Cost-Effectiveness of Alpelisib for Advanced Breast Cancer in a Dutch Setting

Master Thesis Health Economics Policy & Law

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Summary

Background A recent randomized controlled trial called SOLAR-1 evaluated the efficacy and safety of the drug alpelisib in combination with fulvestrant. The population of the trial was patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) PIK3CA mutated advanced breast cancer (ABC) after progressed on hormonal therapy. Based on the trial, it was concluded that treating PIK3CA-mutated, HR+/HER2- ABC patients with alpelisib and fulvestrant prolonged their progression-free survival compared to treatment with fulvestrant only. Therefore, alpelisib was granted market access by the European Medicines Agency. Currently, alpelisib is reimbursed in the Netherlands without assessing the cost-effectiveness. However, analysing the cost-effectiveness of alpelisib in combination with fulvestrant is necessary due to the scarcity of resources in the healthcare sector and its implications. Therefore, this research aims to evaluate the cost-effectiveness of alpelisib combined with fulvestrant relative to fulvestrant only in HR+/HER2- ABC patients with a PIK3CA mutation after disease progression following hormonal monotherapy.

Methods To assess the cost-effectiveness of alpelisib in combination with fulvestrant compared to fulvestrant only, a partitioned survival model was developed with the three mutually exclusive health states: progression-free, progressed disease and death. The cost-effectiveness was measured from a societal perspective in the Dutch healthcare setting over a lifetime horizon. Hereby costs were expresses in monetary units and effects in quality-adjusted life years (QALYs). Input parameters of this model were retrieved from the literature. A base case incremental cost-effectiveness ratio (ICER) was computed on the basis of all input parameters of the model. Furthermore, deterministic sensitivity analyses (DSAs), a probabilistic sensitivity analysis (PSA) and various scenario analyses were assessed to evaluate the sensitivity of the base case ICER. The base case ICER and the ICERs computed from the sensitivity and scenario analyses were benchmarked against the social willingness-to-pay (WTP) threshold of € 80,000 per QALY.

Results The effects gained in the alpelisib in combination with fulvestrant group are 3.05 QALYs or 4.51 life years. The costs for this intervention are estimated at € 314,094. The major driver of the costs were the drug acquisition costs of € 98,962 for alpelisib. For the fulvestrant group, the effects gained are 2.76 QALYs or 4.08 life years and the costs are € 238,874. Therefore, the incremental effects are 0.29 QALYs and 0.43 life years and the incremental costs are € 75,220. This leads to a base case ICER of € 259,802 per QALY and € 173,239 per life year. Compared to the WTP threshold of € 80,000 per QALY this treatment is not considered cost-effective. The scenario and sensitivity analyses confirm this result. The DSAs concluded that the base case ICER is the most sensitive to variation in health state utilities

and the dosage of alpelisib. One of the scenario analyses shows that the price of alpelisib needs to be reduced by at least 60% to turn alpelisib in combination with fulvestrant into a cost-effective treatment option compared to treatment with only fulvestrant.

Conclusion Alpelisib plus fulvestrant has a better effectiveness compared to fulvestrant only. However, treating HR+/HER2- ABC patients with a PIK3CA mutation with alpelisib and fulvestrant is not cost-effective from a Dutch societal perspective.

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1. Introduction

1.1. Problem analysis

Advanced breast cancer (ABC) is a major health issue because in general it is incurable and patients with ABC have a median survival of 2 to 3 years.[1] ABC can be locally advanced which means that the tumour has grown outside the body part it started in but did not spread out. ABC can also be metastatic which is the case when the tumour has spread to other parts of the body.[2] Approximately 5% of all breast cancer patients have metastatic breast cancer at initial diagnosis and another 20% to 30% of them develop ABC after the initial treatment of early-stage breast cancer. These patients are not eligible for curative treatment and therefore receive palliative treatment.[3,4]

There are different subtypes of breast cancer and the most common one is the hormone receptor-positive (HR+), human epidermal growth factor receptor 2 negative (HER2-) subtype, which accounts for approximately 70% of all breast tumours.[5] According to Dutch breast cancer guidelines, there are three types of palliative treatment for HR+/HER2- ABC patients. The first one is hormonal monotherapy; the second option is a combination of hormonal therapy and targeted therapy and the third option is with chemotherapy. Frequently used hormonal therapies include fulvestrant, tamoxifen and aromatase inhibitors and often used chemotherapies include anthracycline, taxanes and capecitabine.[6,7] For a long time, hormonal therapy and chemotherapy were the only options for HR+/HER2- ABC patients, whereby hormonal therapy was preferred due to its fewer (severe) side effects.[8] Since 2017 targeted therapy with CDK4/6 inhibitors is available as an additional treatment option.[9] During treatment, patients can experience the progression of the disease or become resistant to a certain treatment option. As a consequence, one of the other treatment options mentioned above needs to be considered. There is no consensus about the optimal treatment order of the three types of palliative treatments according to the Dutch breast cancer guidelines.[6]

1.2. Alpelisib

According to a recent study, around 40% of the HR+/HER2- breast cancer patients have an activating mutation of the PIK3CA gene.[10] PIK3CA mutations are linked with tumour growth, worse survival, and resistance to hormonal therapy.[10,11] Recently, pharmaceutical company Novartis developed a drug called Piqray, which contains the active substance alpelisib. According to the manufacturer, alpelisib is the first and only medicine on the market explicitly targeted at patients with a PIK3CA mutation in HR+/HER2- ABC.[12] A recent randomized controlled trial (RCT) called SOLAR-1 evaluated the efficacy and safety of alpelisib in combination with fulvestrant in men and postmenopausal women with ABC which

progressed after treatment with an aromatase inhibitor, which is a type of hormonal therapy.[13,14] So far, this is the only phase three RCT that assessed this with published results.[15]

In the SOLAR-1 trial patients with and without PIK3CA mutation were randomized over the treatment and comparator group. The treatment group received alpelisib (at a dose of 300 milligrams (mg) per day) in combination with fulvestrant (at a dose of 500 mg every 28 days and once on day 15).[10,13] The primary outcome measure of the trial was progression-free survival (PFS). PFS was defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. Secondary outcome measures were among other things overall survival (OS) and overall response rate. OS is defined as the time from date of randomization to date of death due to any cause and overall response rate is defined as the proportion of patients with best overall response or complete response or partial response.[13] Firstly, the median PFS in the PIK3CA mutation cohort from the SOLAR-1 trial was 11.0 months at a median follow-up of 20 months (95% confidence interval [CI], 7.5 to 14.5) in the treatment group. In the comparator group, the median PFS was 5.7 months (95% CI, 3.7 to 7.4). Therefore, it was concluded that treating PIK3CA-mutated, HR+/HER2- ABC patients with alpelisib and fulvestrant prolonged their PFS.[10] Secondly, the median OS in the PIK3CA mutation cohort from the SOLAR-1 trial was 39.3 months (95% CI, 34.1 to 44.9) for the intervention arm and 31.4 months (95% CI, 26.8 to 41.3) for the comparator arm. It was concluded that treating patients with PIK3CA-mutated, HR+/HER2- ABC with alpelisib and fulvestrant also prolonged their OS. However, this result was not significant.[16] Thirdly, the overall response rate of all the patients in the cohort with PIK3CA-mutated cancer was greater within the intervention group (26.6%) than within the comparator group (12.8%). Furthermore, the most common grade 3 or 4 treatment-related adverse events (TRAEs) in the treatment arm were hyperglycaemia (36.6%), rash (9.9%) and diarrhoea (6.7%). Moreover, 25% of the patients stopped with alpelisib based treatment due to TRAEs.[10] Based on this evidence, the European Medicines Agency authorized Piqray for use in the European Union in combination with fulvestrant for HR+/HER2- ABC in men and postmenopausal women with the PIK3CA gene mutation after the failure of hormone treatment.[17]

1.3. Societal and scientific relevance

In the Netherlands new intramural drugs, which can only be prescribed by specialists in hospitals such as alpelisib, are usually added to the basic benefit package without price arrangements.[18] However, sometimes assessing the cost-effectiveness is required to decide if the drug will be reimbursed for patients. This is the case when the expected budget impact of the drug is more than € 10 million per year and the costs per patient are more than € 50,000 per year.[18,19] The budget impact is calculated by

multiplying the annual number of patients who will receive the treatment by the costs per year related to the treatment per patient.[20] The key goal of assessing the cost-effectiveness of a new drug is to compare it with another intervention based on the effects and costs of both.[21] This is necessary because there is a rising number of new health interventions available to enhance the health of the population and the health care system. At the same time, the resources to provide the interventions are limited, which creates scarcity and urges health care policymakers to allocate resources. A cost-effectiveness analysis is a tool that is often used for the latter.[22] The expected total budget impact for alpelisib is estimated at € 9,348,000 for the Netherlands. This is based on the forecasted maximum of 300 patients per year who will need alpelisib in the Netherlands and the costs per patient per year, which are between € 29,520 and € 32,800.[23] Furthermore, in the Netherlands, the commission for the evaluation of oncology drugs (in Dutch: de commissie ter Beoordeling van Oncologische Middelen (BOM)) of the Dutch Association for Medical Oncology assesses the clinical value of newly registered medicines, treatment methods and treatment indications in the field of medical oncology. This is done with the intention to achieve better national coordination within the profession regarding the application of new and often expensive oncology drugs.[24] The commission BOM has the possibility of giving a negative assessment to drugs that are considered to have a too low value, even if they have been registered for use in the Netherlands. The opinion of the commission BOM is generally regarded as the norm by oncologists. In many situations, the use of a new drug is postponed until the BOM commission has reported positively about it. A negative assessment of the commission BOM can cause a drug to not be used or to be used less in practice.[25] This commission also assessed the clinical value of alpelisib and concluded that alpelisib deserves a positive advice because in combination with fulvestrant it prolongs the PFS compared to fulvestrant only in HR+/HER2- ABC patients with a PIK3CA mutation.[26] Although the budget impact is estimated to be just below € 10 million and the commission BOM gave a positive advice, it remains relevant to assess the cost-effectiveness of alpelisib. This is especially the case for new cancer drugs because between 2009 and 2013, a relatively short period, a lot of new oncology drugs have been approved by the European Medicines Agency. After approval, the drugs come on the European market while their effectiveness and cost-effectiveness at the time of approval are often marginal and/or uncertain.[27]

Secondly, the recently approved CDK4/6 inhibitors (palbociclib, ribociclib and abemaciclib), which were indicated for the same patient population as alpelisib, were initially not cost-effective according to the National Health Care Institute (NHCI). Only after price arrangements with the manufacturers, the inhibitors were reimbursed.[28,29,30] It could be also the case that alpelisib is not cost-effective at the initial price while it already is reimbursed. By assessing the cost-effectiveness, it can be determinate at what

price alpelisib is cost-effective. This can aid in the process of future price arrangements with the manufacturer of alpelisib.[31]

Thirdly, the SOLAR-1 trial published the effects expressed in the main outcome PFS and secondary outcome OS for a maximum of 31 months and 54 months, respectively.[13] PFS is an intermediate endpoint that is solely not sufficient for making decisions about prioritization in the metastatic cancer field.[32] This is because novel interventions that increase PFS may not be of sufficient worth to patients with advanced-stage cancer unless provided with sensible quantity or quality of life benefits. Therefore, the European Network for Health Technology Assessment advised that the PFS should be accompanied with OS and quality-adjusted life years (QALYs).[32,33] However, even though OS data is provided in the SOLAR-1 trial, these are short term data. Policymakers who need to make decisions about the allocation of scarce resources need longer-term estimates of anticipated survival, and a lifetime horizon is commonly more suitable. Computing long-term estimates of survival and expressing the effects in QALYs can be done when assessing the cost-effectiveness.[34,36]

Finally, evidence on the cost-effectiveness of alpelisib is limited. In the literature, only one abstract was found of a study that assessed the cost-effectiveness of alpelisib in the specified patient population. This abstract reported the aggregated incremental costs, effects and ICER for the United States from a payer perspective.[35] However, these are not applicable to the Dutch setting because in the Netherlands a societal perspective is recommended.[36] The perspective of analysis determines which types of costs and outcomes are included in the study. Therefore, results from different perspectives can differ from each other.[21]

1.4. Objective

This research aims to evaluate the cost-effectiveness of alpelisib combined with fulvestrant relative to fulvestrant only in HR+/HER2- ABC patients with a PIK3CA mutation after disease progression following hormonal monotherapy. This will be measured from a societal perspective in the Dutch healthcare setting over a lifetime horizon.

To reach the aim of this study, the following sub-questions are formulated:

1. What is an appropriate model type and structure for this economic evaluation?
2. What are the expected direct, indirect, medical and non-medical costs related to treatment with a combination of alpelisib and fulvestrant and with fulvestrant only?

3. What are the expected effects expressed in life years and QALYs related to treatment with a combination of alpelisib and fulvestrant and with fulvestrant only?
4. How sensitive are the outcomes to changes in the parameters related to treatment with a combination of alpelisib and fulvestrant and with fulvestrant only?

1.5. Overview

In the next chapter of this thesis, the theoretical background is presented in which relevant concepts are explained. The chapter after that is dedicated to the methods that are used to answer the research questions. This is followed by the results of this research. At last, a chapter is dedicated to the discussion points of this study accompanied by policy recommendations and a conclusion.

2. Theoretical background

2.1. Economic evaluation in health care

An economic evaluation in healthcare can be specified as the comparison of health care interventions, whereby the difference in costs are divided by the difference in effects between the intervention and the comparator (often the standard of care treatment) to obtain the incremental cost-effectiveness ratio (ICER).[21,36] Interventions are often drugs, but can also be for example medical devices, screenings and vaccinations programs.[36] Economic evaluations are important because they can yield value-for-money information to the ones deciding about the allocation of scarce resources in healthcare.[37] There are different types of economic evaluation in health care, whereby the cost-utility analysis (CUA) is the most common one used in practice. In essence, CUAs are a form of cost-effectiveness analysis and are often referred to as cost-effectiveness analysis. In a CUA the costs are measured and valued in monetary units. The effects in a CUA are measured and valued in healthy years which is usually measured as QALYs.[21]

2.2. Quality-adjusted life years

QALYs combine survival and the quality of life into one measure and can be used to compare the effects of interventions for diseases with various kind of health consequences.[21,38] That is why the single or multiple effects that are identified do not have to be the same for the treatment as for the comparator.[21] The survival is measured in the time unit years and the quality of life is measured in utilities. The utilities can be measured with several questionnaires.[21,39] The questionnaires to measure the utility are generic, which means that they are for general application and are universally usable because they usually measure a wide range of quality of life aspects (e.g. functional states, beliefs and social capabilities).[36,40] To calculate the QALYs, the utility which is between 0.0 (death) and 1.0 (perfect health) needs to be multiplied by the time in which a patient is experiencing a certain health condition (i.e. the survival).[36]

2.3. The EuroQol 5-dimension 5-level

The EuroQol 5-dimension 5-level (EQ-5D-5L) is a generic questionnaire that is recommended for measuring the utility of Dutch patients.[36] Furthermore, the questionnaire is preference-based, which entails that the utility index can be derived by utilising preference weights acquired from patients or the general public.[21,39] The EQ-5D-5L consists of five dimensions, which are mobility, self-care, usual activity, pain/discomfort, and anxiety/depression. Each dimension has five levels: no problems, slight problems, moderate problems, severe problems, and unable.[41] Patients can fill these questionnaires

and are thereby categorised into a predefined range of health states. After that, an index score, also known as a utility score, is allocated to each health state by using preference weights (tariffs). These tariffs can be valued by individuals who currently are in the health state (experience-based rating) or by a random sample of the general population (hypothetical rating).[21,42] Unfortunately, the EQ-5D-5L does not capture the TRAEs, especially for cancer treatments.[43] When TRAEs negatively affect the quality of life, they are called disutilities. Because these TRAEs can affect the quality of life, the disutilities and duration of TRAEs need to be incorporated in the CUA.[44]

2.4. Dutch pharmacoeconomic guidelines

There are several choices that needed to be made when carrying out an economic evaluation and these choices can have a major impact on the results.[21] The Dutch pharmacoeconomic guidelines were developed by the NHCI to enhance the comparability of results of economic evaluations in the Netherlands. The most important recommendations of these guidelines will be explained in this paragraph.[36]

First of all, it is recommended to perform an economic evaluation in the form of a CUA whereby the costs are expressed in monetary terms and the effects in QALYs. Secondly, the comparator in the analysis should be the standard care for the patient population in the Netherland. When conducting an evaluation, a societal perspective should be held, whereby the time horizon should be chosen in such a way that all consequences associated with the intervention and comparator under consideration are included in the analysis. That is why a lifetime horizon is recommended.[36]

For the costs, three categories need to be included, which are the costs within the healthcare sector such as costs for medicines and medical costs occurring in gained life years, the costs for patients and their families such as travel expenses to the hospital and the costs for other sectors such as productivity costs. For reference prices, the cost manual of the NHCI should be utilized where possible. Furthermore, QALYs should be measured with the EQ-5D-5L, a generic questionnaire filled by patients themselves. After that, the outcomes from that questionnaire should be valued by the Dutch general public. All costs and effects should be discounted to the same year, whereby the costs need to be discounted with a discount rate of 4% and the effects with a discount rate of 1.5%.[36]

Furthermore, to decide if a new intervention is cost-effective, the NHCI developed thresholds. These thresholds are the reference value for maximum incremental costs per QALY of an intervention versus comparator and are dependent on the burden of the disease.[45] As mentioned before, ABC is in general

incurable and patients with ABC have a low median survival, which leads to a relatively high disease burden.[1,9,46,47] That is why in the Netherlands the highest threshold of € 80.000 per QALY is utilized for ABC.[46]

Moreover, input parameters are surrounded by uncertainty. There are different types of analyses to address this uncertainty. It is advised to perform deterministic sensitivity analyses (DSAs), a probabilistic sensitivity analysis (PSA) and scenario analyses. DSAs are used to gain insight into the individual influence of a certain input parameter such as the unit price of a drug on the ICER. A PSA is performed to address the degree of sensitivity surrounding the ICER due to uncertainty in the input parameters of a model. At last, there are scenario analyses, which involves varying one or more inputs simultaneously to investigate if that leads to a cost-effective ICER.[36]

The following items should be reported in the evaluation: the total costs and effects, the incremental costs and effects, the ICERs, the DSAs with a tornado diagram and a table, the PSA with a cost-effectiveness-plane and cost-effectiveness acceptability curve and the scenario analyses with a table.[36] A tornado diagram portrays how variations in a specific input parameter affect the outcome. The diagram is piled in descending degree of width indicating that variations in the inputs at the top have the largest impact on the outcome, whereas variations in the inputs at the bottom show relatively minor impacts on the outcome.[48] Furthermore, a cost-effectiveness-plane is a figure with four quadrants in which the vertical axis shows the difference in costs and the horizontal axis the difference in effects between intervention and comparator. Moreover, a cost-effectiveness acceptability curve is a graph showing, for a range of thresholds, the likelihood that at a given threshold the intervention will be cost-effective.[36]

2.5. Health economic modelling

Health economic models are tools with a series of numbers and mathematical and statistical relationships to assist decision-making concerning the allocation of scarce resources.[49] They are often used for purposes such as extrapolating data. RCTs are the gold standard for examining causal links between an intervention and the outcome, as randomisation removes many of the biases that are common to other research designs.[50] Unfortunately, RCTs often show short-term effects of an intervention and for making a valid and reliable statement about the differences between the effectiveness and costs of the compared interventions the lifetime results are crucial. This is because costs and effects often do not occur simultaneously in time. By taking a relatively short timeframe, treatment-related improvements that occur years after the costs are made are left out of the evaluation, leading to the fact that some interventions are perceived as less cost-effective.[36,49]

Furthermore, models are used to combine different sources of data. This is necessary because data on effects and costs are usually not measured in one single study. RCTs of cancer drugs often provide the most important information on the effectiveness of the intervention expressed in PFS and/or OS. To conduct a CUA the costs and the quality of life are needed, which can be obtained from other sources. Finally, these different sources of information can differ in quality and can thereby create uncertainty in the results. To address this uncertainty, modelling can be used.[49]

2.6. Modelling approaches

An approach to modelling that is often utilized for economic evaluations is a Markov model. This type of model simulates patients through different health states. These health states are exhaustive and mutually exclusive, whereby the latter means that a patient can only be in one state at a time. A common structure of these models for oncology drugs are with the three health states: progression-free, progressed disease and death.[93] The number of patients in each state over time is determined by the set of transition probabilities between the health states over a series of periods called cycles.[38] The model simulation ends when all patients in the cohort are in a dead state to analyse long-term costs and effects.[49] Markov models use transition probabilities, costs and utilities as input parameters to estimate expected costs and effects of the different interventions.[51]

Furthermore, according to the National Institute for Health and Clinical Excellence, a partitioned survival model is the most frequently utilized decision modelling approach for appraisals of treatments for advanced or metastatic cancers.[39] This model is conceptually similar to a Markov model because both types of models track a hypothetical cohort over time as patients of the cohort transition among a series of exhaustive and mutually exclusive health states. In contrast to a Markov model, the number of individuals in each health state at subsequent points in time is not defined by transition changes. Rather, the model assesses the fraction of a model's population in every health state on the basis of survival curves.[52]

3. Research methods

3.1. Study design

The object of this research was to evaluate the cost-effectiveness of alpelisib combined with fulvestrant in HR+/HER2- ABC patients with a PIK3CA mutation after disease progression following hormonal monotherapy. The chosen comparator was fulvestrant monotherapy because this was one of the treatment options for patients with HR+/HER2-, PIK3CA mutated ABC in the Netherlands and it was the comparator in the SOLAR-1 trial.[6,10,13] To assess the cost-effectiveness a model was used and the input data of this model were retrieved from several published articles, reports and guidelines. Furthermore, in line with the Dutch pharmacoeconomic guidelines, a CUA was conducted from a societal perspective over a lifetime horizon (20 years) which included the costs and effects of all parties involved including the ones that fall outside the healthcare sector. Costs and effects were discounted by rates of respectively 4.0% and 1.5% to the year 2021. The model outcomes were costs, life years, QALYs and ICERs. To address uncertainty DSAs, a PSA and scenario analyses were conducted.[36]

3.2. Model structure

For this research, a partitioned survival model developed in Microsoft Excel was used. The model structure, which was based on models for patients with ABC from the literature[53-58], embodied three mutually exclusive health states: progression-free (PF), progressed disease (PD) and death (Figure 1). The cycle length was 28 days which corresponded with the frequency at which treatment regimens were administered in this patient population.[10,13] All patients started in the PF health state. During each cycle, patients in the PF health state could stay in the PF state or transfer to the PD state or the death state. Patients in the PD state could move to the death state or stay in the same state but could not move to the PF state. The model ended when all patients were in the death state, which is an absorbing state because once a patient is in that state is not possible to make a transition to any other state.[59] In the model a half-cycle correction was applied for certain costs and effects. Half-cycle correction is a method used to deal with the fact that events and transitions can occur at any point during the cycle and not necessarily at the start or end of each cycle.[51]

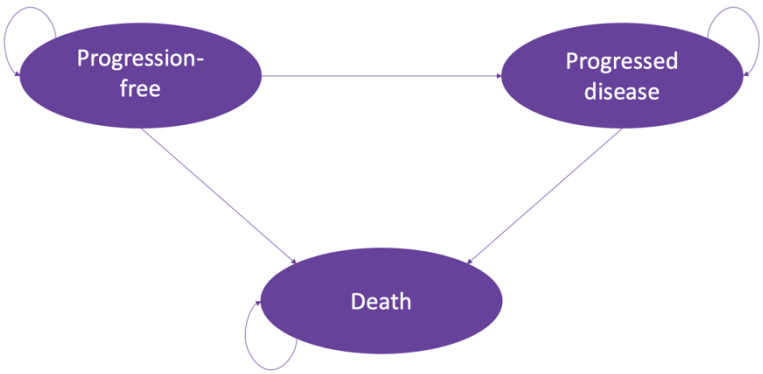

Figure 1 Three state partitioned survival model structure

3.3. Modelling survival curves

Estimates of proportions of patients that are still alive and progression-free are needed to calculate how many patients are in each health state in each cycle. In a partitioned survival model, individual patient data is needed to calculate these proportions.[60] For this study, the published results from the SOLAR-1 trial were used to recreate the individual patient data with the WebPlotDigitizer (version 4.4) software. In this software, the published images of the Kaplan-Meier curves were utilised to extract the underlying numerical data. The recreated data should lead to equivalent Kaplan-Meier curves as the published OS and PFS curves.[61] The X and Y coordinates of the curves and the number at risk were used to estimate the number of events and censorship according to the interpolation method presented by Hoyle & Henley.[62] Subsequently, these data were transferred into the software R Studio and fitted to four distributions, namely the exponential, the Weibull, the loglogistic and the lognormal distribution. After that, the distribution fits for OS and PFS for both treatment arms were assessed for all parametric distributions while using the Akaike Information Criterion (AIC), visual inspection and clinical plausibility such as presented by Latimer.[63] The AIC is a method based on in-sample fit to assess how likely a certain distribution can estimate future values. The distribution with the lowest AIC is the one with the highest likelihood.[64] The AIC only looks at the fit of the distributions with observed data, which says nothing about the validity of the extrapolated data. Furthermore, it was evaluated whether extrapolated data were clinically plausible. This was done by comparing extrapolations with published long-term survival data. Comparing against long-term data is necessary because the mean survival can be very responsive to the adopted model of this study and various mean survivals can arise from the model that fit the RCT data equally well. That is why additional data, beyond the trial input, is used to support selection of distributions.[65] For this, two sources were used: an RCT and the Dutch Cancer Registry. The RCT that was utilised assessed the efficacy of palbociclib plus letrozole versus letrozole only in HR+/HER2− ABC patients.[66] The 5-year OS of this trial was published and because the population of the RCT was comparable to the population of this study, it was seen as a valid source. In addition, data from the Dutch Cancer Registry was used for the 10-year OS because this was the only source that published the 10-year OS of metastatic breast cancer patients in the Netherlands.[67]

3.4. Calculating proportions

The partitioned survival model followed a cohort of 1000 fictitious patients based on the average patient characteristics from the SOLAR-1 trial.[13] The chosen parametric distribution for the PFS in both treatment groups was used to calculate the proportion of patients that are still in the PF state for each cycle of the partitioned survival model. Likewise, the chosen parametric distribution for the OS in both

treatment groups was used to calculate the proportion of patients that are in the death state for each cycle of the model. These proportions were set equal to the area under the created distribution for PFS and OS for both treatment groups. All these patients started in the PF state, which implicated that 1000 patients were in the PF state, 0 in the PD and death state in cycle 0. In each subsequence model cycle, the patients in the PF state were calculated by multiplying the total cohort size (1000 patients) by the proportion that was progression-free at that point in time. To calculate the patients in the death state for each cycle, the following equation was utilised: (1 – the proportion of patients alive in a certain cycle) x the total cohort size. The patients who were progressed in each cycle were calculated by subtracting the total cohort size with the patients in the PF and death state in the concerning cycle.

Utilising different distributions for PFS and OS may lead to unrealistic results in the analysis when the two distributions cross each other at a certain point in time. This can result in negative values for patients in the PD state because the proportion of patients that are alive is then smaller than the proportion of patients who are progression-free in certain cycles. This can happen because the two survival functions are extrapolated independently.[60] Therefore, it is important to verify if, in each cycle of the model, the proportion of OS was higher than the proportion of PFS. In this study, a correction was embedded in the model in such a way that the number of patients in the PF state was based on the lowest proportion between the OS and PFS in each cycle.

3.5. Model inputs

In this part, all the model inputs will be described. The exact value of every input for every cycle can be found in Table 1. If a model input is altered from the published value to make it applicable for this CUA, the published value and the alteration are described in Appendix 1 Table 2 to 9.

Health state utilities

The effects of this analysis needed to be expressed in life years and QALYs. To calculate the effects in life years for each cycle, the average number of patients in the concerning and subsequent cycle were multiplied by the time of every cycle (28 days) expressed in years. Thereafter, the life years gained in the cycle were multiplied by the utility values to calculate the effects in QALYs. This was done for all health states and in every cycle of the model. To collect these utilities for the different health states of the partitioned survival model, a targeted literature review was conducted which included the systematic literature review from Paracha et al.[68] The goal was to collect the utilities for the specific patient population i.e. Dutch HR+/HER2- ABC patients with a PIK3CA mutation. When health states utilities for the specific population were not available in the literature, subsequently a broader

population was held ranging from HR+/HER2- ABC patients to simply advanced cancer patients. Furthermore, utilities measured with the EQ-5D-5L were preferred over measurements with other instruments. When estimates based on the EQ-5D-5L were not available in the literature, data based on other questionnaires were utilised. The search strategy for the review was done in the databases PubMed and MEDLINE with the search strategy included in Appendix 2. At last, utilities were also searched in published reports such as in economic evaluations of the NHCI. The utilities were calculated for each cycle in the treatment as well as the comparator group.

Treatment-related adverse events disutilities and durations

TRAEs can result in higher rates of morbidity and thereby adversely influencing health-related quality of life.[44] To estimate the QALYs lost due to TRAEs, the disutilities and the duration of those events were used. These QALYs were calculated as a one-off effect in the first cycle of the model. This was done by multiplying the duration of a TRAE (in years) with the disutility of that TRAE, the cohort size of the model and the incidence of the concerning TRAE. After that, this multiplication for all the TRAEs was added up to calculate the aggregated loss of effects expressed in QALYs. Disutilities were applied for all grade 3 and 4 TRAEs that occurred in more than 5% of patients in at least one of the treatment arms of the RCT, which were hyperglycaemia, diarrhoea and rash (Appendix 1 Table 2).[10,13] To collect data for TRAEs, a targeted literature review was conducted, just like for the health state utilities (Appendix 2). Hereby, the goal was also to collect this data for the specific patient population i.e. Dutch HR+/HER2- ABC patients with a PIK3CA mutation.

Costs

For this CUA a societal perspective was used, which implies that all costs related to the disease needed to be considered. All costs were based on the prices of 2021 for the Netherlands by utilizing consumer price indices of total goods published by the Statistics Netherlands (Appendix 1 Table 1).[69] Furthermore, for the conversion of costs expressed in foreign currency to euros, the purchasing power parities published by the Organisation for Economic Co-operation and Development was used.[70]

Direct medical costs for the progression-free health state

Screening costs

In order to detect if an HR+/HER2- ABC patient has a mutation in the PIK3CA gene, accurate screening is essential. The therascreen PIK3CA RGQ PCR Kit is a PCR-test for the detection of 11 mutations in the PIK3CA gene and can therefore identify if patients are eligible for treatment with alpelisib.[71,72] This test can be performed on the Rotor-Gene Q MDx 5plex High-Resolution Melt instrument.[72] To identify eligible patients, all patients with HR+/HER2- ABC need to be screened to detect if they have the genetic

mutation. This implied that there were also screening costs for patients without the PIK3CA mutation and these costs should be taken into account to make a proper comparison. Because 40% of all HR+/HER2- ABC patients had the mutation it was assumed that 2500 patients had to be tested to identify a treatment cohort of 1000 patient. Therefore, treatment costs for 2500 patients were added in the first cycle of the alpelisib group for screening.[10]

Drug acquisition costs

For the PF patients in the treatment arm, the drug acquisition costs were the costs for alpelisib and fulvestrant. For the PF patients in the comparator arm, the drug acquisition costs were only the costs for fulvestrant.[10,13] The drug prices were retrieved from medicijnkosten.nl and farmacotherapeutischkompas.nl.[73,74] These reference prices were multiplied by the recommended dose of the drug and the frequency of use per cycle. The recommended dose for alpelisib was 300 mg and for fulvestrant, this was 500 mg. The frequency of use per cycle was 28 times for alpelisib and for fulvestrant, this was 2 times in the first cycle and 1 time in subsequent cycles.[10,13]

Drug administration costs

Alpelisib is provided in a pill and was therefore not bounded with administration costs.[73] On the contrary, fulvestrant is provided as a solution that needs to be injected intramuscularly in the buttocks.[74] Because both groups received fulvestrant, there were drug administration costs for the intervention and comparator group. The costs are an aggregation of different costs, including the costs of admission day care unit, active healthcare professional time, premedication and consumables (Appendix 1 Table 3).[75]

Drug monitoring costs

Furthermore, both treatment groups incurred monitoring costs due to efficacy, safety and tolerability assessments. These costs were calculated by multiplying the resource use with the unit costs of the corresponding resource. Resources use of monitoring were obtained from the protocol of the SOLAR-1 trial and included imaging and laboratory assessments.[10] For this CUA all the mandatory imaging assessments to assess the efficacy were taken into account which included CT scans and MRI scans conducted every 8 weeks in the first 18 months (~20cycles) and after that every 12 weeks.[10] Besides the efficacy assessments, there were also safety and tolerability assessments conducted. According to the trial protocol safety was tracked by evaluating physical examination, height, weight, vital signs, ECOG performance status evaluation, 12 lead ECGs, cardiac imaging (ECHO, MUGA scan) and laboratory evaluations for haematology and biochemistry. For the physical examination, height, weight, vital signs,

ECOG performance status evaluation, 12 lead ECGs and cardiac imaging (ECHO, MUGA scan) it was assumed that they took place during one outpatient visit per cycle. The laboratory tests assessments included analysis of haematology, fasting chemistry, fasting plasma glucose, HbA1c, coagulation and fasting lipase and amylase (Appendix 1 Table 4).[10] Assessments that only took place at baseline, in the first and/or second cycle of the trial were not considered in this CUA because it was assumed that the costs for these assessments will be similar in the treatment and intervention group due to relatively small differences in the number of patients in each health state between the treatment and intervention group.

Treatment-related adverse events costs

The costs of TRAEs was calculated based on the incidence and unit costs of grade 3 and 4 TRAEs. The TRAEs were registered in the SOLAR-1 trial.[10,13] Only TRAEs of grade 3 or higher were included in this analysis because these are severe, undesirable and can lead to high care consumption such as hospitalization.[76] It was assumed that all patients that had a TRAE, were hospitalized and therefore all incurred inpatients care costs. For this analysis, only the following three TRAEs were relevant: hyperglycaemia, rash and diarrhoea (Appendix 1 Table 2).[10,13] The costs for TRAEs were charged as one-off costs in the first cycle of the PF state of both groups.

Direct medical costs for the progressed disease health state

Drug acquisition and administration costs

Once patients progress, the initial treatment, with alpelisib and fulvestrant or fulvestrant alone, was stopped.[10] The Dutch breast cancer guidelines did not determine what the treatment after progression must entail. Various options were possible, depending on the situation of a patient.[6,7] Therefore, the treatment regimens were based on an earlier CUA by the NHCI of the CDK4/6 inhibitor palbociclib. This CUA was conducted for HR+/HER2- ABC patients, which includes the patients with a PIK3CA gene mutation.[24] The PD health state consisted of a combination of active treatment and best supportive care. It was assumed that 83.3% of the patients in the PD state would receive an active treatment. The patients in the PD state were assumed to receive treatment with anastrozole (60%), capecitabine (20%), paclitaxel (10%) or docetaxel (10%). These proportions were also based on the CUA of palbociclib assessed by the NHCI.[30] Based on this, the costs per cycle for the acquisition and administration were calculated. It was assumed that patients keep receiving the exact treatment as long as they are in the PD state.

Monitoring costs

After progression, there were also monitoring costs related to the patient's treatment, which were not disclosed by the manufacturer of alpelisib. That is why the monitoring costs of the PD state were based on data of the cost-effectiveness by the NHCI of palbociclib in combination with fulvestrant versus the use of only fulvestrant. In this CUA of the NHCI, the patient population was Dutch HR+/HER2- ABC patients, which included patients with the PIK3CA. The resource use of monitoring patients in the PD health state consisted of outpatient visits, CT scans, MRI scans of the vertebral column, bone scans and CA 15-3 tests. It was assumed that the patients needed each of the four tests and an outpatient visit once every three months. There were only monitoring costs for the 83.3% of patients in the PD state that receive an active treatment.[30]

Best supportive care costs

Best supportive care can be defined as the best available care as assessed by the treating physician, according to the institutional guidelines.[77] In this study, best supportive care was provided when a patient stopped with any active treatment. Furthermore, it was also assumed to be equivalent to the best supportive care of palbociclib in combination with fulvestrant versus the use of only fulvestrant. Best supportive care was provided to 17.6% of the patients in the PD state. Best supportive care comprised of outpatient visits with a physician and outpatient visits with a nurse, whereby both took place every two cycles. Moreover, one visit per six months to the general practitioner was incurred for the best supportive care.[30] This resource use was multiplied by the reference prices of the Dutch costing manual.[36]

Costs for death health state

End of life costs

The costs made in the lasts 14 days of a patient's life can be considered as the end of life costs.[30] The end of life costs were based on the study of Bekelman and colleagues which investigated the mean hospital expenditure per capita of decedents older than 65 years who died with cancer. These costs were based on the last 30 days.[78] To transform the costs for the last 30 days to the costs for the last 14 days it was assumed that the latter were two-third of the costs for the last 30 days. This was in accordance with the CUA of palbociclib.[30]

Indirect medical costs

In this CUA the indirect medical costs were also included which were the healthcare costs occurring in life years gained due to the use of alpelisib. These costs were estimated with the tool called Practical Application to Include future Disease costs, version 3.0, of the Institute for Medical Technology Assessment.[79,80] The costs included the future costs related to diseases other than breast cancer. The

mean age in the SOLAR-1 trial was 63 years.[13] Therefore, it was considered that every patient in the cohort was of that age when they were diagnosed, which was the first cycle in the model. The future medical costs were only estimated for women because more than 99% of the participant in the trial were women.[13] The future annual health care expenditure in the last year and other years is placed in Appendix 1 Table 7. Each cycle, a patient got approximately 0.07666 (28/365.25) years older. Therefore, in each cycle, four weeks of future medical costs were charged for patients that were alive. Furthermore, for patients that had died the costs attached to the final life year were used. To prevent double-counting by charging for costs for being alive and dying in the identical year at the same time, the costs for other years charged for patients who have died in the last 13 cycles, which is equal to one year, were removed. The amount of new dead patients was gained with the next formula:

Newly died patients = $(1 - OS)_t - (1 - OS)_{t-1}$were t stands for the current cycle in the model, and t–1 the preceding cycle.

Direct non-medical costs

Travel costs

The travel costs were calculated for every time a patient had to go to the hospital or to the general practitioner. These costs were based on the average distance to the hospital of 7 kilometres, the average distance to the general practitioner of 1.1 kilometres and parking costs of € 3.02 per hospital visit.[36] It was assumed that patients had to travel to the hospital for the one-time screening of PIK3CA gene mutation before starting treatment with alpelisib. Furthermore, patients needed to travel to the hospital for every time they got a grade 3 or 4 TRAE, every time they have to get a treatment that could not be self-administrated and for every time they had to be monitored and need to discuss the results of the monitoring with a medical professional. For the best supportive care, patients also needed to travel to the general practitioner and to the hospital for outpatient visits. For the monitoring in the PD health state, it was assumed that for all the four test one consult took place to discuss the results and that only time travelling was needed for this each cycle.

Informal care costs

Informal care can be described as the unpaid care given to elderly and needy individuals by someone with whom they have a social relationship, for example a spouse or child.[132] The amount of informal care use was based on a study accessing the cost-effectiveness of nivolumab in advanced squamous cell carcinoma of the lung in the Netherlands. Therefore, it was assumed that the time for providing

informal care was on average 8 hours per week for the PF health state and 12 hours per week for the PD state.[76]

Indirect non-medical costs

Productivity costs

The indirect non-medical costs are the costs that are incurred outside the health care sector and not directly related to the treatment. These are mainly productivity costs due to the loss of working capability caused by the disease. To calculate this, the friction cost method was applied. The friction cost method is based on the idea that within a production process, ultimately everyone can be replaced. Productivity losses and additional productivity costs only occur during the period needed to fill the vacancy created by long absences. The length of this period depends, among other things, on the level of unemployment and the degree of mobility in the labour market. Productivity costs may arise during this adjustment period, the so-called friction period, due to a temporary decrease in production. Secondly, it may exist because extra costs have to be incurred to maintain production. At last, it could be caused by a combination of both possibilities.[36,81]

The productivity costs were calculated for every cycle by multiplying the average wage, the number of newly progressed patients in the cycle, the average hours of work per cycle, the friction period and the net employment rate. The productivity costs were applied in the first 3 years and 4 months (~ 43 cycles). This is because the retirement age in the Netherlands was 66 years and 4 months for 2021, while the mean age in the SOLAR-1 trial was 63 years.[13,82] Furthermore, the productivity costs were applied to the newly progressed patients because it was assumed that only patient in the PD health state did incur these productivity costs.[46]

The average wage was obtained from the Dutch economic evaluation manual.[36] Secondly, the average hours of work and the net employment rate were based on the data of the first quarter of 2021 retrieved from the database of the Statistics Netherlands.[83,84] The net employment rate was used because it was assumed that not every patient in the cohort was working. The average hours of work per week was calculated by taking the value for the age category 55-65 years. This was done because the median age in the trial was 63 years.[13] In addition, the friction period was estimated based on data of the Statistics Netherlands of open and fulfilled vacancies the friction period. These data were based on the annual numbers of 2020 because the annual numbers of 2021 were not yet available.[85] The friction period was calculated with the following formula:

Friction period = 365 / (fulfilled vacancies / open vacancies) + 4 weeks

These four weeks are an estimation of the period that employers are assumed to use before deciding to post a vacancy for a temporary or permanent replacement of the employee who is absent due to illness.[36]

3.6. Model output

The total mean costs per patients in the fulvestrant group was subtracted from the total mean costs per patient in the alpelisib group. These incremental costs were divided by the incremental health effects in QALYs and life years. The incremental effects were obtained by subtracting the mean QALYs and life years per patient in the alpelisib group with the mean QALYs and life years per patient in the fulvestrant group. The ICER was set against the societal willingness-to-pay (WTP) threshold. The disease burden of HR+/HER2- ABC is 0.85-0.88 on a scale from 0 to 1. Because the burden is higher than 0.7 the disease falls in the highest burden-of-disease cluster and consequently, a WTP threshold of €80.000 per QALY gained was utilized.[46]

3.7. Sensitivity analyses

Deterministic sensitivity analyses

To determinate the sensitivity of the model to individual parameter modifications, DSAs were carried out. This is a type of sensitivity analysis, whereby the input parameters are allocated point estimate values.[86] This was conducted with the upper and lower bound value of the base case value for several individual parameters. This portrayed the effect of each parameter on the base case ICER. DSAs were done by varying some of the most influential model's inputs, which were the utilities of the PF and PD health state. The lower bound and the upper bound of the PF health state utility were 0.700 and 0.750, respectively. The lower bound and the upper bound of the PD health state utility were 0.582 and 0.701, respectively. Furthermore, the monitoring costs in the PD health state and the costs of intravenous chemotherapy administration were varied with 20%. In addition, the change in the base case ICER due to the variation of 5% in the dosage of alpelisib was assessed. The results of changes in these parameters were presented graphically in the form of a tornado diagram and were compared with results from the base case analysis.

Probabilistic sensitivity analyses

To explore the impact of the uncertainty around the input parameters, a PSA was conducted.[36] The following input parameters were varied: (dis)utilities, probabilities, proportions, durations, incidence,

costs of TRAEs, screening costs, drug acquisition costs (except for alpelisib), dosage of alpelisib, end of life costs, monitoring costs, administration costs, future medical care costs, travel costs, informal care use and productivity costs. It is noteworthy to state that the Dutch list price of alpelisib was seen as fixed for the PSA because the current single manufacturer of alpelisib has a monopoly on producing the drug.[105] Furthermore, the utility of the dead state was also assumed to be fixed. The dosages except for alpelisib were also assumed to be fixed because those dosages are nationally standardized per medical protocols.[74,97,98,99,100] The PSA was assessed by varying each parameter at the same time. Hereby, the probability distributions were fitted to the ranges of the input parameters of a model, and randomly samples from these distributions were drawn to yield an empirical distribution of the ICER.[86] These distributions were dependent on the type of parameter used. For the cohort of 1000 patients, 1000 sets of simulations (i.e. randomly picked input values) were assessed to generate 1000 different ICERs. For the (dis)utilities, incidences, and proportions beta distributions were utilized because these inputs are constrained on an interval of 0 to 1. For the costs and resource use, gamma distributions were used because these are constrained on an interval from 0 to positive infinity.[51] To calculate the PSA the following equations were utilized for each input parameter with a beta or gamma distribution in the model:

Alpha = base case value * (((base case value * (1-base case value)) / (standard error^2))-1)
Beta = (1-base case value) * (((base case value * (1-base case value)) / (standard error^2))-1)

If published standard errors were available, these were used as much as possible. If a standard error was not available, the second option was to estimate it from the standard deviation. However, in some cases assumptions for the standard errors had to be made, which led to the estimation of standard errors of 5%, 10% or 20% of the input parameters. These estimations were dependent on the level of expected variation of each parameter caused for example by their level of aggregation. That is why a relatively aggregated input parameter as the indirect medical costs was estimated to have a standard error that was 20% of the base case input value and the disutility values to have a standard error that was 10% of the base case input value. But the drug dosage of alpelisib to have a standard error that was 5% of the base case input value. For a set of more than two proportions that need to add up to one, a beta distribution could not be used. This was the case for the proportion of treatment in the PD health state, whereby there were four treatment options. Therefore, a Dirichlet distribution was used, which is an extension of beta for more than two options.[87] This was done by first calculating the values of the inverse gamma distributions of each proportion. After that, each inverse gamma estimate was divided by the sum of all the inverse gamma estimates to calculate the probabilistic parameter value.

The results of the PSA were plotted in a cost-effectiveness plane, which visualized the ICERs as the outcome of the simulations with the surrounding uncertainty. From the cost-effectiveness plane, a cost-effectiveness acceptability curve was plotted to visualize the probability that the intervention is cost-effective for a range of WTP thresholds.[36]

Scenario analyses

To investigate the impact of some of the main assumptions on the ICERs, scenario analyses were performed.[36] Scenario analyses were performed by changing the following parameters: treatment duration, treatment dosage, unit costs, distribution for OS, time horizon, utility for the PF health states and productivity costs. For the first scenario analysis, the treatment duration of alpelisib and fulvestrant is changed to a maximum of 29 months instead of a lifelong treatment. This was done because in the SOLAR-1 trial the median duration of exposure of alpelisib and fulvestrant was 5.5 months, ranging from 0.0 to 29.0 months. Furthermore, the median duration of fulvestrant only was 4.6 months, ranging from 0.0 to 30.1 months.[10] A second scenario analysis was conducted by changing the daily alpelisib dose from 300 mg to 200 mg. According to the trial protocol, there could be dose reduction of 50 mg or 100 mg.[10] The choice of a reduction of 100 mg was based on the fact that in the SOLAR-1 trial 74.0% of participants in the PIK3CA cohort who received alpelisib had at least one dose interruption during their treatment. Hereby, 68.6% was due to TRAEs. Furthermore, the share of patients with at least one dose reduction in the PIK3CA cohort who got alpelisib was 63.9%, whereby 62.1% was due to TRAEs. In addition, the dose discontinuation in the PIK3CA group who received alpelisib was 25.4%.[10] All these percentages were more than halved in the PIK3CA cohort of the comparator arm compared to the treatment arm (Appendix 3). Thirdly, a combination of the first and second scenario was analysed. Fourthly, alternative distributions for the OS were chosen because the extrapolation of the OS curves with different distributions were more diverged from each other after 20 years than the extrapolation of PFS. In addition, the unit costs of alpelisib was reduced with 60%. This was done because it was assumed that this could lead to an ICER below the WTP threshold of € 80,000 per QALY. Furthermore, an alternative time horizon was tested by considering a shorter time horizon of 10 years. This was done because commonly, the health gains occur later in time than the points where the costs are incurred.[36] The utility for the PF state was also increased by 0.1 in another scenario analysis. The last scenario analysis estimated the effect with no productivity costs. This was done because according to a study the average age of HR+/HER2- ABC women in Europe who receive initial treatment is 67.1 years and above the retirement age in the Netherlands of 66 years and 4 months.[82,88] The results of scenario analyses were presented in tabular form showing the incremental costs and effects and the ICER.

3.8. Validation of the model

During the development of the economic model of this CUA the recommendations for good modelling practices of Weinstein and colleagues were followed. This was done to enhance the quality of the model.[89] The model created was based on the literature on ABC.[53-58] Internal testing and debugging were conducted to confirm that the mathematical results were valid and in accordance with the model's design features. The model was monitored and reviewed throughout the modelling phase to detect any potential errors in data processing. Null and extreme input values were considered and the replication test with similar input values was conducted to test whether the expected output would be produced. Irregularities were identified and programming bugs were resolved.

Table 1 Model inputs

	Base case value	Distribution for sensitivity analyses	Standard error for sensitivity analyses	Alpha	Beta	Refe-rence
Health states utilities						
Utility progression-free	0.726	Beta	0.025	230.344	86.934	[46]
Utility progressed disease	0.642	Beta	0.060	40.345	22.498	[46]
Utility death	0	-	-	-	-	[36]
TRAEs disutilities						
Disutility hyperglycaemia	0.119	Beta	10%	87.981	651.355	[90,91]
Disutility rash	0.06	Beta	10%	93.940	1471.727	[92]
Disutility diarrhoea	0.103	Beta	10%	89.597	780.277	[61]
TRAEs incidences						
Hyperglycaemia (alpelisib and fulvestrant)	36.97%	Beta	10%	62.658	106.818	[93]
Rash (alpelisib and fulvestrant)	9.86%	Beta	10%	90.042	823.243	[93]
Diarrhoea (alpelisib and fulvestrant)	7.04%	Beta	10%	92.887	1226.113	[93]
Hyperglycaemia (fulvestrant)	1.05%	Beta	10%	98.944	9366.722	[93]
Rash (fulvestrant)	0.35%	Beta	10%	99.648	28488.352	[93]
Diarrhoea (fulvestrant)	0.70%	Beta	10%	99.296	14149.704	[93]

TRAEs median duration (days per year)						
Hyperglycaemia	6	Gamma	10%	100.000	0.060	[93]
Rash	11	Gamma	10%	100.000	0.110	[93]
Diarrhoea	18	Gamma	10%	100.000	0.180	[93]
Direct medical costs						
TRAEs costs (per event)						
Hyperglycaemia grade 3/4	€ 3608.62	Gamma	€ 566.56	40.568	88.952	[94]
Rash grade 3/4	€ 3727.36	Gamma	20%	25.000	149.094	[95]
Diarrhoea grade 3/4	€ 2329.60	Gamma	20%	25.000	93.184	[95]
Screening						
Screening for PIK3CA mutation	€ 105.96	Gamma	20%	25.000	4.238	[96]
Drug acquisition costs						
Unit costs alpelisib per 150 mg	€ 70.07	-	-	-	-	[73]
Unit costs fulvestrant per 50mg/ml for 5ml	€ 201.34	Gamma	10%	100.000	2.013	[74]
Unit costs anastrozole per mg	€ 0.26	Gamma	10%	100.000	0.003	[97]
Unit costs capecitabine per 150 mg for 60 pieces	€ 29.74	Gamma	10%	100.000	0.297	[98]
Unit costs paclitaxel per 6mg/ml for 5 ml	€ 66.79	Gamma	10%	100.000	0.668	[99]
Unit costs docetaxel per 20mg/ml for 1 ml	€ 90.37	Gamma	10%	100.000	0.904	[100]
Drug dosages						
Alpelisib for each cycle	8400 mg	Gamma	5%	400.000	21.000	[10,13]
Fulvestrant for the first cycle	1000 ml	-	-	-	-	[10,13]
Fulvestrant for subsequent cycles	500 ml	-	-	-	-	[10,13]
Anastrozole for each cycle	28 mg	-	-	-	-	[97]
Capecitabine for each cycle	46666.67 mg/m^2	-	-	-	-	[98]

Paclitaxel for each cycle	233.33 mg/m^2	-	-	-	-	99
Docetaxel for each cycle	133.33 mg/m^2	-	-	-	-	100
Probabilities of treatment administration for progressed disease						
Probabilities of receiving treatment	0.833	Beta	10%	15.867	3.181	46
Probabilities of receiving best supportive care	0.167	Beta	10%	83.133	414.669	46
Anastrozole	0.6	Dirichlet	-	-	-	46
Capecitabine	0.2	Dirichlet	-	-	-	46
Paclitaxel	0.1	Dirichlet	-	-	-	46
Docetaxel	0.1	Dirichlet	-	-	-	46
End of life						
End of life care costs in the last 14 days	€ 2692.43	Gamma	€ 82.05	1076.891	2.500	78
Resource use unit costs						
Intravenous administration health care costs	€ 752.91	Gamma	20%	25.000	13.261	75
Subcutaneous administration health care costs	€ 331.52	Gamma	20%	25.000	30.116	75
Outpatient (specialist) visit	€ 145.6	Gamma	10%	100.000	1.456	36
CT scan estimated average	€ 258.48	Gamma	10%	100.000	2.585	101
MRI scan estimated average	€ 423.30	Gamma	10%	100.000	4.233	101
Haematology	€ 1.16	Gamma	10%	100.000	0.012	102
Fasting chemistry	€ 83.26	Gamma	10%	100.000	0.833	102
Fasting plasma glucose	€ 0.95	Gamma	10%	100.000	0.009	103
HbA1c	€ 5.94	Gamma	10%	100.000	0.059	102
Coagulation	€ 3.03	Gamma	10%	100.000	0.030	102
Fasting lipase and amylase	€ 3.26	Gamma	10%	100.000	0.033	102
Outpatient nurse visits (haematology)	€ 56	Gamma	10%	100.000	0.560	36

General practitioner standard consult	€ 52.80	Gamma	10%	100.000	0.528	[36]
Monitoring costs progressed disease per cycle	€ 1905.49	Gamma	20%	25.000	76.220	[46]
Resource use per cycle						
Outpatient visits for imaging first 20 cycles	0.5	Gamma	10%	100.000	0.005	[10]
Outpatient visit for imaging after 20th cycle	0.33	Gamma	10%	100.000	0.003	[10]
CT scan in the first 20 cycles	0.25	Gamma	10%	100.000	0.003	[10]
CT scan in the after the 20th cycle	0.167	Gamma	10%	100.000	0.002	[10]
MRI-scan in the first 20 cycles	0.25	Gamma	10%	100.000	0.003	[10]
MRI-scan after the 20th cycle	0.167	Gamma	10%	100.000	0.002	[10]
Probability of having bone lesion in alpelisib group	77.5	Beta	10%	21.725	6.307	[10]
Probability of having bone lesion in fulvestrant group	70.3	Beta	10%	28.997	12.251	[10]
Outpatient visits for laboratory assessments	1	Gamma	10%	100.000	0.010	[10]
Haematology testing cycle 2	2	Gamma	10%	100.000	0.020	[10]
Haematology testing other cycles	1	Gamma	10%	100.000	0.010	[10]
Fasting chemistry testing from 2nd cycle	1	Gamma	10%	100.000	0.010	[10]
Fasting plasma glucose testing first 2 cycles	2	Gamma	10%	100.000	0.020	[10]

Fasting plasma glucose testing first 2 cycles from 3rd cycle	1	Gamma	10%	100.000	0.010	10
HbA1c testing cycle 2	1	Gamma	10%	100.000	0.010	10
HbA1c testing other cycles	0.33	Gamma	10%	100.000	0.003	10
Coagulation testing per cycle	0.5	Gamma	10%	100.000	0.005	10
Fasting lipase and amylase testing per cycle	1	Gamma	10%	100.000	0.010	10
Outpatient specialist visits per cycle for best supportive care	0.5	Gamma	10%	100.000	0.005	46
Outpatient nurse visits per cycle for best supportive care	0.5	Gamma	10%	100.000	0.005	46
General practitioner visits for best supportive care per cycle	0.15	Gamma	10%	100.000	0.002	46
Frequency of fulvestrant administration first cycle	2	-	-	-	-	10
Frequency of fulvestrant administration subsequent cycle	1	-	-	-	-	10
Frequency administration of paclitaxel every cycle	1.33	-	-	-	-	99
Frequency administration of docetaxel every cycle	1.33	-	-	-	-	100
Indirect medical costs						
Average costs other years year (63 till 82 years)	€ 9,608.91	Gamma	20%	*	*	80
Average costs last year (63 till 82 years)	€62,340.34	Gamma	20%	*	*	80
Direct non-medical costs						

Travel distance to the hospital in km	7	Gamma	10%	100.000	0.070	[36]
Travel distance to the general practitioner in km	1.1	Gamma	10%	100.000	0.011	[36]
Travel costs per km with car	€ 0.30	Gamma	10%	100.000	0.003	[36]
Parking costs	€ 4.80	Gamma	10%	100.000	0.048	[36]
Informal care per hour	€ 22.40	Gamma	10%	100.000	0.224	[36]
Hours of informal care in a week (PF state)	12	Gamma	20%	25.000	0.320	[76]
Hours of informal care in a week (PD state)	8	Gamma	20%	25.000	0.480	[76]
Indirect non-medical costs						
Hours of work per week	26	Gamma	20%	25.000	1.040	[84]
Replacement period in weeks	14.64	Gamma	20%	25.000	0.585	[36,85]
Productivity costs per hour	€ 50.56	Gamma	20%	25.000	2.022	[36]
Probability of having a job	63.8%	Beta	20%	8.412	4.773	[83]
Retirement age	66 years and 3 months	-	-	-	-	[82]
Patients characteristics						
Median age	63	-	-	-	-	[13]
Average body surface area in m^2	1.7	Gamma	5%	400.000	0.004	[104]

* the alpha and beta are not presented here because in the excel model the alpha and beta are based on the individual last year and other years cost parameters.

4. Results

4.1. Parametric distributions

Progression-free survival

In figure 2 and 3, the results from the SOLAR-1 trial and the modelled PFS curves with different parametric distributions are presented for the alpelisib plus fulvestrant and the fulvestrant group, respectively. The median PFS in the PIK3CA mutation cohort from the SOLAR-1 trial was 11.0 months (95% CI, 7.5 to 14.5) in the alpelisib plus fulvestrant group at a median follow-up of 20 months. In the fulvestrant only group the median PFS was 5.7 months (95% CI, 3.7 to 7.4). Therefore, it was concluded that treating patients with PIK3CA-mutated, HR+/HER2- ABC with alpelisib and fulvestrant prolonged their PFS.[10] The lognormal distribution yielded the lowest AIC for the PFS in both arms, which was 912 for the alpelisib group and 1015 for the fulvestrant group. All the other values for the AIC are in Appendix 4. Furthermore, the median PFS in the alpelisib group of the RCT was the closest to the median of the modelled PFS curves using a loglogistic and the lognormal distribution. The median PFS of the latter two were both 11.6 months. Other median estimates of the modelled PFS curve in the alpelisib group were 12.5 months with the exponential curve and 12.6 months with the Weibull curve. The median PFS in the fulvestrant group of the RCT was also the closest to the modelled median with the loglogistic curve (6.1 months). Other median modelled PFS values in the fulvestrant group were 7.8 months with the exponential curve, 7.5 months with the Weibull curve and 6.5 months with the lognormal curve. Moreover, all distributions had a good visual fit. This was accessed by looking at the overlap between the observed Kaplan Meier curves and the modelled distributions. For the PFS in both arms, the lognormal distribution was chosen based on the AIC, visual fit and median extrapolated PFS values.

Overall survival

In figure 4 and 5, the results from the SOLAR-1 trial and the modelled OS curves with different parametric distributions are presented for the alpelisib plus fulvestrant and the fulvestrant group, respectively. The median OS in the PIK3CA mutation cohort from the SOLAR-1 trial was 39.3 months (95% CI, 34.1 to 44.9) for the alpelisib plus fulvestrant group and 31.4 months (95% CI, 26.8 to 41.3) for the fulvestrant group. Hereby, the hazard ratio was 0.86 (95% CI, 0.64 to 1.15; P = 0.15).[16] The hazard ratio is the chance of the event (in this case death) occurring in the treatment arm divided by the chance of the same event occurring in the control arm.[106] A hazard ratio of 0.86 means that alpelisib plus fulvestrant provides a 14% risk reduction of death compared to fulvestrant only. It was concluded that treating patients with PIK3CA-mutated, HR+/HER2- ABC with alpelisib and fulvestrant prolonged their OS. However, this result was not significant.[16]

For the OS in the alpelisib plus fulvestrant and fulvestrant only group, the Weibull distribution yielded the lowest AIC and the loglogistic distribution yielded the second-lowest AIC (see Appendix 4). Furthermore, the median OS in the alpelisib arm of the RCT was the closest to the median survival modelled with the exponential curve (39.0 months). Other modelled median OS values in the alpelisib group were 37.8 months with the Weibull curve, 38.8 months with the lognormal curve and 38.6 months with the loglogistic curve. The median OS in the fulvestrant group of the RCT was the closest to the median survival modelled with the lognormal curve (31.5 months). Other modelled median OS values in the fulvestrant group were 32.2 months with the exponential curve, 32.3 months with the Weibull curve and 31.7 months with the loglogistic curve. In addition, all distributions for the intervention had a less good visual fit than for the comparator. This was accessed by looking at the overlap between the observed Kaplan Meier curves and the modelled distributions.

The extrapolated survival curves were compared to published 5- and 10-year OS rates of patients with ABC to see if the extrapolated survival curves yielded clinical plausible outcomes. The 5-year OS rates were obtained from the published long-term results of the PALOMA-1 RCT because this trial had a similar patient population as this study. In this RCT, patients with HR+/HER2- ABC were treated with palbociclib plus letrozole or letrozole only. The OS rate of patients with HR+/HER2- ABC treated with palbociclib plus letrozole or letrozole only in the intervention and the comparator arm after five years was estimated at 28%.[66] This value came the closest the OS rate with the loglogistic distribution in the alpelisib plus fulvestrant group (31.5%). The 5-year survival rates of other distributions were 34.5%, 24.2% and 34.3% for the exponential, the Weibull curve and lognormal curve, respectively. Furthermore, the 5-year survival rate from the PALOMA-1 trial was the closest to the OS rate of the exponential and loglogistic distribution in the fulvestrant only group after 5 years (27.5%). For the fulvestrant group, the 5-year survival rates of other distributions were 22.2% for the Weibull curve and 29.2% for the lognormal curve.

The 10-year survival rate was obtained from the Dutch Cancer Registry which includes all subtypes of metastatic breast cancer patients. The 10-year survival rate of metastatic breast cancer was 9%.[67] This value came the closest with the equivalent rate of the exponential and the loglogistic distribution for OS in the alpelisib plus fulvestrant group (11.9%). Other modelled 10-year survival rates were 1.6% and 14.8% for the Weibull and lognormal distribution, respectively. Furthermore, the 10-year survival rate from the Dutch Cancer Registry was the closest to the 10-year survival rate of the exponential distribution in the fulvestrant only group (7.5%). For the fulvestrant group, the 10-year survival rates of

other distributions were 2.8%, 12.9% and 11.7% for the Weibull curve, the lognormal curve and the loglogistic curve, respectively.

The loglogistic is one of the closest estimates to the long-term survivals and the median survivals in the SOLAR-1 trial. Furthermore, the loglogistic distribution yields the second-lowest AIC in both treatment groups and has a good visual fit in the fulvestrant group. Therefore, the loglogistic distribution was chosen for the alpelisib plus fulvestrant group and the fulvestrant only group.

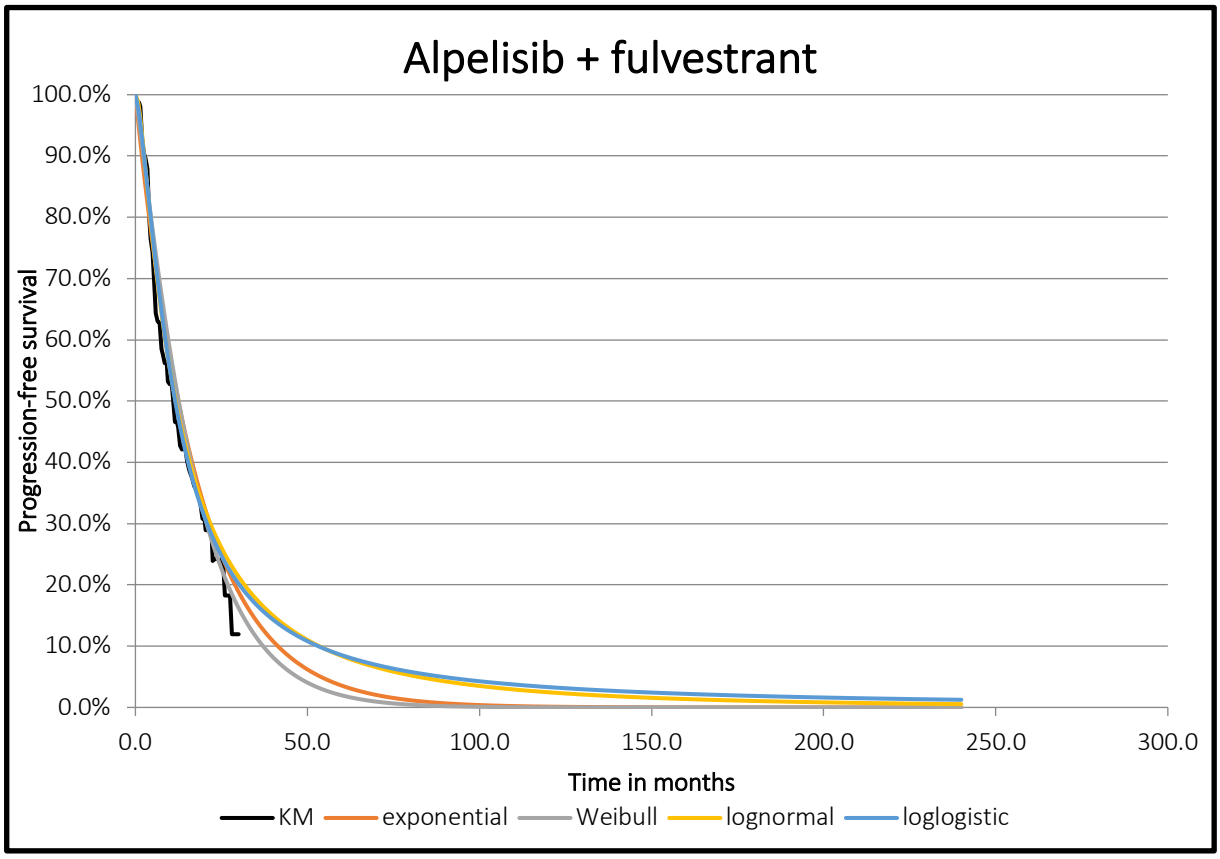

Figure 2 Extrapolation of the progression-free survival for the alpelisib plus fulvestrant group including the Kaplan Meier (KM) curve

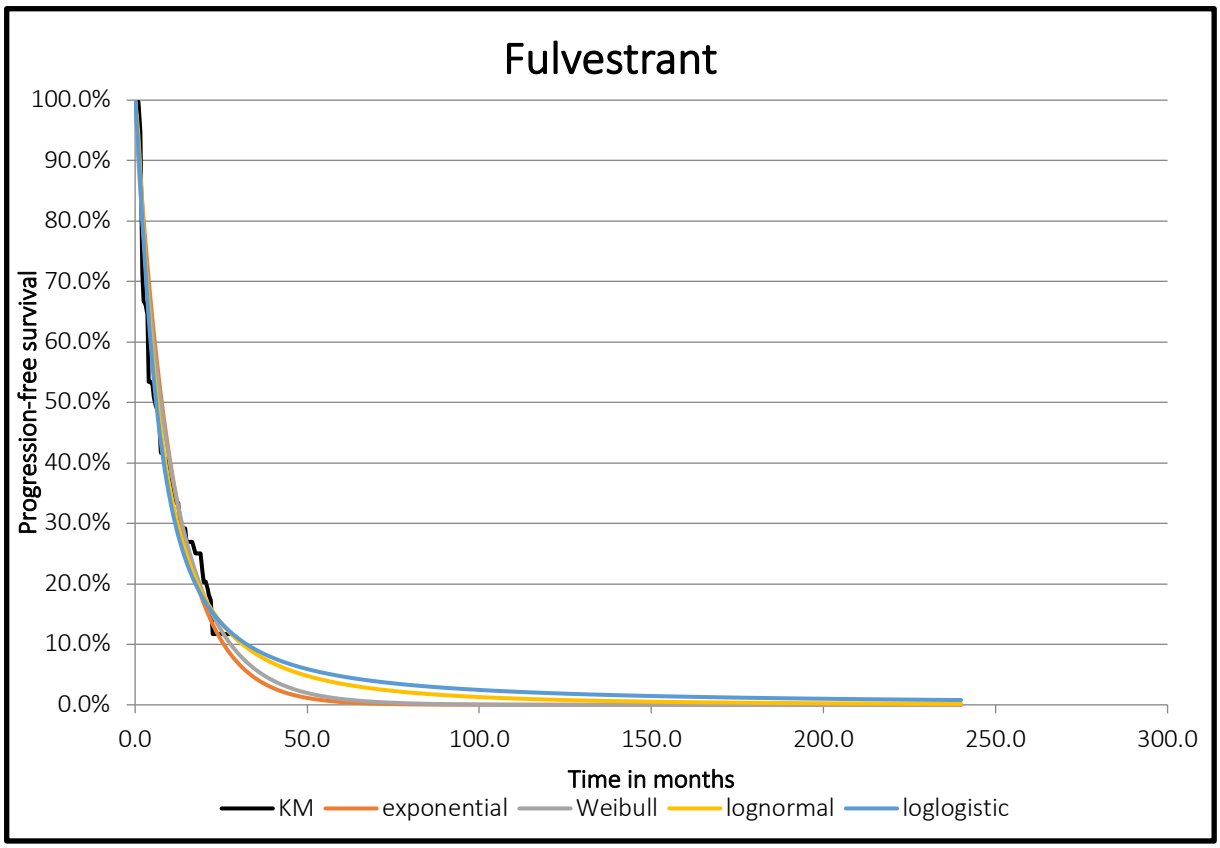

Figure 3 Extrapolation of the progression-free survival for the fulvestrant group including the Kaplan Meier (KM) curve

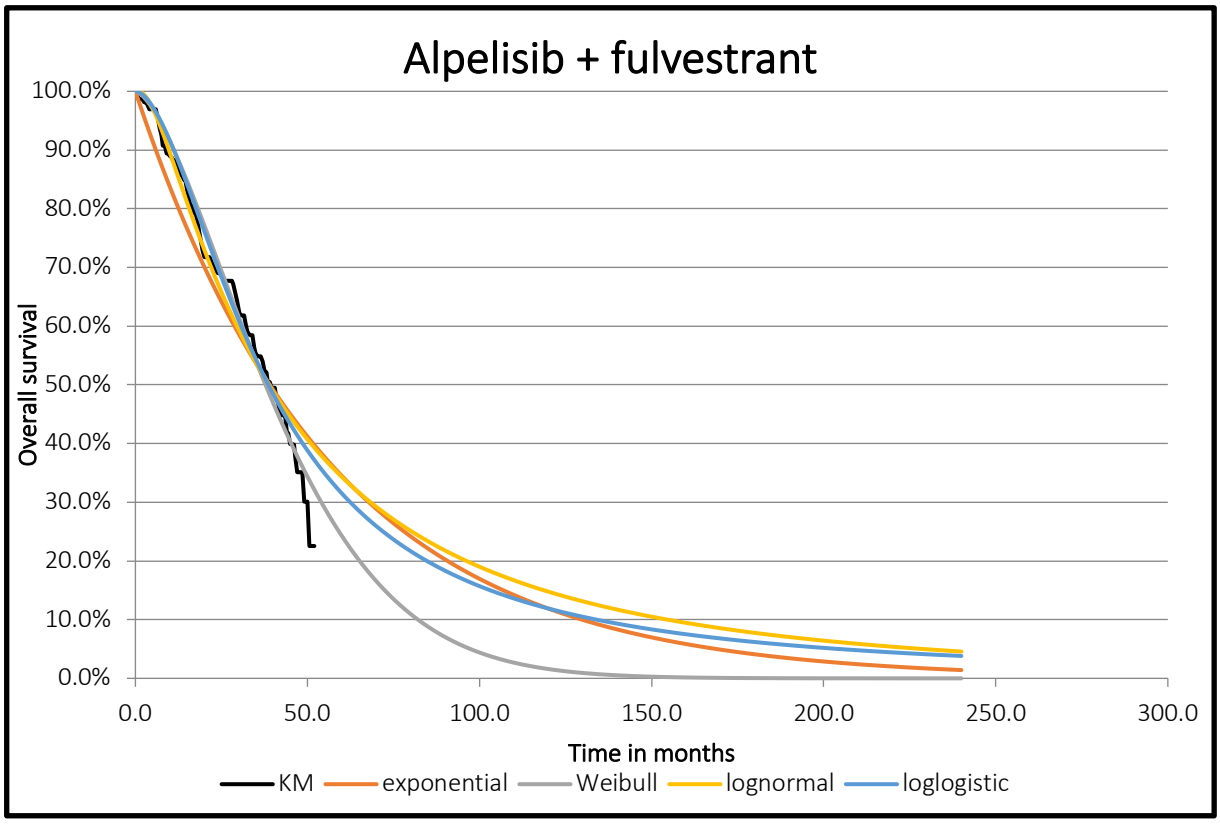

Figure 4 Extrapolation of the overall survival for the alpelisib plus fulvestrant group including the Kaplan Meier (KM) curve

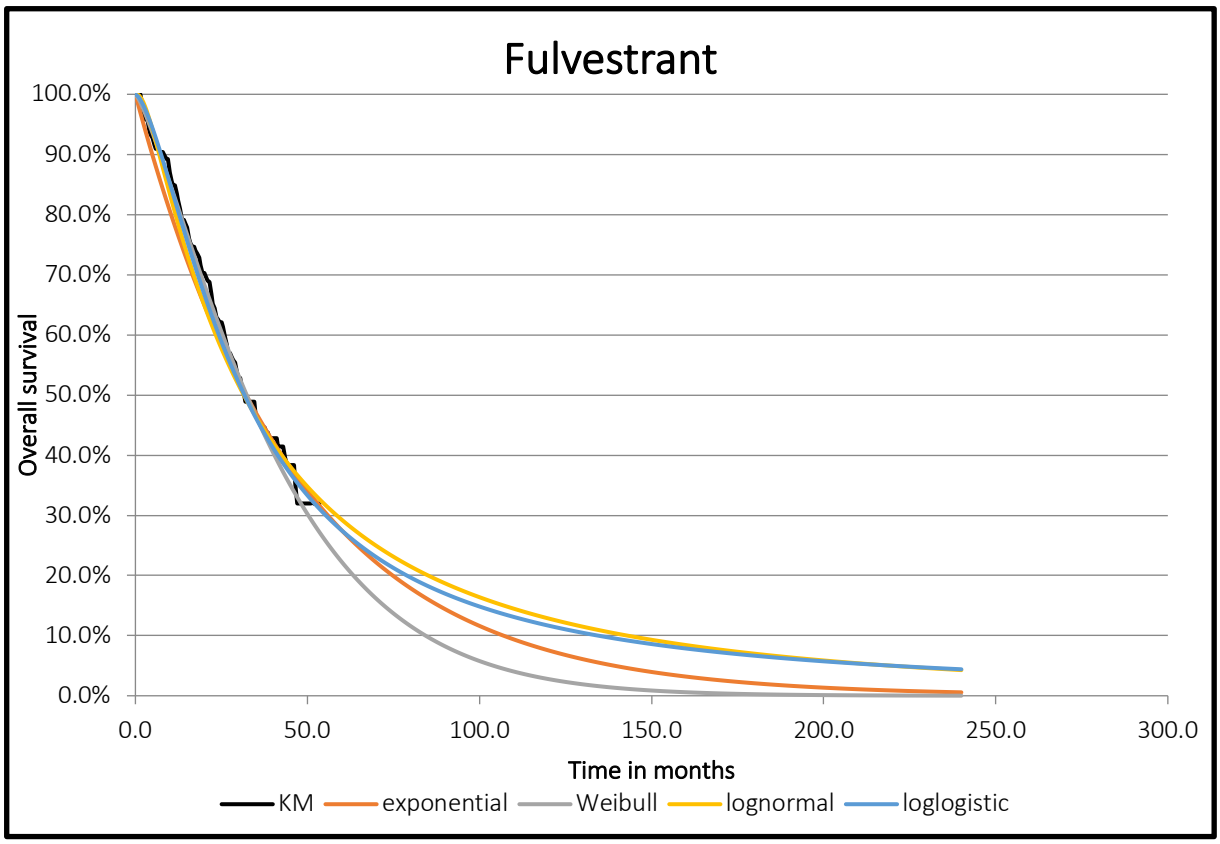

Figure 5 Extrapolation of the overall survival for the fulvestrant group including the Kaplan Meier (KM) curve

4.2. Base case results

Discounted effects

The total estimated discounted effects that alpelisib in combination with fulvestrant yields over a period of 20 years are 4.51 life years or 3.05 QALYs (Table 2). The total discounted effects that fulvestrant yields over 20 years are 4.08 life years or 2.76 QALYs. Therefore, the incremental effects of alpelisib plus fulvestrant versus fulvestrant are 0.43 life years or 0.29 QALYs. Furthermore, there are more life years and QALYs gained in the PF than the PD health state for the fulvestrant group and more life years and QALYs gained in the PD than the PF health state for the alpelisib group (Table 3). In addition, the QALYs lost due to TRAEs were less than 0.01 in both groups.

Discounted costs

The total estimated discounted costs due to the use of alpelisib in combination with fulvestrant per person over a lifetime horizon (of 20 years) from a societal perspective are € 314,094 (Table 2). The total discounted costs incurred because of treatment with fulvestrant are € 230,412. That is why the incremental costs are € 73,264. The drug acquisition costs in the PF health state yield the highest incremental costs of € 92,880 (Table 3). This was because the drug acquisition costs in the alpelisib group are € 98,962 compared to € 6,082 in fulvestrant group. This relatively big increment is caused by

the high unit costs of alpelisib compared to the unit cost of fulvestrant. Therefore, drug acquisition costs are the most influential drivers of the total costs in the alpelisib group. Furthermore, the chemotherapy administration costs in the PD health state have the second biggest increment of € 18,627 (Table 3). This was because the chemotherapy administration costs in the alpelisib group are € 51,129 compared to € 69,756 in fulvestrant group. This difference is mainly caused by the fact that in the fulvestrant group patients progress faster than in the alpelisib group. After progression, 20% of the treatments need to be administrated intravenously. Therefore, the comparator group incurs more chemotherapy administration costs.

Undiscounted results

The undiscounted incremental costs, effects, and ICERs are higher than the discounted incremental costs, effects, and ICERs, respectively (Table 4). This is caused by the fact that with discounting costs and effects that are incurred in the future are given a lower weight than costs and effects that are incurred in the present. Without discounting the screening costs and TRAE costs do not change (Table 5). This is because both costs are applied as one-off costs in the first cycle of the model. Furthermore, the absolute discounted incremental end of life costs, productivity costs and travel costs are higher than the undiscounted increments of these costs (Table 4 and 5). The main reason for this is the fact that in the alpelisib group these costs are higher (or lower) in earlier cycles and lower (or higher) in later cycles than in the fulvestrant group. For the productivity costs, it can be explained by the fact that in the first nine cycles the number of newly progressed patients was lower in the alpelisib group compared to the fulvestrant group. In the other subsequent cycles, the number of newly progressed patients was higher in the alpelisib group compared to the fulvestrant group. For the end of life year costs, it can be explained that by the fact that in the first 25 cycles the number of newly died patients was lower in the alpelisib group compared to the fulvestrant group. In the other subsequent cycles, the number of newly died patients was higher in the alpelisib group compared to the fulvestrant group. For the travel costs, it can be explained by the fact that more patients have to travel for the administration and monitoring in the first few cycles in the alpelisib group than in the fulvestrant group. In later cycles, the number of patients that have to travel for the administration and monitoring was lower in the alpelisib group compared to the fulvestrant group.

Table 2 Deterministic discounted aggregated base case results

Treatment	QALY	Life years (LYs)	Costs
Alpelisib plus fulvestrant	3.05	4.51	€ 314,094
Fulvestrant	2.76	4.08	€ 238,874

Increment	0.29	0.43	€ 75,220
ICERs:	incremental costs per QALY	incremental costs per LY	
	€ 259,802	€ 173,239	

Table 3 Deterministic discounted base case results per category

	Alpelisib and fulvestrant	Fulvestrant	Increment
Life years accrued in the PF state	1.83	1.02	0.80
Life years accrued in the PD state	2.68	3.05	-0.37
Total life years	**4.51**	**4.08**	**0.43**
QALYs accrued in the PF state	1.33	0.80	0.53
QALYs accrued in the PD state	1.72	1.96	-0.24
QALYs lost due to TRAEs	0.00	0.00	0.00
Total QALYs	**3.05**	**2.76**	**0.29**
Drug acquisition costs in the PF state	€ 98,962	€ 6,082	€ 92,880
Chemo admin costs in the PF state	€ 7,884	€ 5,007	€ 2,876
Monitoring costs in the PF state	€ 14,078	€ 8,756	€ 5,321
Screening costs in the PF state	€ 265	€ 0	€ 265
AE costs in the PF state	€ 1,866	€ 67	€ 1,799
Informal care costs in the PF state	€ 15,947	€ 9,737	€ 6,210
Travel costs in the PF and PD state	€ 1,816	€ 1,788	€ 28
Drug acquisition costs in the PD state	€ 7,926	€ 9,008	-€ 1,082
Chemo admin costs in the PD state	€ 51,129	€ 69,756	-€ 18,627
Monitoring costs in the PD state	€ 48,646	€ 55,285	-€ 6,639
BSC costs in the PD state	€ 556	€ 632	-€ 76
End of life costs	€ 2,208	€ 2,244	-€ 35
Indirect medical costs	€ 19,917	€ 22,298	-€ 2,381
Informal care costs in the PD state	€ 32,952	€ 37,449	-€ 4,497
Productivity costs in the PD state	€ 9,942	€ 10,764	-€ 823
Total costs	**€ 314,093**	**€ 238,874**	**€ 75,219**

Table 4 Deterministic undiscounted aggregated base case results

Treatment	QALY	Life years (LYs)	Costs
Alpelisib plus fulvestrant	3.26	4.83	€ 369,591
Fulvestrant	2.96	4.38	€ 289,880
Increment	0.30	0.45	€ 79,712
ICERs:	incremental costs per QALY	incremental costs per LY	
	€ 262,711	€ 177,249	

Table 5 Deterministic undiscounted base case results per category

	Alpelisib and fulvestrant	Fulvestrant	Increment
Life years accrued in the PF state	1.90	1.05	0.85
Life years accrued in the PD state	2.92	3.32	-0.40
Total life years	**4.83**	**4.38**	**0.45**
QALYs accrued in the PF state	1.38	0.82	0.56
QALYs accrued in the PD state	1.88	2.14	-0.26
QALYs lost due to TRAEs	0.00	0.00	0.00
Total QALYs	**3.26**	**2.96**	**0.30**
Drug acquisition costs in the PF state	€ 109,701	€ 6,514	€ 103,187
Chemo admin costs in the PF state	€ 8,706	€ 5,363	€ 3,344
Monitoring costs in the PF state	€ 15,513	€ 9,387	€ 6,126
Screening costs in the PF state	€ 265	€ 0	€ 265
AE costs in the PF state	€ 1,866	€ 67	€ 1,799
Informal care costs in the PF state	€ 17,751	€ 10,521	€ 7,231
Travel costs in the PF and PD state	€ 2,177	€ 2,161	€ 16
Drug acquisition costs in the PD state	€ 9,829	€ 11,172	-€ 1,343
Chemo admin costs in the PD state	€ 63,400	€ 86,514	-€ 23,114
Monitoring costs in the PD state	€ 60,322	€ 68,567	-€ 8,245
BSC costs in the PD state	€ 690	€ 784	-€ 94
End of life costs	€ 2,589	€ 2,580	€ 10
Indirect medical costs	€ 25,570	€ 28,715	-€ 3,144

Informal care costs in the PD state	€ 40,861	€ 46,447	-€ 5,585
Productivity costs in the PD state	€ 10,347	€ 11,087	-€ 740
Total costs	**€ 369,588**	**€ 289,879**	**€ 79,710**

4.3. Deterministic sensitivity analyses

The results of the DSAs are visualized in Figure 6. In this tornado diagram, the five input parameters with the most influence on the ICER are portrayed. These input parameters are listed in descending order with the most influential input parameters presented above and the least below. For each input parameter, the lower and upper bound of the ICER is presented. These bounds are calculated by changing the input parameter with a certain value or percentage presented between square brackets. The upper and lower bound of each parameter is pictured as a bar deviating from the base case ICER of € 259,802 per QALY. The base case ICER of € 259,802 per QALY is portrayed as the middle line in the tornado diagram. The longer the bar, the more influence the change in the parameter has on the base case ICER. Compared to other parameters, the utility values of the PD and PF health state had the strongest influence on the ICER. Furthermore, the dosage of alpelisib and the costs for intravenous chemotherapy administration influenced the ICER substantially. Of all the DSAs, the change of the monitoring costs in the PD health state had the least impact on the ICER. None of these variations leads to an ICER below the WTP threshold of € 80,000 per QALY.

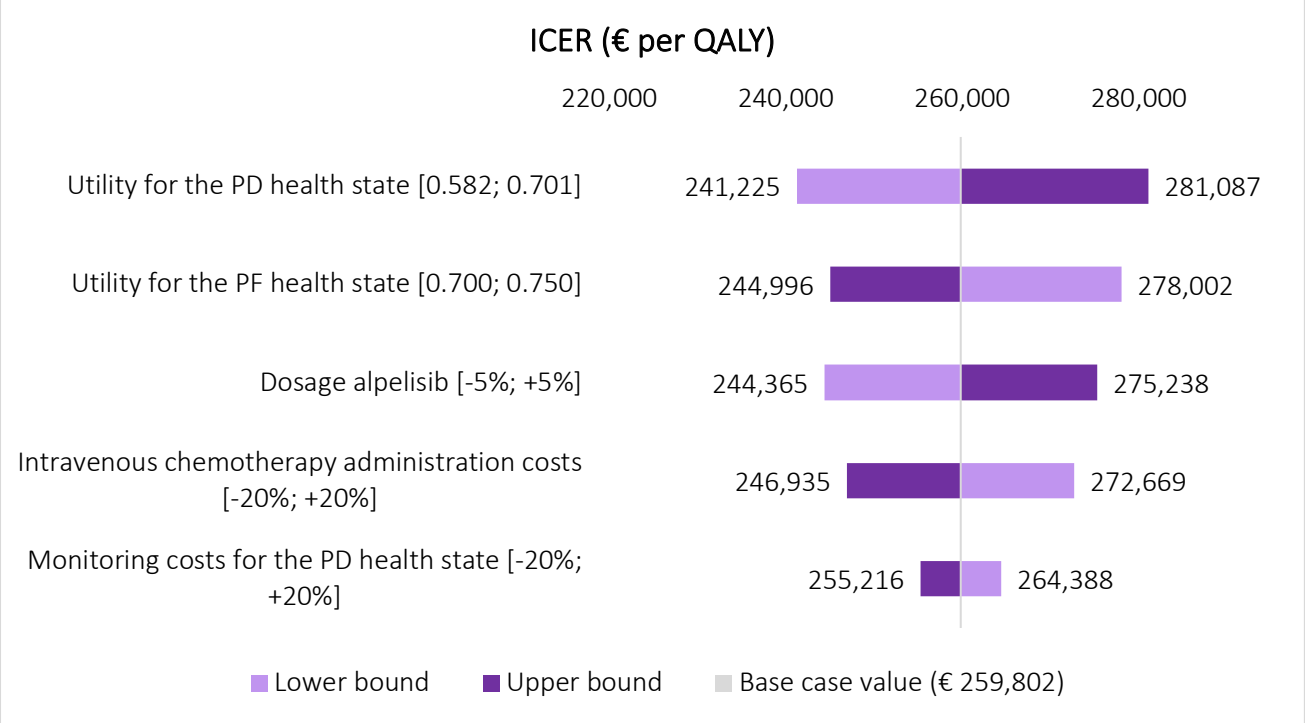

Figure 6 Tornado diagram of the deterministic sensitivity analyses

4.4. Probabilistic sensitivity analysis

A PSA is an assessment of the extent of uncertainty surrounding the base case ICER as a result of uncertainty around the input parameters of the model. To graphically represent this uncertainty, a cost-effectiveness-plane can be used, which has four quadrants in which the incremental costs are on the y-axis and the incremental effects on the x-axis.[36] In this study, the PSA produced 1000 different probabilistic ICERs. The cost-effectiveness plane generated by the PSA is shown in Figure 7. In this figure each square represents a probabilistic ICER. Of all the ICERs computed from the PSA, 72.7% is located in the northeast quadrant, demonstrating that alpelisib in combination with fulvestrant is associated with better health outcomes, but also with higher costs than therapy with only fulvestrant. The other 27.3% of the ICERs are in the northwest quadrant. This implies that in 27.3% of the simulations alpelisib in combination with fulvestrant is associated with worse health outcomes and higher costs than therapy with only fulvestrant. This means that in those simulations alpelisib is dominated by fulvestrant as treatment. When the commonly used WTP threshold of € 80.000 (the diagonal line in Figure 7) per QALY is considered, no simulation shows that alpelisib is cost-effective compared to fulvestrant, as no simulation yields an ICER lower than this WTP threshold.

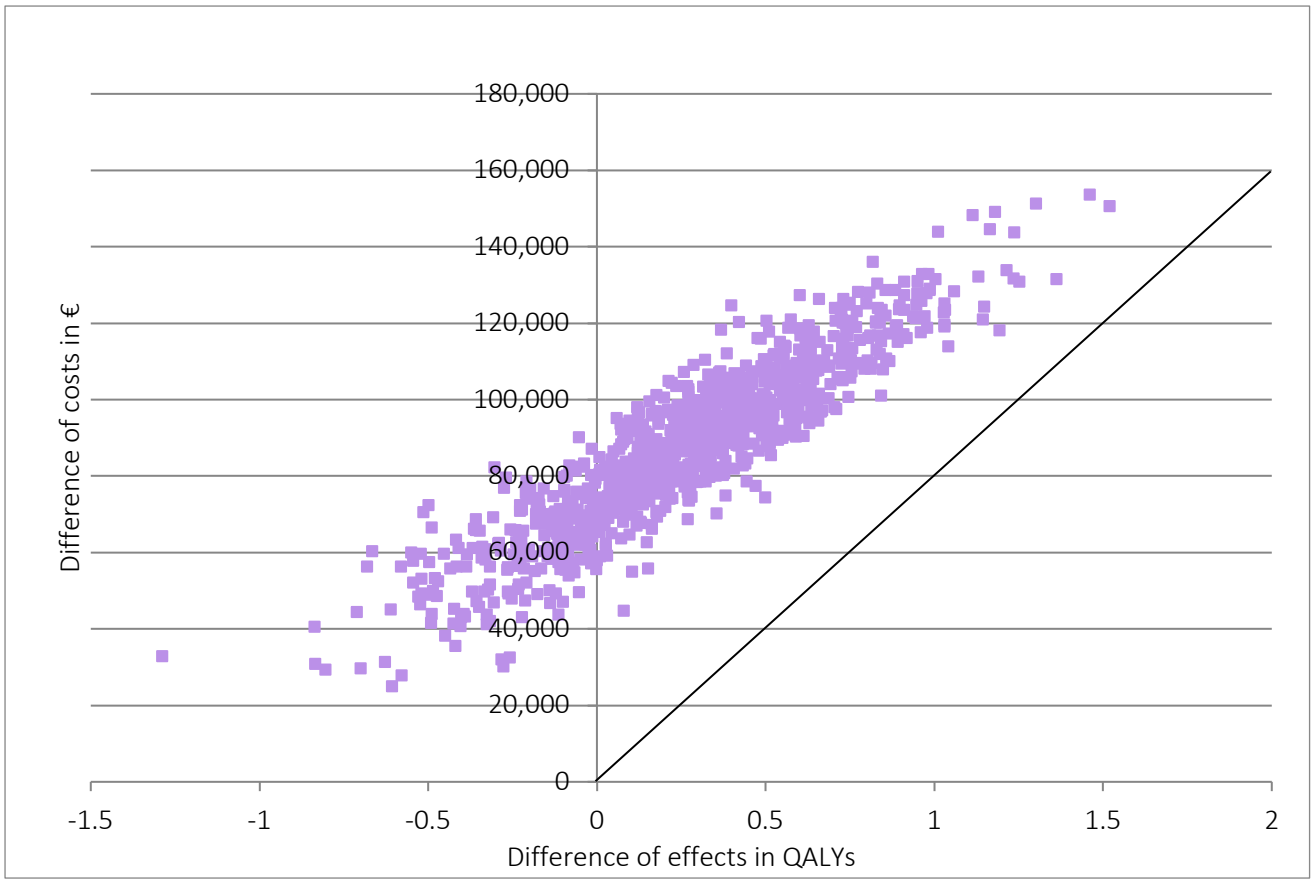

Figure 7 Cost-effectiveness-plane with 1000 different ICERs and the WTP threshold of € 80,000 per QALY

Furthermore, a cost-effectiveness acceptability curve can be used to graphically present the probabilities of an intervention versus a comparator being cost-effective at a range of thresholds.[36] The cost-effectiveness acceptability curve has the threshold values on the x-axis and the probabilities of being cost-effective on the y-axis. The probabilities of alpelisib plus fulvestrant being cost-effective compared to fulvestrant only at thresholds varying from € 0 to € 1,600,00 per QALY are portraited in Figure 8. From this Figure 8 it can be stated that a higher threshold leads to a higher probability of being cost-effective. Furthermore, it can be concluded that the probability that alpelisib is cost-effective compared to fulvestrant at a threshold of € 80.000 per QALY is 0.00. This result is in line with the outcomes in the cost-effectiveness plane and of the DSAs.

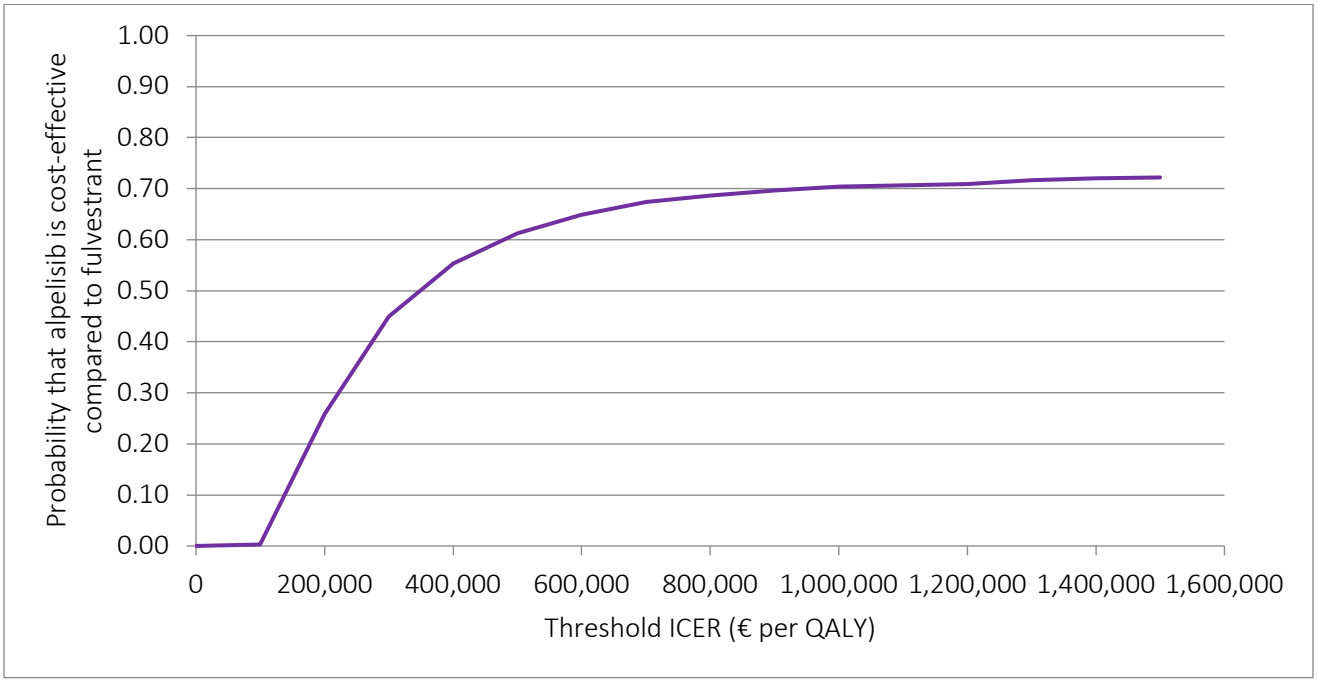

Figure 8 Cost-effectiveness acceptability curve of alpelisib

4.5. Scenario analyses

In total 11 scenarios are explored to compare their cost-effectiveness to the base case ICER (Table 6). In the first scenario, the treatment with alpelisib and fulvestrant was stopped after 29 months instead of lifelong treatment for progression-free patients. This resulted in an ICER of € 156,460 per QALY, which is € 103,342 per QALY lower than the base case ICER. In the second scenario analysis, the daily dosage of alpelisib was reduced to 200 mg. This leads to an ICER of € 156,891 per QALY, which was € 102,911 per QALY lower than the base case ICER. The third scenario is a combination of the first two scenarios and resulted in an ICER of € 86,060 per QALY. In the fourth scenario, the unit price of alpelisib was decreased by 60%, which yielded an ICER of € 74,563 per QALY. This was the only ICER that was lower than the WTP threshold of € 80,000 per QALY compared to all the other 10 scenarios. In addition,

the first four scenarios only change the costs and not the effects. The fifth, sixth and seventh scenario are about changing the distribution for OS. Hereby, the Weibull distribution leads to the highest ICER of € 351,055 per QALY. The lognormal and exponential yield lower ICERs than the base case ICER, which are € 213,453 per QALY and € 185,669 per QALY, respectively. In other words, the Weibull distribution for the OS leads to a higher ICER and the lognormal and exponential distribution for the OS leads to a lower ICER compared to the base case ICER of € 259,802. Furthermore, a shorter time horizon of 10 years leads to an ICER of € 256,273, which differs € 3,529 per QALY from the base case ICER. Also, a higher utility value of 0.826 instead of 0.726 for the PF health state yields an ICER of € 207,541 per QALY. Moreover, when the productivity costs are disregarded, the ICER becomes € 262,643 per QALY, which has of all scenarios the lowest difference of € 2,841 per QALY with the base case ICER. At last, equating the OS curve for the intervention and comparator groups leads to the largest ICER of all eleven scenarios. The ICER was € 922,911 per QALY, differing € 653,109 per QALY from the base case ICER.

Table 6 Scenario analyses

Base case	Scenario	Costs alpelisib and fulvestrant (€)	Costs fulvestrant (€)	Incremental costs (€)	Effects alpelisib and fulvestrant (QALYs)	Effects fulvestrant (QALYs)	Incremental effects (QALYs)	ICER (€ per QALY)
Base case	-	314,094	238,874	75,220	3.05	2.76	0.29	**259,802**
Treatment duration alpelisib plus fulvestrant and fulvestrant only: life-long	Treatment duration: maximum of 29 months	282,958	237,659	45,300	3.05	2.76	0.29	**156,460**
Dosage alpelisib per day: 300 mg	Dosage alpelisib per day: 200 mg	284,299	238,874	45,425	3.05	2.76	0.29	**156,891**
Treatment duration alpelisib (dosage of 300 mg per day) plus fulvestrant and fulvestrant only: life-long	Treatment duration alpelisib (dosage of 200 mg per day) plus fulvestrant and fulvestrant only: maximum of 29 months	262,676	237,659	24,917	3.05	2.76	0.29	**86,060**
Unit costs alpelisib: € 70.07	Unit costs alpelisib: € 28.03	260,462	238,874	21,588	3.05	2.76	0.29	**74,563**

OS distribution: loglogistic	OS distribution: Weibull	257,300	187,346	69,954	2.36	2.16	0.20	**351,055**
OS distribution: loglogistic	OS distribution: lognormal	327,358	244,610	82,748	3.21	2.82	0.39	**213,453**
OS distribution: loglogistic	OS distribution: exponential	304,627	210,771	93,856	2.94	2.43	0.51	**185,669**
Time horizon: 20 years	Time horizon: 10 years	285,512	208,577	76,935	2.69	2.39	0.30	**256,273**
Utility PF health state: 0.726	Utility PF health state: 0.826	314,094	238,874	75,220	3.23	2.87	0.36	**207,541**
Productivity costs included	Productivity costs excluded	304,153	228,110	76,043	3.05	2.76	0.29	**262,643**
Different OS probabilities for alpelisib and fulvestrant	The same OS probabilities for alpelisib and fulvestrant	314,094	263,031	51,063	3.05	2.99	0.06	**922,911**

5. Discussion and conclusion

5.1. Key findings

The goal of this study was to evaluate the cost-effectiveness of alpelisib combined with fulvestrant relative to fulvestrant only in HR+/HER2- ABC patients with a PIK3CA mutation after disease progression following hormonal monotherapy. This was evaluated from a societal perspective in the Dutch healthcare setting over a lifetime horizon. This CUA shows that treatment with alpelisib is not cost-effective compared to fulvestrant only. This was also the case in the various sensitivity and scenario analyses. From the DSAs it was concluded that the main driver of the total costs is the drug acquisition costs of alpelisib. The price of alpelisib needed to be reduced by at least 60% to turn alpelisib in combination with fulvestrant into a cost-effective treatment option compared to treatment with only fulvestrant.

This is the first economic evaluation that assessed the cost-effectiveness of alpelisib in combination with fulvestrant compared to monotherapy with fulvestrant in HR+/HER2- ABC patients with a PIK3CA genetic mutation from a Dutch societal perspective over a lifetime horizon. In the literature, only one published economic evaluation was found that compared the costs and effects of alpelisib in combination with fulvestrant to the costs and effects of fulvestrant only. This study found 0.43 incremental QALYs, approximately $ 280,000 incremental costs and an ICER of approximately $ 650,000 per QALY for alpelisib in combination with fulvestrant compared to fulvestrant only.[35] Nevertheless, it is difficult to compare the results of this American study to the results of this study as the American evaluation was conducted from a United States payer perspective and it only reports incremental costs, incremental QALYs and the ICER. However, it is notable that the QALYs gained in the American study were higher than in the current study (0.434 versus 0.29 QALYs, respectively). This may be caused by the fact that the American economic evaluation used OS data from another RCT (the PALOMA-3 trial). This was done because the OS data from the SOLAR-1 trial was not available at the moment of conducting the American CUA.[35] Although the PALOMA-3 trial reported a median OS that was 0.4 months higher for the intervention arm than the SOLAR-1 trial (39.7 versus 39.3 months, respectively), the median OS for the control group was lower with 29.7 months in the POLAMA-3 versus 31.4 months in the SOLAR-1.[16,107] This implies that the difference in effects between the intervention and control group is larger in the PALOMA-3 trial which may have caused the larger incremental effects in terms of QALYs gained in the American economic evaluation. This study used the OS from the SOLAR-1 trial. The SOLAR-1 trial is a more appropriate source for the OS as it reported the survival for the specific group of HR+/HER2- ABC patients with the PIK3CA mutation.[16] On the contrary, the PALOMA-3 trial followed and reported results for HR+/HER2- ABC patients, without making a distinction between

patients based on the presence of the PIK3CA mutation.[107] Therefore, the results of this CUA represent the patient population better than the American evaluation. The higher incremental costs in the American CUA than in the current study could be caused by for example the unit price of alpelisib. The unit price of alpelisib that was considered in the American evaluation was not stated. However, unit prices of drugs are often substantially higher than in Europe.[108] Nevertheless, conclusions regarding cost-effectiveness are similar in both studies, as it is very unlikely for alpelisib to be cost-effective at such high ICERs.

The results of this CUA could be compared to the cost-effectiveness of the CDK4/6 inhibitor palbociclib plus fulvestrant versus fulvestrant only to analyse the differences and similarities in costs and effectiveness outcomes. The cost-effectiveness of the CDK4/6 inhibitor palbociclib was assessed by the NHCI for the Netherlands.[46] The comparison with palbociclib is relevant because the CDK4/6 inhibitors are alternative treatment options for HR+/HER2- ABC patients including for those with a PIK3CA mutation.[28,29,30] In addition, the CDK4/6 inhibitors are believed to have better outcomes than alpelisib as the NHCI utilized a median PFS of 11.2 months for palbociclib which was longer than the median PFS of 11.0 months for alpelisib.[10,46] Furthermore, for the comparator a median PFS of 5.7 months and 4.6 months were used in this CUA and the CUA of palbociclib, respectively.[16,46] The median survival of palbociclib was estimated for HR+/HER2- ABC patients including for those with a PIK3CA mutation who had been treated with hormonal therapy before.[46] For the effects, it can be stated that the difference between alpelisib and palbociclib expressed in life year gained was smaller compared to the difference between alpelisib and palbociclib expressed in QALYs. The palbociclib group gained 3.13 QALYs or 4.56 life years, whereas the alpelisib group gained 3.05 QALYs or 4.51 life years.[46] The difference in the effects expressed in QALYs can be explained by the fact that the utility of patients that receive palbociclib was higher than the utility for patients who receive alpelisib (0.761 versus 0.742, respectively). The comparator (fulvestrant only) had a utility of 0.742 in both CUAs.[46] Based on the SOLAR-1 trial, it was stated that quality of life did not differ between the alpelisib plus fulvestrant arm and the fulvestrant only arm. However, there was a difference in the quality of life between health states. That is why the utility of PF patients who received alpelisib plus fulvestrant and fulvestrant only was set equal.[109] Therefore, the utility of alpelisib was lower than the utility of palbociclib. Furthermore, in both CUAs the utility of the PD patients who had been treated with alpelisib plus fulvestrant or fulvestrant only before progression was equal (0,643).[46]

In the CUA of the NHCI, the total costs of palbociclib plus fulvestrant were € 130,278.[46] In comparison, the total costs of alpelisib plus fulvestrant were € 314,093 in this study. This difference is mainly caused

by the drug acquisition costs in the PF health state and the administration and monitoring costs in the PF and PD health state. The drug acquisition costs in the PF health state were € 98,962 in this CUA and € 89,321 in the CUA of palbociclib. This difference in acquisition costs is predominantly created by the unit costs of the drugs as the costs per day were € 128.57 and € 140.14 of palbociclib and alpelisib, respectively. The administration costs in the PF and PD health state were € 59,013 in this CUA and € 1,939 in the CUA of palbociclib.[46] For this analysis, the administration costs were based on a micro-costs study, which is published after the CUA of palbociclib.[75] The CUA of palbociclib based the administration on the price of a standard outpatient visit as calculated by the economic evaluation guidelines of the NHCI.[36,46] Furthermore, the monitoring costs in the PF and PD health state were € 62,724 and € 5,461 for the alpelisib group and the palbociclib group, respectively.[46] This difference could be caused by an overestimation of the monitoring costs in this CUA, as it was assumed that most of the efficacy, safety and tolerability assessments that took place during the RCT also would take place in practice.[10] However, in real life, there might be less monitoring than in RCTs.[110] In the CUA of palbociclib, the resource use for monitoring was based on the opinion of three clinical experts.[46] Therefore, overestimation of administration costs is less likely to be the case. Furthermore, the total costs of the comparator fulvestrant only in the CUA of alpelisib were € 50,122.[46] In this evaluation, the total costs of the comparator fulvestrant only were estimated at € 238,874. The difference between these two total costs can be explained by the differences in administration and monitoring costs, just as is done with palbociclib versus alpelisib. The incremental costs were € 80,156 and € 75,220 in the CUA of palbociclib and this CUA, respectively and did not differ as much as the total costs of each group in both CUAs.[46] It is also possible that another factor may have influenced the difference in total costs. This potential factor is the consumer price index. The CUA of palbociclib calculated all the costs for the year 2016, which has a consumer price index of 0.3.[46,70] This CUA calculated all the costs for the year 2021, which has a consumer price index of 1.6.[70] A higher consumer price index leads to a bigger inflation of costs.

To sum up, the effects in life years and QALYs are similar and explainable. The total costs between the two interventions and the two comparators differ substantially and were mainly driven by the unit costs for alpelisib and palbociclib and the assumptions for the resource use of administration and monitoring in the PF and PD health state. The difference in total costs could also be explained by the difference in consumer price indices that the two CUA used. No RCT has studied the efficacy of alpelisib versus palbociclib in HR+/HER2- ABC patients with a PIK3CA mutation, until now.[15] Therefore, to make conclusions about which drug yields more effects in HR+/HER2- ABC patients with a PIK3CA mutation

and at what costs, more research is needed on the cost-effectiveness of alpelisib versus palbociclib and the other two CDK4/6 inhibitors.

5.2. Strengths

This CUA has its strengths and limitations. To start with the strengths, this CUA was performed following the guidelines for conducting economic evaluations in the Netherlands.[36] This makes it possible to compare the results of this CUA with the results of evaluations that are conducted using the same guidelines. Secondly, for this study, the SOLAR-1 trial was utilized because it was the only head-to-head, RCT that accessed the efficacy and safety of alpelisib with fulvestrant compared to the use of only fulvestrant in the patient population of this study.[15] In addition, RCTs are the gold standard for examining causal links between an intervention and the outcome, as randomisation removes many of the biases that are common to other research designs.[50] Furthermore, the mature OS results of the trial were utilized. This decreases the degree of uncertainty of the model results compared to the use of premature OS data that is often used in economic evaluations.[111,112] In the model, all costs related input parameters were based on studies conducted in a Dutch context. Health state utilities were based on the EQ-5D-5L scores of HR+/HER2- ABC patients obtained in the PALOMA-2 trial, as EQ-5D-5L data from the SOLAR-1 trial was not published yet.[13,113] The EQ-5D-5L data of the PALOMA-2 trial were scored using the Dutch scoring algorithms of Lamers et al.[114] Versteegh et al. published more recent Dutch scoring algorithms than Lamers et al. However, Versteegh et al. published their algorithms around the same time as when the utilities used in this CUA were scored, leading to the fact that the researchers who scored the EQ-5D-5L data used the older algorithms of Lamers et al.[115] Moreover, the robustness of the model and the sensitivity of various input parameters were assessed with DSAs, a PSA and different scenario analyses.

5.3. Limitations

As with every study, it is necessary to acknowledge the limitations and to critically think about the assumptions and data on which the conclusions have been based. Firstly, the starting population that entered the model was the population from the SOLAR-1 trial.[10,13] The assumption was made that this population was sufficiently representative of the population of men and postmenopausal women in the Netherlands diagnosed with HR+/HER2- ABC with the PIK3CA gene mutation after the failure of hormonal treatment. That is also why it was assumed that TRAE rates in the trial were comparable to the model population. However, patients included in RCTs need to meet eligibility criteria and can, on average, be significantly different from the diverse patient population that clinicians will observe and care for in everyday clinical practice.[13] Generally, the participants of trials are in a better overall health

condition than the patients in real life. This could cause the fact that the effectiveness of alpelisib plus fulvestrant in daily clinical practice is considerably different than the efficacy as observed in the RCT of alpelisib plus fulvestrant.[116]

Secondly, the comparator in this study is not the most appropriate for the situation in the Netherlands. This is because besides fulvestrant there are also other more promising treatment options in the Netherlands for HR+/HER2- ABC patients, such as the CDK 4/6 inhibitors.[28,29,30] Fulvestrant was selected as a comparator because this was the comparator in the SOLAR-1 trial and for this CUA data from that RCT was used.[10,13] To draw conclusions about the cost-effectiveness of alpelisib compared to the CDK4/6 inhibitors, more research is needed. Ideally, this cost-effectiveness needs to be based on a head-to-head RCT in which the drugs are compared in HR+/HER2- ABC patients with a PIK3CA mutation.

Thirdly, extrapolation of survival curves was performed to calculate the proportions of patients in each health state for every cycle due to the relatively short follow up of the PFS and OS in the SOLAR-1 trial.[10,13,16] The choice of distributions had a relatively big impact on the results. The selection of distribution was among other things based on the 5-year survival in HR+/HER2- ABC patients of the PALOMA-1 RCT and 10-year survival in metastatic breast cancer patients from the Dutch Cancer Registry.[66,67] This method of selecting the distributions still has some limitations. This is because the 10-year survival of metastatic breast cancer patients includes other subtypes than HR+/HER2- such patients the triple-negative and HER2+ disease.[117] Patients with triple-negative breast cancer, which occurs in 11% of all breast cancer patients in the Netherlands, have worse survival than patient with non-triple negative breast cancer and could lead to the lower OS of metastatic breast cancer.[118,119] On the contrary, patient with HER2+ disease, which occurs in 13.1% of all breast cancer patients in the Netherlands, are getting treated with trastuzumab for HER2+ ABC.[118,120] This treatment improved the OS substantially and could lead to the higher OS of metastatic breast cancer.[120] Due to lack of 10-year survival specifically for HR+/HER2-, the average 10-year survival of metastatic breast cancer patients was utilised.[67] In the scenario analyses, the OS distribution was changed from loglogistic to Weibull, lognormal and exponential. This led to the conclusion that the other distributions yield substantially different ICERs but none of these ICERs was below the WTP threshold of € 80,000 per QALY. Future research could collect the 10-year survival specifically for HR+/HER2- patients. This data could be used to select distributions for OS in reassessments of already performed CUA such as this one and assessments of new ABC drugs for HR+/HER2- patients.

A fourth constraint is that there may be an overestimation of treatment costs. This overestimation may be caused by the assumption that patients received full dose until disease progression, while in the alpelisib arm of the SOLAR-1 trial 74.0% of the patients had a dose interruption, 63.9% had a reduction and 25.4% had discontinuation due to the occurrence of TRAEs (Appendix 3).[10] For this reason, the impact of reducing the dosage, the treatment duration or both were explored in different scenario analyses. These scenarios were considered to establish how much impact treatment duration and dosage have on the base case ICER. The analyses showed that the ICER could be € 156,460, € 156,891 or € 86,060 per QALY, by only reducing the treatment duration to 29 months, only reducing the dosage with 100 mg or both, respectively. These ICERs were substantially lower than the base case ICER of € 259,802 per QALY. However, the scenario in which the treatment duration was changed to the maximum treatment duration observed in the RCT (29 months) is probably not very realistic. This is because the maximum treatment duration is based on observed data but the follow-up is not yet complete.[10] Therefore, it is likely that patients in the trial have been treated with alpelisib plus fulvestrant and fulvestrant only for a longer period than 29 months. To conclude, this scenario is very extreme and leads to a substantially low ICER. Therefore, this ICER should be interpreted with caution. Furthermore, the choice to decrease the dosage of alpelisib with 100 mg (from 300 mg to 200 mg) for all patients was based on one of the dose reductions in the RCT. However, this assumption was on the high side for different reasons. First, it was stated that 63.9% of all patient in the alpelisib group of the RCT has a dosage reduction and not all patients. Secondly, this 63.9% was the aggregated amount of patient that received a dose reduction of 50 mg (i.e. a dose of 250 mg) and 100 mg (i.e. a dose of 200 mg) and not only the latter.[10] Even though the dose reduction and the shorter treatment duration are extreme scenarios, these scenarios still did not yield an ICER below the WTP of € 80,000 per QALY. However, these three scenarios do confirm that the treatment duration and dose have a major impact on the ICER.

Fifthly, it was assumed that there is no drug wastage. This might not be the case in real life as a dose modification might be necessary while the dose cannot be split or saved for later use.[121] Drug wastage can have a substantial impact on the costs.[122] That is why it could be more accurate if wasted medicines were considered in this CUA where appropriate. Further research could take the wastage of drugs into account. Furthermore, it was assumed that patients who progress are treated with anastrozole (60%), capecitabine (20%), paclitaxel (10%) or docetaxel (10%). These (proportions of) treatments were based on the post-progression treatment of HR+/HER2- ABC patients and not specifically patients with the PIK3CA mutation.[46] However, patients can also be treated with other post-progression treatments in practice than those used in this model, for example with one of the CDK4/6 inhibitors. Therefore, there

is uncertainty regarding the choice and subsequently the costs of post-progression treatments. The CDK4/6 inhibitors are more expensive than the post-progression treatment in this CUA and it is not yet clear whether they can be used after alpelisib.[28,29,46] Ideally, the model should consider the costs of treatments that are currently utilized in Dutch clinical practice and that may have a substantial impact on the ICER. A study concluded that high ICERs may be driven by other costs than those for the drug that is evaluated, such as the post-progression costs. If incremental post-progression survival costs are improperly estimated then incremental survival costs are likely to be overestimated in economic evaluation.[123] However, there is little evidence about how patients are treated in daily practice. Especially information about treatment lines is limited. Therefore, it is recommended for further research to collect real-world data on the treatments that HR+/HER2- ABC patients (with a PIK3CA mutation) receive in the Netherlands.

5.4. Policy recommendations

After market authorization of alpelisib by the European Medicines Agency, the drug was automatically added to the basic benefit package and therefore reimbursed in the Netherlands.[18,73] Alpelisib was added to the basic benefit package without assessing the cost-effectiveness and subsequently also without price arrangements. The cost-effectiveness was not assessed because the expected budget impact of the drug is less than € 10 million per year and the costs per patient are less than € 50,000 per year. This was based on the forecast that in the Netherlands a maximum of 300 patients per year needs alpelisib and that the costs per patient per year are between € 29,520 and € 32,800.[23] In addition, the commission BOM assessed the clinical value of alpelisib and concluded that alpelisib deserves a positive advice for use in practice. The advice of the commission BOM was based on the fact that alpelisib in combination with fulvestrant prolongs the PFS compared to fulvestrant only in HR+/HER2- ABC patients with a PIK3CA mutation.[26] Despite the clinical benefits of a significant increase in PFS and a non-significant increase in OS and a relatively small budget impact, the results of this study show that treatment with alpelisib and fulvestrant is considered not cost-effective compared to treatment with fulvestrant only in the Netherlands.

At the moment, alpelisib is being reimbursed for patients in the Netherlands.[73] The Dutch Healthcare Authority designated alpelisib as an add-on drug.[73] Add-on drugs are drugs that can be billed separately from the treatment (i.e. the specialist medical care) by the hospital to the health insurer of the patient.[124] However, hospital need to negotiate with insurers on the reimbursement for add-on drugs.[125] Furthermore, hospitals can negotiate with the manufacturers about the net purchasing price of add-on drugs.[126] A price analyses of the Dutch Healthcare Authority indicated that hospitals are

getting better at negotiating lower net purchasing prices with manufacturers and lower contract prices with insurers. However, this development is occurring especially for drugs with more than one manufacturer. This negotiation power of hospitals is smaller if only one manufacturer produces a drug.[126,127] This is also the case with alpelisib as Novartis is the only manufacturer of this drug at the moment. On hospital level, this study can aid in the price volume agreements between hospitals and health insurers or the manufacturer of alpelisib Novartis. The results of this study show that the treatment with alpelisib and fulvestrant is considered not cost-effective and that the costs of alpelisib have a major influence on the ICER. These results can thereby be used by hospitals to know at which price alpelisib is cost-effective and aid in the negotiations with Novartis to lower the price of alpelisib. There is no literature that reviewed on what basis hospitals and manufacturers negotiate for the price. However, it can be stated that on the national level the Ministry of Health, Welfare and Sport has negotiated about the price of expensive medicines with the pharmaceutical industry in exceptional cases if the drug has a potentially high budget impact or unfavourable cost-effectiveness.[126] This implies that cost-effectiveness results are used in negotiations with pharmaceutical companies. Therefore, it is expected that cost-effectiveness results can also be used in the negotiations on the hospital level. The bargaining position can even be better if groups of hospitals jointly purchase drugs from the manufacturer.[126,127] However, it should be borne in mind that only if the price of alpelisib is reduced by more than 60% (ceteris paribus), the deterministic ICER will be below the threshold of € 80.000 per QALY.

This CUA also provides the possibility is to present the results to medical oncologists with the aim of considering the results in the guidelines. The commission BOM only stated that the costs related to treatment with alpelisib are unknown. However, the commission does try to incorporate the costs of new oncology drugs in their advice, especially since the costs are constantly rising. The demand for efficiency and cost reduction entails that society and also clinicians take this into account. The BOM committee reports the costs of a drug as comprehensive as possible.[128] In addition, the Dutch Council for Quality of Healthcare (in Dutch: Regieraad Kwaliteit van Zorg) was asked by the Minister of Health, Welfare and Sport to issue a vision on the development of clinical guidelines in the Netherlands. The council stated that understanding the financial consequences of recommendations is necessary to make socially responsible choices in spending healthcare resources. If necessary, an economic evaluation should be performed, such as a cost-effectiveness analysis. Economic considerations in the guideline can be used in policy decisions at the local, regional or national level.[129] Therefore, this CUA can be used in the development of clinical guidelines for HR+/HER2- ABC patients.

As the results of this study show that the treatment with alpelisib and fulvestrant is considered not cost-effective compared to fulvestrant only in the Netherlands, it implies that treatments can be not cost-effective while still being reimbursed in the Netherlands. It may be expected that this will occur more often in the future because new oncology drugs are increasingly targeted at specific mutations. These increasingly specific mutations occur in fewer patients which results in smaller patient populations and a smaller budget impact. Therefore, increasingly new intramural drugs can be added to the basic benefit package without knowing their cost-effectiveness.[130] In addition, with the development of an increasing number of new targeted cancer treatments, it is essential to be aware of the rising prices of new cancer drugs and their cumulative impact on the total health care budget. Moreover, money spent on interventions with a budget impact of € 10 million per year or less cannot be spent on other health interventions that have more value for money.[22] That is why is it advised to the NHCI to revise the small budget impact criteria as a compelling factor to reimburse oncology drugs without assessing the cost-effectiveness. The NHCI should look at for example the National Institute for Health and Care Excellence, which assesses the cost-effectiveness of all new drugs that are approved for the UK market.[131]

At last, it is noteworthy to mention that a cost-effectiveness lower than the WTP threshold is not the only criterion to add a drug to the basic benefit package. As mentioned before, new intramural drugs with a budget impact of € 10 million per year or less and whereby the costs per patient are € 50,000 per year or less are added automatically in the basic benefit package.[18,19] Intramural drugs with a higher estimated budget impact can be placed in the so-called drug lock which entails that those drugs are temporarily excluded from the basic benefit package. The lock procedure was implemented to tackle budgetary problems. During the time that a drug is in the lock, the NHCI assesses if the drug should be added to the basic benefit package. This assessment of the NHCI involves a scientific evaluation of the drug and is based on four package criteria (necessity, effectiveness, cost-effectiveness and feasibility). Necessity includes the burden of the disease and feasibility is about whether or not the inclusion of the drug in the package is feasible in practice, also considering the anticipated budget impact. Because other criteria besides the cost-effectiveness are taken into account, a drug can be considered not cost-effective while still being reimbursed on the basis of the other three criteria.[133] However, assessing the cost-effectiveness remains a justified criterion to decide what drugs to reimburse.[134]

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Appendices

Appendix 1 Calculations of input parameters

Table 1 Consumer price indices between 2010 and 2021 in the Netherlands[69]

Year	Year mutation consumer price index
2010	1.3
2011	2.3
2012	2.5
2013	2.5
2014	1
2015	0.6
2016	0.3
2017	1.4
2018	1.7
2019	2.6
2020	1.3
2021	1.6

Table 2 Incidence of relevant treatment related adverse events in both treatment arm specified by grade[93]

Treatment Related Adverse Event	Alpelisib plus fulvestrant group N = 284		Placebo plus fulvestrant group N = 287	
	Grade 3	Grade 4	Grade 3	Grade 4
Hyperglycaemia	93 (32.7)	11 (3.9)	1 (0.3)	1 (0.3)
Diarrhoea	19 (6.7)	0	1 (0.3)	0
Rash	28 (9.9)	0	1 (0.3)	0

Table 3 Disaggregated costs of intravenous and subcutaneous administration for 2016[75]

Costs category	Intravenous administration	Subcutaneous administration
Hospital costs		
Admission day care unit	€ 95.95	€ 38.05
Preparation of drug		
Active healthcare professional time	€ 8.36	€ 3.83
Consumables	€ 5.46	€ 2.00
Administration of drug		

Active healthcare professional time	€ 22.34	€ 17.71
Premedication	€ 0.19	€ 0.13
Consumables	€ 8.88	€ 0.43
IV infusion related (e.g. infusion line, IV cannula)	€ 7.85	€ 0.00
Sodium chloride/aqua for infusion/injection	€ 0.30	€ -
Syringes and needles	€ 0.30	€ 0.14
Disinfectant, gauzes, bandages, and plasters	€ 0.15	€ 0.12
Protective materials (e.g. gloves, gown, mask)	€ 0.28	€ 0.18

Table 4 Laboratory prices for specific tests

Type laboratory assessment	Specific laboratory assessment	Costs	Honorarium	Units	Reference
Haematology	Haemoglobin (incl. (optional) haematocrit and celindices (MCV, MCH and MCHC and erythrocyte)).	€ 1.66	€ 0.16	1	[102]
Fasting Chemistry (full)	Calcium	€ 1.66	€ 0.48	1	[102]
	Magnesium	€ 3.27	€ 0.79	1	[102]
	Potassium	€ 1.66	€ 0.32	1	[102]
	Sodium	€ 1.66	€ 0.32	1	[102]
	Alkaline phosphatase	€ 1.66	€ 0.48	1	[102]
	Bilirubin, kwantatif, total or direct, every	€ 1.66	€ 0.16	3	[102]
	Gamma-glutamyl-transpeptidase	€ 1.66	€ 0.48	1	[102]
	Protein	€ 1.66	€ 0.16	1	[102]
	Albumin	€ 1.66	€ 0.16	1	[102]
	Creatinin	€ 1.66	€ 0.32	1	[102]
	Urea	€ 1.66	€ 0.32	1	[102]
	Uric Acid	€ 1.66	€ 0.32	1	[102]
	Amino acid chromatogram	€ 45.83	€ 5.55	2	[102]
Fasting plasma glucose	Glucose	€ 1.54	-	1	[103]
HbA1c	HbA1c	€ 7.85	€ 1.43	1	[102]
Coagulation	Thromboplastin time (PTT)	€ 4.58	€ 0.16	1	[102]
	Lipase	€ 2.23	€ 0.16	1	[102]

Fasting lipase and amylase	Amylase	€ 2.23	€ 0.48	1	[102]

Table 5 Calculations of base case values of health state utilities and adverse event disutilities

	Source value	Calculation	Base case value	Ref-erence
Health states utilities				
Utility progression-free	0.726	-	0.726	[46]
Utility progressed disease	0.642	-	0.642	[46]
Utility death	0	-	0	[36]
Calculation utility of a health state per cycle	Patient in cycle in PF/PD * utility			
TRAEs disutilities				
Disutility hyperglycaemia	0.119	-	0.119	[90,91]
Disutility rash	0.06	-	0.06	[92]
Disutility diarrhoea	0.103	-	0.103	[61]
TRAEs incidences				
Hyperglycaemia (alpelisib and fulvestrant)	36.97%	-	36.97%	[93]
Rash (alpelisib and fulvestrant)	9.86%	-	9.86%	[93]
Diarrhoea (alpelisib and fulvestrant)	7.04%	-	7.04%	[93]
Hyperglycaemia (fulvestrant)	1.05%	-	1.05%	[93]
Rash (fulvestrant)	0.35%	-	0.35%	[93]
Diarrhoea (fulvestrant)	0.70%	-	0.70%	[93]
TRAEs median duration (days per year)				
Hyperglycaemia	6	-	6	[93]
Rash	11	-	11	[93]
Diarrhoea	18	-	18	[93]
Calculation disutility of an TRAE	Patients in cohort * TRAE incidence * TRAE duration * disutility			

Table 6 Calculations of base case values of direct medical costs

	Source value	Calculation	Base case value	Reference
Direct medical costs				
TRAEs costs (per event)				
Hyperglycaemia grade 3/4	€ 2932 (2010)	€ 2932/1.3*1.6	€ 3608.62	[94]
SD Hyperglycaemia grade 3/4	€ 2762 (2010)	€ 2762/1.3*1.6	€ 3399.38	[94]
N Hyperglycaemia grade 3/4	36	-	36	[94]
SD Hyperglycaemia grade 3/4	-	€ 3399.38/SQRT(36)	€ 566.56	[94]
Rash grade 3/4	€ 2329.6 (2014)	€ 2329.6/1*1.16	€ 3727.36	[95]
Diarrhoea grade 3/4	€ 1456 (2014)	€ 1456/1*1.16	€ 2329.60	[95]
Calculation TRAE costs	Patients in cohort * TRAE incidence * TRAE costs			
Screening costs				
Costs per cancer patients HRM EGFR+KRAS+BRAF hotspot (8 amplicons)	€ 97.62 (2020)	€ 97.62/1.3*1.6	€ 120.15	[96]
Costs per cancer patients HRM BRAF+NRAS hotspot (3 amplicons)	€ 74.56 (2020)	€ 74.56/1.3*1.6	€ 91.77	[96]
Screening for PIK3CA mutation	-	(€ 120.15 + € 91.77)/2	€ 105.96	[96]
Calculation screening costs	Patients in cohort * 100/40* screening costs			
Drug acquisition costs				
Unit costs alpelisib per 150 mg	€ 70.07	-	€ 70.07	[73]
Unit costs fulvestrant per 50 mg/ml for 5ml	€ 201.34	-	€ 201.34	[74]
Unit costs anastrozole per mg	€ 0.26	-	€ 0.26	[97]
Unit costs capecitabine per 150 mg for 60 pieces	€ 29.74	-	€ 29.74	[98]

Unit costs paclitaxel per 6 mg/ml for 5 ml	€ 66.79	-	€ 66.79	[99]
Unit costs docetaxel per 20 mg/ml for 1 ml	€ 90.37	-	€ 90.37	[100]
Drug dosages				
Alpelisib for each time of intake	300 mg		300 mg	[10,13]
Frequency of alpelisib intake every cycle	Every day	-	Every day	[10,13]
Alpelisib for each cycle	-	300 mg * 28 times	8400 mg	[10,13]
Fulvestrant for each time of adminstration	500 mg	-	500 mg	[10,13]
Frequency of fulvestrant administration first cycle	Day 1 and day 15 of the cycle	-	Day 1 and day 15 of the cycle	[10,13]
Fulvestrant for first cycle	-	500 mg * 2 times	1000 mg	[10,13]
Frequency of fulvestrant administration subsequent cycle	Day 1 of the cycle	-	Day 1 of the cycle	[10,13]
Fulvestrant for subsequent cycles	-	500 mg * 1 times	500 mg	[10,13]
Anastrozole for each time of intake	1 mg	-	1 mg	[97]
Frequency of anastrozole intake every cycle	Every day	-	Every day	[97]
Anastrozole for each cycle	-	1mg * 28 times	28 mg	[97]
Body surface area	1.7 m^2	-	1.7 m^2	[104]
Capecitabine for each time of drug intake	1250 mg/m²	-	1250 mg/m²	[98]
Frequency of capecitabine intake every cycle	Every 12 hours for 2 weeks followed by 1 week of stop every 3 weeks	1*4 weeks/3 weeks	Every 12 hours for 2 weeks for 1.33 times	[98]
Capecitabine for each cycle	-	1250 mg/m² * 1.7 m^2 * 2 * 14 * 1.33	79,333.33 mg	[98]

Paclitaxel for each time of administration	175 mg/m²	-	175 mg/m²	[99]
Frequency administration of paclitaxel every cycle	1 time every 3 weeks	1*4 weeks/3 weeks	1.33 times	[99]
Paclitaxel for each cycle	-	175 mg/m² * 1.7 m^2 * 1.33	396.67 mg	[99]
Docetaxel for each time of administration	100 mg/m^2	-	100 mg/m^2	[100]
Frequency administration of docetaxel every cycle	1 time every 3 weeks	1*4 weeks/3 weeks	1.33 times	[100]
Docetaxel for each cycle	-	100 mg/m^2 * 1.7 m^2 * 1.33	226.67 mg	[100]
Probabilities of treatment administration for progressed disease				
Probabilities of receiving treatment	0.833	-	0.833	[46]
Probabilities of receiving best supportive care	0.167	-	0.167	[46]
Anastrozole	0.6	-	0.6	[46]
Capecitabine	0.2	-	0.2	[46]
Paclitaxel	0.1	-	0.1	[46]
Docetaxel	0.1	-	0.1	[46]
Calculation drug acquisition costs	Patients in a cycle of PF/PD * probability of receiving treatment * probability of receiving a certain treatment * unit costs / dosage in one unit * drugs for each cycle			
End of life care costs				
End of life care costs in the last 30 days	$ 3646 (2010)	-	$ 3646 (2010)	[59]
Share of costs that take place in the last 14 days	2/3	-	2/3	[46]
PPP of 1 USD in Euro	0.9 (2010)	-	0.9 (2010)	[70]

End of life care costs in the last 14 days for 2010	-	$ 3,646*0.9*2/3	€ 2,187.6	[59]
End of life care costs in the last 14 days	-	€ 2,187.6/1.3*1.6	€ 2,692.43	[59]
N end of life care costs	9520	-	9520	[59]
SD end of life care costs	$ 7227 (2010)	-	$ 7227 (2010)	[59]
SE end of life care costs	-	$ 7227/SQRT(9520) *0.9/1.3*1.6	$ 91.16	[46,59,70]
Calculation end of life care costs	Newly died patients in cycle * end of life care costs			
Resource use unit costs				
Administration costs				
Subcutaneous administration health care costs	€ 62.16 (2016)	€ 62.16/0.3*1.6	€ 331.52	[75]
Intravenous administration health care costs	€ 141.17 (2016)	€ 141.17/0.3*1.6	€ 752.91	[75]
Calculation administration costs	Patients in cycle of PF/PD * times of treatment administration * price of administration			
Outpatient (specialist) visit	€ 91 (2014)	91/1*1.6	€ 145.60	[36]
CT scan estimated average	€ 234.98	234.98*1.10	€ 258.48	[101]
MRI scan estimated average	€ 384.82	€ 384.82*1.10	€ 423.30	[101]
Haematology	€ 1.82 (2013)	€ 1.82/2.5*1.6	€ 1.16	[102]
Fasting chemistry	€ 130.10 2013)	€ 130.10/2.5*1.6	€ 83.26	[102]
Fasting plasma glucose	€ 1.54 2019)	€ 1.54/2.6*1.6	€ 0.95	[103]
HbA1c	€ 9.28 2013)	€ 9.28/2.5*1.6	€ 5.94	[102]
Coagulation	€ 4.74 92013)	€ 4.74/2.5*1.6	€ 3.03	[102]

Fasting lipase and amylase	€ 5.10 2013)	€ 5.10/2.5*1.6	€ 3.26	[102]
Outpatient nurse visit	€ 35 (2014)	€ 35/1*1.6	€ 56.00	[36]
Outpatient general practitioner visit	€ 33 (2014)	€ 33/1*1.6	€ 52.80	[36]
Monitoring costs PD health state	€ 357.28 (2016)	€ 357.28/0.3*1.6	€ 1905.49	[46]
Resource use				
Outpatient visits for imaging first 20 cycles	0.5	-	0.5	[10]
Outpatient visit for imaging after 20th cycle	0.33	-	0.33	[10]
CT scan in the first 20 cycles	0.25	-	0.25	[10]
CT scan in the after the 20th cycle	0.167	-	0.167	[10]
MRI-scan in the first 20 cycles	0.25	-	0.25	[10]
MRI-scan after the 20th cycle	0.167	-	0.167	[10]
Probability of having bone lesion in alpelisib group	77.5	-	77.5	[10]
Probability of having bone lesion in fulvestrant group	70.3	-	70.3	[10]
Outpatient visits for laboratory assessments	1	-	1	[10]
Haematology testing cycle 2	2	-	2	[10]
Haematology testing other cycles	1	-	1	[10]
Fasting chemistry testing from 2nd cycle	1	-	1	[10]
Fasting plasma glucose testing first 2 cycles	2	-	2	[10]
Fasting plasma glucose testing first 2 cycles from 3rd cycle	1	-	1	[10]
HbA1c testing cycle 2	1	-	1	[10]
HbA1c testing other cycles	0.33	-	0.33	[10]
Coagulation testing per cycle	0.5	-	0.5	[10]

Fasting lipase and amylase testing per cycle	1	-	1	[10]
Calculation monitoring costs	Patient in cycle of PF/PD * resource uses * resource price			
Outpatient specialist visit for BSC per cycle	0.5	-	0.5	[46]
Outpatient general practitioner visit per cycle	0.15	-	0.15	[46]
Outpatient nurse visit per cycle	0.5	-	0.5	[46]
Probability of receiving BSC	16.7%	-	16.7%	
Calculating BSC costs	Patient in cycle of PD * probability of receiving BSC * resource use * resource price			

Table 7 Calculations of base case values of indirect medical costs

	Source value	Calculation	Base case value	Ref-erence
Indirect medical costs				
Per capita annual health care expenditure last year of life				
63	€ 55,968 (2017)	€ 55,968/1.4*1.6	€ 63,963.43	[61]
64	€ 55,758 (2017)	€ 55,758/1.4*1.6	€ 63,723.43	
65	€ 55,592 (2017)	€ 55,592/1.4*1.6	€ 63,533.71	
66	€ 55,347 (2017)	€ 55,347/1.4*1.6	€ 63,253.71	
67	€ 54,939 (2017)	€ 54,939/1.4*1.6	€ 62,787.43	
68	€ 54,403 (2017)	€ 54,403/1.4*1.6	€ 62,174.86	
69	€ 53,833 (2017)	€ 53,833/1.4*1.6	€ 61,523.43	
70	€ 53,310 (2017)	€ 53,310/1.4*1.6	€ 60,925.71	
71	€52,899 (2017)	€52,899/1.4*1.6	€ 60,456.00	
72	€ 52,637 (2017)	€ 52,637/1.4*1.6	€ 60,156.57	
73	€ 52,553 (2017)	€ 52,553/1.4*1.6	€ 60,060.57	
74	€ 52,657 (2017)	€ 52,657/1.4*1.6	€ 60,179.43	
75	€ 52,926 (2017)	€ 52,926/1.4*1.6	€ 60,486.86	
76	€ 53,305 (2017)	€ 53,305/1.4*1.6	€ 60,920.00	
77	€ 53,743 (2017)	€ 53,743/1.4*1.6	€ 61,420.57	
78	€ 54,272 (2017)	€ 54,272/1.4*1.6	€ 62,025.14	
79	€54,981 (2017)	€ 54,981/1.4*1.6	€ 62,835.43	
80	€ 55,921 (2017)	€ 55,921/1.4*1.6	€ 63,909.71	
81	€ 57,165 (2017)	€ 57,165/1.4*1.6	€ 65,331.43	
82	€ 58,747 (2017)	€ 58,747/1.4*1.6	€ 67,139.43	
*Per capita annual health care expenditure o*ther years				
63	€ 4,829 (2017)	€ 4,829/1.4*1.6	€ 5,518.86	[61]
64	€ 4,981 (2017)	€ 4,981/1.4*1.6	€ 5,692.57	
65	€ 5,149 (2017)	€ 5,149/1.4*1.6	€ 5,884.57	

66	€ 5,332 (2017)	€ 5,332/1.4*1.6	€ 6,093.71	
67	€ 5,531 (2017)	€ 5,531/1.4*1.6	€ 6,321.14	
68	€ 5,751 (2017)	€ 5,751/1.4*1.6	€ 6,572.57	
69	€ 6,003 (2017)	€ 6,003/1.4*1.6	€ 6,860.57	
70	€ 6,297 (2017)	€ 6,297/1.4*1.6	€ 7,196.57	
71	€ 6,642 (2017)	€ 6,642/1.4*1.6	€ 7,590.86	
72	€ 7,050 (2017)	€ 7,050/1.4*1.6	€ 8,057.14	
73	€ 7,526 (2017)	€ 7,526/1.4*1.6	€ 8,601.14	
74	€ 8,074 (2017)	€ 8,074/1.4*1.6	€ 9,227.43	
75	€ 8,695 (2017)	€ 8,695/1.4*1.6	€ 9,937.14	
76	€ 9,391 (2017)	€ 9,391/1.4*1.6	€ 10,732.57	
77	€ 10,165 (2017)	€ 10,165/1.4*1.6	€ 11,617.14	
78	€ 11,032 (2017)	€ 11,032/1.4*1.6	€ 12,608.00	
79	€ 12,021 (2017)	€ 12,021/1.4*1.6	€ 13,738.29	
80	€ 13,164 (2017)	€ 13,164/1.4*1.6	€ 15,044.57	
81	€ 14,491 (2017)	€ 14,491/1.4*1.6	€ 16,561.14	
82	€ 16,032 (2017)	€ 16,032/1.4*1.6	€ 18,322.29	

Table 8 Calculations of base case values of direct non-medical costs

	Source value	Calculation	Base case value	Reference
Direct non-medical costs				[36]
Travel costs				[36]
Travel distance to the hospital in km	7	-	7	[36]
Travel distance to the general practitioner in km	1.1	-	1.1	[36]
Travel costs per km with car	€ 0.19 (2014)	€ 0.19/1*1.6	€ 0.30	[36]
Parking costs	€ 3.00 (2014)	€ 3.00/1*1.6	€ 4.80	[36]
Calculation travel costs	Times travelling * (travel distance * 2 *travel costs per km + parking costs)			
Informal care costs				
Informal care price per hour	€ 14.00 (2014)	€ 14.00/1*1.6	€ 22.40	[36]
Hours of informal care (PF state)	12 hours in a week	12 hours per week * 4 weeks	48 hours	[76]
Hours of informal care (PD state)	8 hours in a week	8 hours per week * 4 weeks	32 hours	[76]
Calculation informal care costs	Patient in cycle of PF/PD * informal care price per hour * hours of informal care			

Table 9 Calculations of base case values of indirect non-medical costs

	Source value	Calculation	Base case value	Reference
Indirect non-medical costs				
Productivity costs				
Average hours of work in weeks	26	-	26	[84]
Filled vacancies	1085	-	1085	[85]
Open vacancies	221.3	-	221.3	[85]
Friction period in weeks	-	(365/(1085/221.3)+28)/7	14.64	[36,85]
Productivity costs per hour	€ 31.60	€ 31.60/1*1.6	€ 50.56	[36]
Probability of having a job	63.8%	-	63.8%	[83]
Retirement age	66 years and 3 months	-	66 years and 3 months	[82]
Median age	63			[13]
Calculation productivity costs (applied for 3 years and 3 months)	Newly progressed patient in cycle * probability of having a job * average hours of work * productivity costs per hour * friction period in weeks			

Appendix 2 Search strategy for the utilities and disutilities

Table 1 MeSH terms for conducting a targeted literature review to collect utilities and disutilities in PubMed/MEDLINE

MeSH terms											
AND	Breast Neoplasms	OR	Neoplasm Metastasis	OR	Neoplasm Staging						
	Cost-Benefit Analysis	OR	Decision Making	OR	Health Status	OR	Models, Economic	OR	Quality of Life	OR	Technology Assessment, Biomedical

Table 2 Criteria for selecting (dis)utilties for health states and TRAEs

	Health states and TRAEs
Criteria	Estimated for advanced breast cancer Estimated for HR+/HER2- breast cancer Measured in Dutch patients Based on the EQ-5D-5L Valued by the Dutch general public/based on Dutch tariffs Estimated for patients with PIK3CA mutation

Appendix 3 Dose adjustments

Table 1 Treatment exposure and dose adjustments for alpelsib and fulvestrant[10]

Treatment exposure	PIK3CA-mutant	
	Alpelisib + fulvestrant (N=169)	Placebo + fulvestrant (N=171)*
Exposure to alpelisib/placebo		
Median duration of exposure, months (range) [n exposed]	5.5 (0.0–29.0) [168]	4.6 (0.0–30.1) [170]
Median relative dose intensity, %	82.7	100
Dose adjustments, n (%)		
Patients with dose interruptions (≥1)	125 (74.0)	55 (32.2)
Dose interruptions due to treatment-related adverse events	116 (68.6)	27 (15.8)
Patients with dose reductions (≥1)	108 (63.9)	15 (8.8)
Dose reductions due to treatment-related adverse events	105 (62.1)	8 (4.7)
Dose discontinuations due to treatment-related adverse events	43 (25.4)	8 (4.7)

*1 patient in the placebo arm of the *PIK3CA*-mutant cohort did not receive fulvestrant or placebo.

Appendix 4 AIC values

Table 1 AIC values for the modelled PFS and OS curves with survival distributions for alpelisib and fulvestrant

	AIC values							
	Alpelisib				Fulvestrant			
	exponential	*Weibull*	*lognormal*	*loglogistic*	*exponential*	*Weibull*	*lognormal*	*loglogistic*
PFS	918.421	918.9246	910.8697	912.2103	1045.386	1045.607	1015.536	1025.069
OS	1066.771	1049.926	1068.429	1058.517	1030.815	1027.339	1029.514	1027.919