosteroid for the First-Line Treatment of Multiple Myeloma: A Systematic Review and Economic Evaluation. *Health Technology Assessment*.

Prieto, & Sacristán. (2003). Problems and solutions in calculating quality-adjusted life years (QALYs).

PSSRU. (2019). *Unit Costs of Health and Social Care 2019.* Canterbury: Personal Social Services Research Unit.

PSSRU. (2020). *Unit costs of health and Social care 2020.*

Pudar Hozo, D. H. (2005). Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methology*.

Robertson, B. T. (2016). Fulvestrant 500 mg versus anastrozole 1 mg for hormone receptor-positive advanced breast cancer (FALCON): an international, randomised, double-blind, phase 3 trial. *The Lancet*, 2997-3005.

Roche. (2011). *Bevacizumab in combination with capecitabine for the treatment of breast cancer Single technology appraisal.* NICE.

Rugo, A. Y. (2020). Time course and management of key adverse events during the randomized phase III SOLAR-1 study of PI3K inhibitor alpelisib plus fulvestrant in patients with HR-positive advanced breast cancer. *Annals of oncology*, 1001-1010.

Rugo, L. C.-B. (2021). Alpelisib plus fulvestrant in PIK3CA-mutated, hormone receptor-positive advanced breast cancer after a CDK4/6 inhibitor (BYLieve): one cohort of a phase 2, multicentre, open-label, non-comparative study. *The Lancet Oncology*, 489-498.

Saokaew, Tassaneeyakul, Maenthaisong, & Chaiyakunapruk. (2014, April 14). Cost-effectiveness acceptability curve. Thailand.

Sayed, I. K. (2019). Endocrine and Targeted Therapy for Hormone-Receptor-Positive, HER2-Negative Advanced Breast Cancer: Insights to Sequencing Treatment and Overcoming Resistance Based on Clinical Trials. *Frontiers in oncology*, 510.

Sculpher. (2004, August 17). The Use of a Probabilistic Sensitivity AnalysisThe Use of a Probabilistic Sensitivity Analysis for decision making: The example of Drug Eluting Stents. York, UK.

Sonnenberg, & Beck. (1993). *Markov Models in Medical Decision making.* Retrieved from Medical decision making: http://www.med.mcgill.ca/epidemiology/courses/EPIB654/Summer2010/Modeling/Markov%20modles%20in%20med%20dec%20making.pdf

Varley-Campbell, M. M.-B. (2016). *Everolimus, lutetium-177 DOTATATE and sunitinib for treating unresectable or metastatic neuroendocrine tumours with disease progression.* Exeter: University of Exeter Medical School.

Vera-Llonch M, W. D. (2011). Healthcare costs in women with metastatic breast cancer receiving chemotherapy as. *BMCCancer*, 250.

West Midlands Cancer alliance. (2018). *Management of Systemic Anti-cancer Therapy Induced Diarrhoea in Adult Patients v2.3.* NHS.

Xie, Z. G. (2019). Treatment after Progression on Fulvestrant among Metastatic Breast Cancer Patients in Clinical Practice: a Multicenter, Retrospective Study. *Scientific reports*, 1710.

Zhou, T. X. (2016). Systematic Literature Review of the Impact of Endocrine Monotherapy and in Combination with Targeted Therapy on Quality of Life of Postmenopausal Women with HR+/HER2- Advanced Breast Cancer. *Advances in therapy*, 2566-2584.

Zorginstituut Nederland. (2021). *Farmacotherapeutisch Kompas*. Retrieved from https://www.farmacotherapeutischkompas.nl/

Appendices

Appendix 1: List of abbreviations

ABC	Advanced breast cancer
AE	Adverse events
AI	Aromatase inhibitor
AIC	Akaike information criterion
ALT	Alanine Aminotransferase
aPPT	Activated Partial Thromboplastin Time
BNF	British National Formulary
CEAC	Cost-effectiveness acceptability curve
CE-plane	Cost-effectiveness plane
CI	Confidence interval
CT	Chemotherapy
CTCAE	Common Terminology Criteria for Adverse Events
ER	Estrogen receptor
ERG	Evidence review group
ET	Endocrine Therapy
FDA	Food and drug administration
FPG	Fasting plasma glucose
GGT	Gamma Glutamyl Transferase
GP	General practitioner
HCC	Half cycle correction
HCHS	Hospital and community health services
HER2	Human epidermal growth receptor-2
ICER	Incremental cost-effectiveness ratio
i.m.	intramuscular
KM-curve	Kaplan Meier curve
LY	Life year
NHS	National health service
NHSCII	National health service cost inflation index
NICE	The National Institute for Health and Care Excellence
QALY	Quality adjusted life year
QoL	Quality of life
ORS	Oral rehydration salts
OS	Overall survival
PD	Progressed disease
PFS	Progression-free survival
PIK3Ca	Phosphatidylinositol-4,5-biphosphate-3-kinase
PSS	Personal social services
PSSRU	Personal Social Services Research Unit
PSA	Probabilistic sensitivity analysis
PR	Progesterone receptor
RECIST	Response Evaluation Criteria In Solid Tumors
SA	Scenario analysis
SD	Stable disease
SE	Standard error
ST	Subsequent therapy

TA	Technology appraisal
TT	Targeted therapy
UK	United Kingdom
WTP	Willingness to pay

Appendix 2 KM-curves OS and PFS with corresponding data

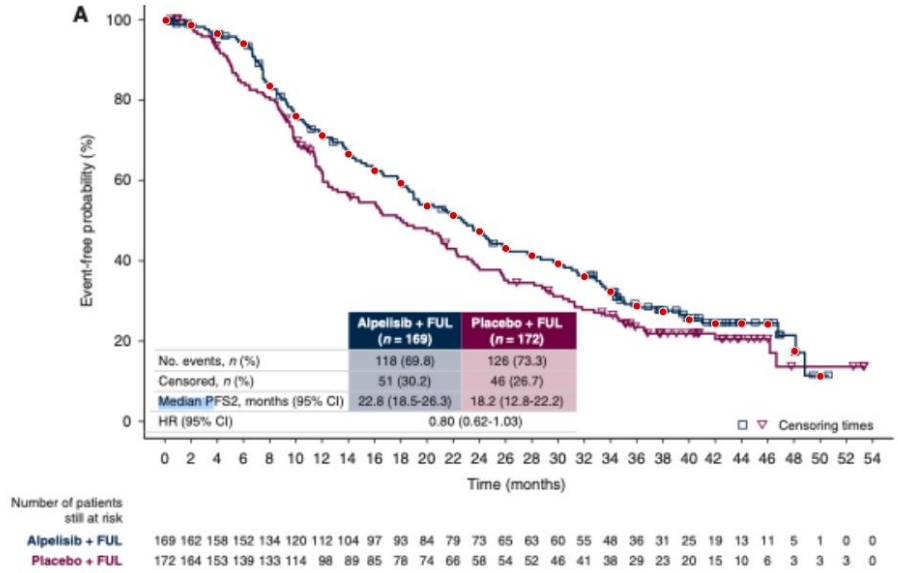
The obtained data on PFS and OS obtained from the published KM-curves are provided in Tables 22-25. The data was determined using webplotdigitizer 4.4, every two months on the curve, the survival probability was determined. This is shown in Figures 4-7.

Progression free survival alpelisib plus fulvestrant

Table 22 Probability of progression-free survival alpelisib plus fulvestrant

Months	**Probability of survival**
0,00	1,0000
2,00	0,9860
4,00	0,9600
6,00	0,9420
8,00	0,8350
10,00	0,7590
12,00	0,7110
14,00	0,6670
16,00	0,6220
18,00	0,5960
20,00	0,5380
22,00	0,5120
24,00	0,4720
26,00	0,4300
28,00	0,4120
30,00	0,3920
32,00	0,3600
34,00	0,3210
36,00	0,2880
38,00	0,2750
40,00	0,2540
42,00	0,2450
44,00	0,2450
46,00	0,2460
48,00	0,2130
50,00	0,1120

Figure 4 KM-curve progression free survival alpelisib plus fulvestrant

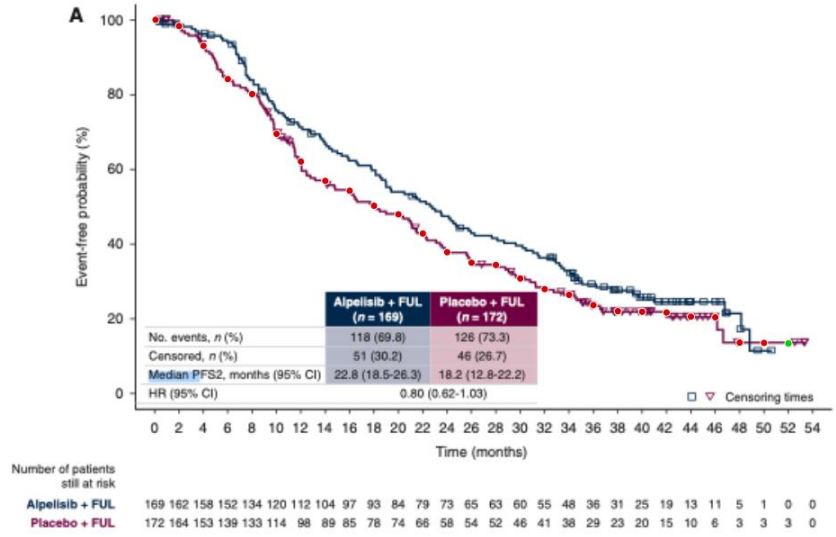


Progression free survival placebo plus fulvestrant

Table 23 Probability of progression-free survival placebo plus fulvestrant

Months	Probability of survival
0,00	1,0000
2,00	0,9840
4,00	0,9310
6,00	0,8410
8,00	0,8010
10,00	0,6950
12,00	0,6210
14,00	0,5690
16,00	0,5420
18,00	0,5020
20,00	0,4790
22,00	0,4280
24,00	0,3780
26,00	0,3500
28,00	0,3440
30,00	0,3080
32,00	0,2790
34,00	0,2640
36,00	0,2360
38,00	0,2200
40,00	0,2190
42,00	0,2170
44,00	0,2050
46,00	0,2040
48,00	0,1360
50,00	0,1350
52,00	0.1340

Figure 5 KM-curve progression free survival placebo plus fulvestrant

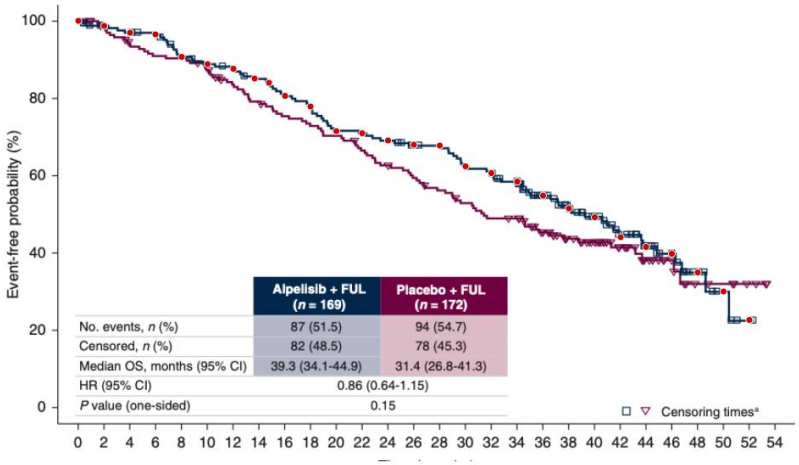


Overall survival alpelisib plus fulvestrant

Table 24 Probability of overall survival alpelisib plus fulvestrant

Months	Probability of survival
0,00	1,0000
2,00	0,9870
4,00	0,9690
6,00	0,9650
8,00	0,9070
10,00	0,8880
12,00	0,8760
14,00	0,8500
16,00	0,8060
18,00	0,7790
20,00	0,7150
22,00	0,7090
24,00	0,6910
26,00	0,6800
28,00	0,6780
30,00	0,6240
32,00	0,6060
34,00	0,5840
36,00	0,5480
38,00	0,5150
40,00	0,4920
42,00	0,4410
44,00	0,4160
46,00	0,3980
48,00	0,3500
50,00	0,3000
52,00	0,2270

Figure 6 KM-curve overall survival alpelisib plus fulvestrant

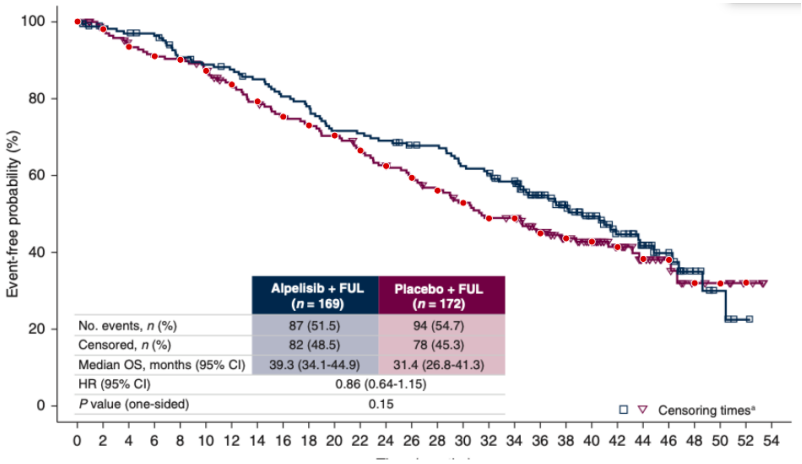


Overall survival placebo plus fulvestrant

Table 25 Probability of overall survival placebo plus fulvestrant

Months	Probability of survival
0,00	1,0000
2,00	0,9800
4,00	0,9340
6,00	0,9100
8,00	0,9010
10,00	0,8720
12,00	0,8360
14,00	0,7920
16,00	0,7530
18,00	0,7300
20,00	0,7040
22,00	0,6650
24,00	0,6240
26,00	0,5940
28,00	0,5610
30,00	0,5290
32,00	0,4880
34,00	0,4880
36,00	0,4490
38,00	0,4360
40,00	0,4280
42,00	0,4140
44,00	0,3830
46,00	0,3800
48,00	0,3200
50,00	0,3190
52,00	0,3210

Figure 7 KM-curve overall survival placebo plus fulvestrant



Appendix 3 Code used in R

```
rm(list=ls(all=TRUE))
library(survival)

data<-read.table("name file",header=T)
attach(data)
data

times_start <-c(  rep(start_time_censor, n_censors), rep(start_time_event, n_events) )
times_end <-c(  rep(end_time_censor, n_censors), rep(end_time_event, n_events)  )

#  adding times for patients at risk at last time point
times_start <- c(times_start, rep(30,4))
times_end <- c(times_end, rep(10000,4))

model_exp <- survreg(Surv(times_start, times_end, type="interval2")~1, dist="exponential")   # Exponential function, interval censoring
model_wei <- survreg(Surv(times_start, times_end, type="interval2")~1, dist="weibull")   # Weibull function, interval censoring
model_logn <- survreg(Surv(times_start, times_end, type="interval2")~1, dist="lognormal")   # Lognormal function, interval censoring
model_logl <- survreg(Surv(times_start, times_end, type="interval2")~1, dist="loglogistic")   # Loglogistic function, interval censoring

AIC_exp<- -2*summary(model_exp)$loglik[1] + 2*1   #  AIC for exponential distribution
AIC_exp
AIC_wei<--2*summary(model_wei)$loglik[1] + 2*2   #  AIC for Weibull, which is a 2-parameter distribution
AIC_wei
AIC_logn<--2*summary(model_logn)$loglik[1] + 2*2   #  AIC for lognormal, which is a 2-parameter distribution
AIC_logn
AIC_logl<--2*summary(model_logl)$loglik[1] + 2*2   #  AIC for log-logistic, which is a 2-parameter distribution
AIC_logl

#  Intercept and logscale parameters
intercept_exp <- summary(model_exp)$table[1]   # intercept parameter for exponential
intercept_exp
intercept_wei <- summary(model_wei)$table[1]   # intercept parameter for Weibull
log_scale_wei <- summary(model_wei)$table[2]   # log scale parameter for Weibull
intercept_wei
log_scale_wei

intercept_logn <- summary(model_logn)$table[1]   # intercept parameter for lognormal
log_scale_logn <- summary(model_logn)$table[2]   # log scale parameter for lognormal
intercept_logn
log_scale_logn
intercept_logl <- summary(model_logl)$table[1]   # intercept parameter for loglogistic
log_scale_logl <- summary(model_logl)$table[2]   # log scale parameter for loglogistic
intercept_logl
log_scale_logl

#  For the Probabilistic Sensitivity Analysis, we need the Cholesky matrix, which captures the variance and covariance of parameters
cholesky_exp<-t(chol(summary(model_exp)$var))   #  Cholesky matrix for exponential
```

```
cholesky_exp
cholesky_wei<-t(chol(summary(model_wei)$var))   #  Cholesky matrix for weibull
cholesky_wei
cholesky_logn<-t(chol(summary(model_logn)$var))   #  Cholesky matrix for lognormal
cholesky_logn
cholesky_logl<-t(chol(summary(model_logl)$var))   #  Cholesky matrix for loglogistic
cholesky_logl
```

Appendix 4 Output data R Studio

Table 26 Output R studio – Progression-free survival alpelisib plus fulvestrant

	exponential	Weibull	lognormal	loglogistic
AIC	865.6673	853.4655	849.045	849.6302
(rank)	(4)	(3)	(1)	(2)
intercept	3.41567	3.392823	3.041665	3.049701
log(scale)	-	-0.31575	-0.06843	-0.60164

Abbreviates: AIC, Akaike Information Criterion.

Table 27 Output R studio - Progression-free survival placebo plus fulvestrant

	exponential	Weibull	lognormal	loglogistic
AIC	908.9624	904.2392	897.7107	899.6041
(rank)	(4)	(3)	(1)	(2)
intercept	3.235709	3.237626	2.836375	2.843944
log(scale)	-	-0.20096	0.010144	-0.51479

Abbreviates: AIC, Akaike Information Criterion.

Table 28 Output R studio – Overall survival alpelisib plus fulvestrant

	exponential	Weibull	lognormal	loglogistic
AIC	752.2588	738.0955	749.4178	744.1864
(rank)	(4)	(1)	(3)	(2)
intercept	3.955918	3.810748	3.570522	3.578768
log(scale)	-	-0.41576	0.039601	-0.56642

Abbreviates: AIC, Akaike Information Criterion.

Table 29 Output R studio – Overall survival placebo plus fulvestrant

	exponential	Weibull	lognormal	loglogistic
AIC	801.4241	796.7661	807.4311	801.3926
(rank)	(3)	(1)	(4)	(2)
intercept	3.813805	3.734448	3.433907	3.44496
log(scale)		-0.24712	0.174202	-0.42965

Abbreviates: AIC, Akaike Information Criterion.

Table 30 Cholesky decompostions of variance - covariance matrices for progression-free survival

Progression-free survival

		Alpelisib			Placebo	
		intercept			intercept	
Exponential	intercept	0.092864		intercept	0.088411	
		intercept	log(scale)		intercept	log(scale)
Weibull	intercept	0.067734	0	intercept	0.072392	0
	log(scale)	0.001369	0.078452	log(scale)	-0.00337	0.074115
		intercept	log(scale)		intercept	log(scale)
Lognormal	intercept	0.078591	0	intercept	0.081983	0
	log(scale)	0.012349	0.069168	log(scale)	0.009073	0.066524
		intercept	log(scale)		intercept	log(scale)
Loglogistic	intercept	0.077755	0	intercept	0.082341	0
	log(scale)	0.006566	0.076984	log(scale)	0.004676	0.073856

Table 31 Cholesky decompostions of variance - covariance matrices for overall survival

Overall survival

		Alpelisib			Placebo	
		intercept			intercept	
Exponential	intercept	0.106607		intercept	0.101543	
		intercept	log(scale)		intercept	log(scale)
Weibull	intercept	0.074187	0	intercept	0.082693	0
	log(scale)	0.030411	0.090801	log(scale)	0.025851	0.087584
		intercept	log(scale)		intercept	log(scale)
Lognormal	intercept	0.097241	0	intercept	0.106156	0
	log(scale)	0.029665	0.077005	log(scale)	0.026486	0.075078
		intercept	log(scale)		intercept	log(scale)
Loglogistic	intercept	0.085027	0	intercept	0.093278	0
	log(scale)	0.020822	0.09009	log(scale)	0.018292	0.086847

Appendix 5 Survival curves and extrapolations

Figure 8 Extrapolations progression-free survival alpelisib plus fulvestrant

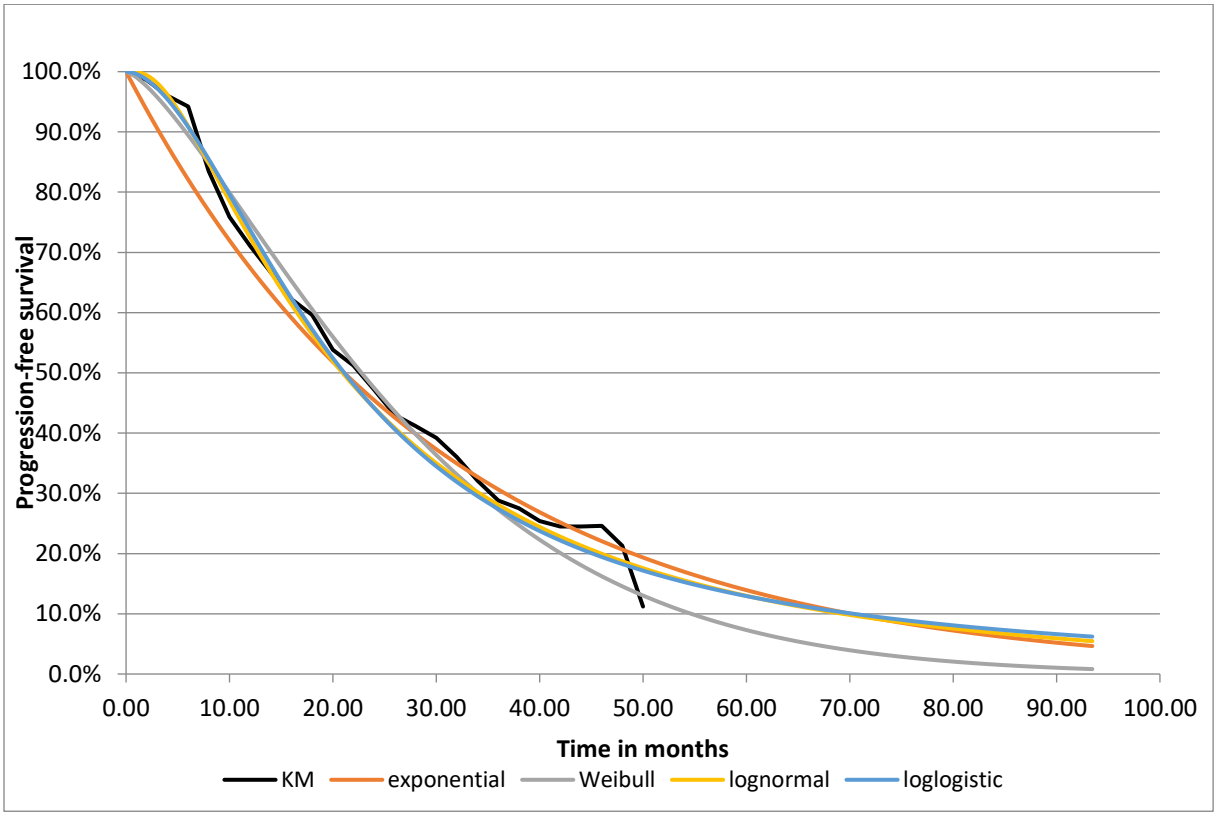


Figure 9 Extrapolations progression-free survival placebo plus fulvestrant

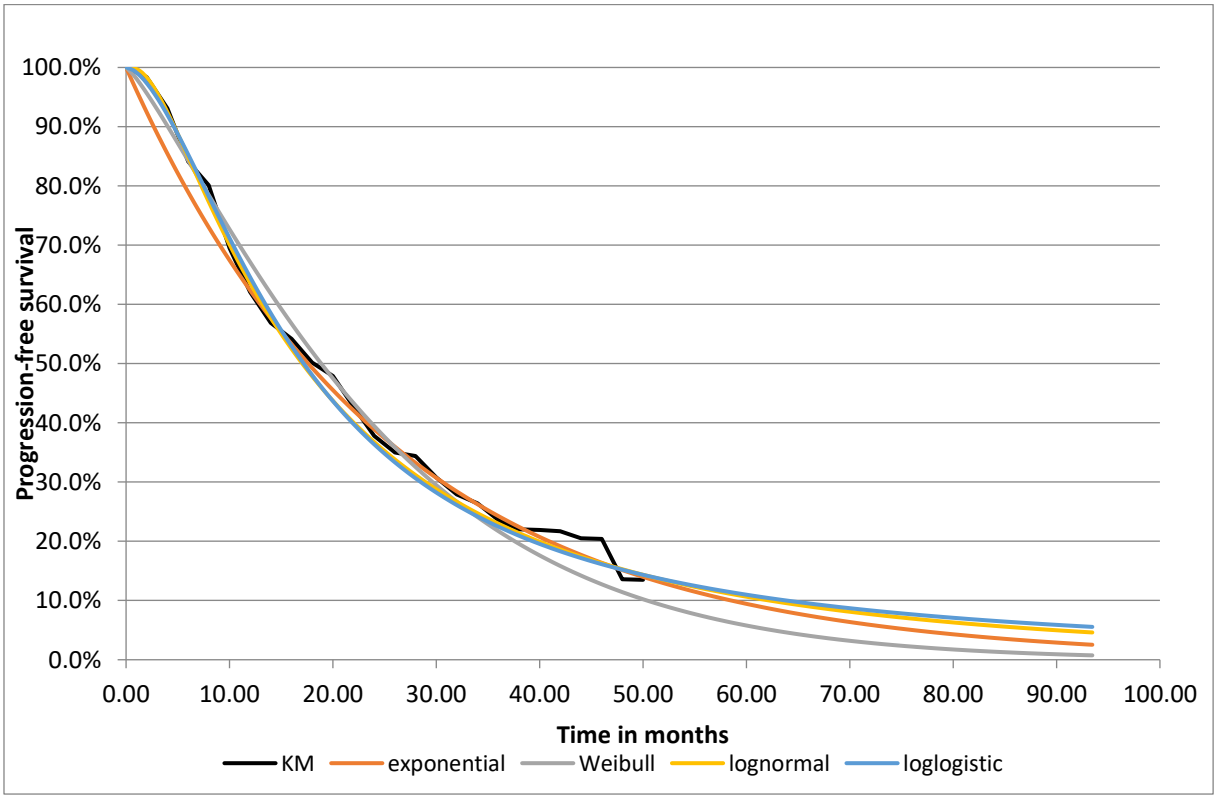


Figure 10 Extrapolations overall survival alpelisib plus fulvestrant

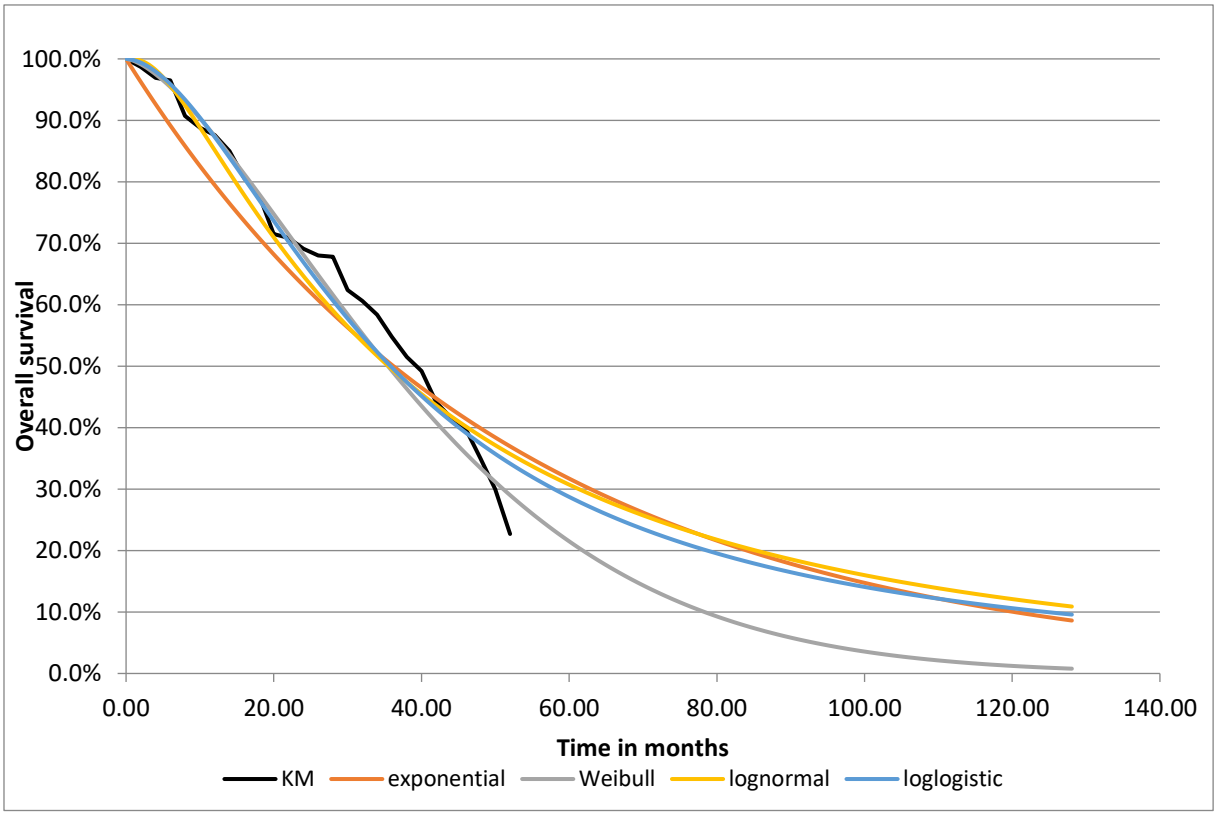
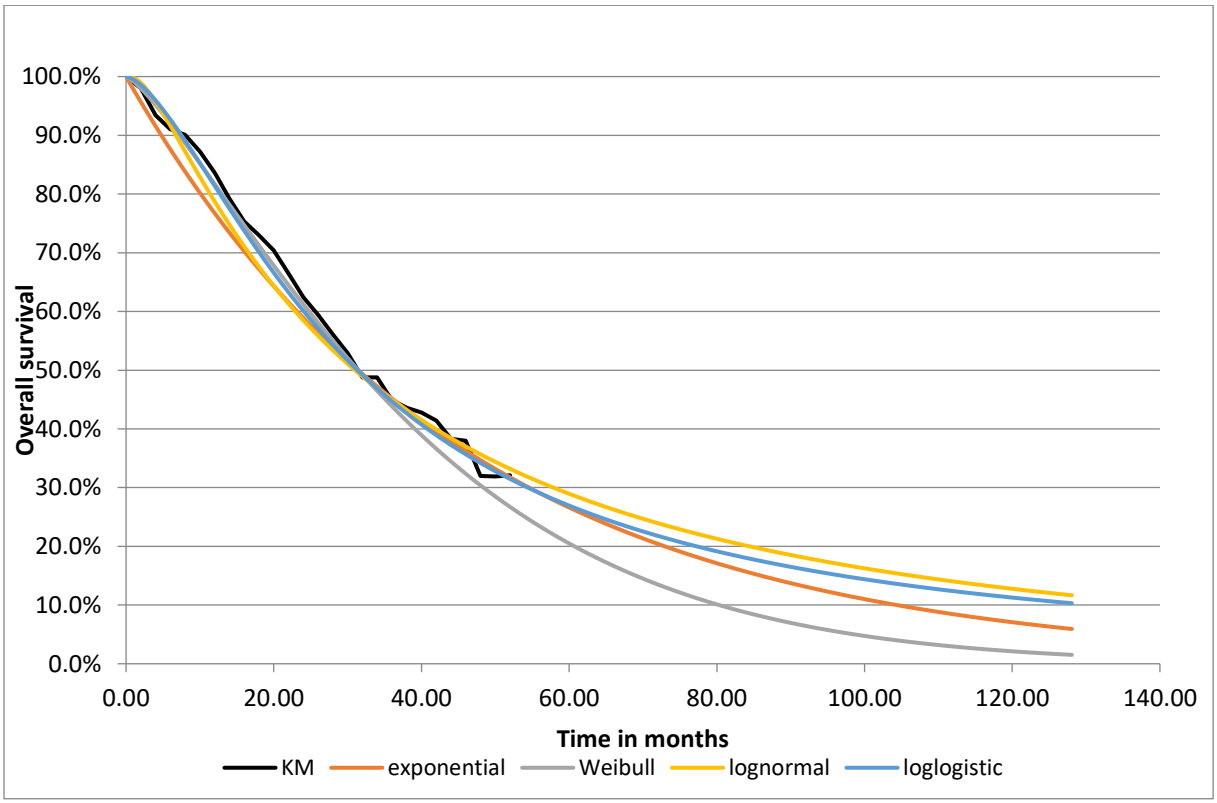


Figure 11 Extrapolations overall survival placebo plus fulvestrant



Appendix 6 Incidences of adverse events in the SOLAR-1 trial

Table 32 Most frequently reported adverse events (≥20% incidence of any grade event in either treatment group) in the safety population

AE, *n* (%)	Alpelisib plus fulvestrant (*n* = 284)					Placebo plus fulvestrant (*n* = 287)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Any AE	282 (99.3)	12 (4.2)	54 (19.0)	183 (64.4)	33 (11.6)	264 (92.0)	69 (24.0)	92 (32.1)	87 (30.3)	15 (5.2)
Hyperglycemia[b]	181 (63.7)	32 (11.3)	45 (15.8)	93 (32.7)	11 (3.9)	28 (9.8)	19 (6.6)	7 (2.4)	1 (0.3)	1 (0.3)
Diarrhea	164 (57.7)	93 (32.7)	52 (18.3)	19 (6.7)	0	45 (15.7)	30 (10.5)	14 (4.9)	1 (0.3)	0
Nausea	127 (44.7)	90 (31.7)	30 (10.6)	7 (2.5)	0	64 (22.3)	49 (17.1)	14 (4.9)	1 (0.3)	0
Decreased appetite	101 (35.6)	75 (26.4)	24 (8.5)	2 (0.7)	0	30 (10.5)	21 (7.3)	8 (2.8)	1 (0.3)	0
Rash[c]	101 (35.6)	48 (16.9)	25 (8.8)	28 (9.9)	0	17 (5.9)	14 (4.9)	2 (0.7)	1 (0.3)	0
Vomiting	77 (27.1)	64 (22.5)	11 (3.9)	2 (0.7)	0	28 (9.8)	18 (6.3)	9 (3.1)	1 (0.3)	0
Decreased weight	76 (26.8)	34 (12.0)	31 (10.9)	11 (3.9)	0	6 (2.1)	1 (0.3)	5 (1.7)	0	0
Stomatitis	70 (24.6)	39 (13.7)	24 (8.5)	7 (2.5)	0	18 (6.3)	15 (5.2)	3 (1.0)	0	0
Fatigue	69 (24.3)	36 (12.7)	23 (8.1)	10 (3.5)	0	49 (17.1)	36 (12.5)	10 (3.5)	3 (1.0)	0
Asthenia	58 (20.4)	25 (8.8)	28 (9.9)	5 (1.8)	0	37 (12.9)	29 (10.1)	8 (2.8)	0	0

Abbreviates: AE, adverse events.

Source: (Rugo, 2020)

Appendix 7 Elaborated equations duration adverse events

Mean $x = \frac{a+2m+b}{4}$

Variance range/6 for any random distribution

$m = median$

$a = lower\ limit\ range$

$b = higher\ limit\ range$

Source: (Pudar Hozo, 2005)

Hyperglycaemia

$m = 6\ days$

$a = 4\ days$

$b = 7\ days$

Mean $x = \frac{4+2*6+7}{4} = 5.75$

Variance $s^2 = \frac{7-4}{6} = 0.5$

s.e. $s = \sqrt{0.5} = 0.70$

Diarrhoea

$m = 18\ days$

$a = 9\ days$

$b = 45\ days$

Mean $x = \frac{9*2*18+45}{4} = 22.5$

Variance $s^2 = \frac{45-9}{6} = 6$

s.e. $s = \sqrt{6} = 2.45$

Rash

$m = 11\ days$

$a = 8\ days$

$b = not\ evaluable$

For the upper limit is assumed four times the lower limit to median, because in some cases rash can be very persistent, thus 23 days.

Mean $x = \frac{8+2*11+23}{4} = 13.25$

Variance $s^2 = \frac{23-8}{6} = 2.5$

s.e. $s = \sqrt{2.5} = 1.58$

Appendix 8 First new antineoplastic medication after discontinuation of study treatment, cohort of patients with PIK3CA-mutated cancer

Patients, *n* (%)	**Alpelisib + fulvestrant (*n* = 169)**	**Placebo + fulvestrant (*n* = 172)**
Patients starting subsequent medication/patients discontinuing treatment, *n/N* (%)	116[a]/148 (78.4)	134[a]/164 (81.7)
Chemotherapy	38 (32.8)	49 (36.6)
Chemotherapy + other[b]	20 (17.2)	26 (19.4)
Hormonal therapy alone	20 (17.2)	21 (15.7)
Hormonal therapy + other[c]	37 (31.9)	35 (26.1)
Everolimus	20 (17.2)	21 (15.7)
CDK4/6i	17 (11.5)	22 (13.4)
Targeted therapy alone	1 (0.1)	2 (1.5)
Other	0	1 (0.1)

A patient was counted only once in one of the medication types. Medication type was based on medical review.

CDK4/6, cyclin-dependent kinase 4/6.

a Used as the denominator for the percentages.

b Includes patients who received chemotherapy plus hormonal therapy.

c Includes patients who received hormonal therapy plus targeted therapy plus other.

Table 33 Subsequent therapy after progression on alpelisib plus fulvestrant or placebo plus fulvestrant, as published by André, at al.

Source: (André, et al., 2021)