What is the cost-effectiveness of veliparib in combination with carboplatin and paclitaxel, compared to carboplatin with paclitaxel only, for patients with BRCA-positive, triple-negative, or HER2-negative, advanced breast cancer, who received up to two chemotherapy regimens for advanced disease, in the UK?

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Master Thesis
MSc. Health Economics, Policy, and Law
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Location: Rotterdam, Netherlands
Date: 23.06.2021
Wordcount: 19348

Summary

Background: Veliparib in combination with carboplatin and paclitaxel, is seeking market authorization in the UK for the treatment of BRCA-mutated, HER2 negative, advanced breast cancer. To guarantee an efficient allocation of resources, the National Institute of Health and Care Excellence (NICE) in the UK evaluates new treatments based on their effectiveness and cost-effectiveness. To contribute to the reimbursement decision of veliparib the economic evaluation in this study compared veliparib as combination therapy to carboplatin with paclitaxel.

Methods: A cost-utility analysis based on the NICE reference case was conducted, using a three-health state Markov cohort model with a life-time horizon. Costs were calculated as monetary values and from a NHS and PSS payer perspective. Health effects were captured via Quality Adjusted Life Years (QALYs) and included for patients receiving treatment. A base-case analysis was conducted to calculate the Incremental Cost-Effectiveness Ratio (ICER). To identify the uncertainty around the results, deterministic sensitivity analyses (DSAs), scenario analyses and a probabilistic sensitivity analysis (PSA) were used. The ICER was compared to the national willingness-to-pay threshold (WTP) in the UK of £30,000 per QALY.

Results: Costs per patients were higher in the veliparib arm (£202,591.09 vs. £155,583.49). QALYs gained were slightly higher with veliparib (1.99 vs. 1.95), however, Life Years (LYs) gained were lower (2.94 vs. 3.00). An ICER of £1,355,064.49 was calculated. Scenario analyses showed that the results were sensitive to variations in utilities and in the price of veliparib. The probability of veliparib being cost-effective was around 5% at the threshold value.

Conclusion: Due to high costs and only moderate health benefits, veliparib was not considered cost-effective. However, one should keep in mind, that patients in the control group received cross-over treatment, leading to potential bias in survival and cost outcomes.

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ABC	Advanced breast cancer
AE	Adverse event
AIC	Akaike information criterion
BIC	Bayesian information criterion
BRCA	Breast Cancer gene
BSA	Body surface area
BSC	Best supportive care
CEA	Cost-effectiveness analysis
CEAC	Cost-effectiveness acceptability curve
CI	Confidence Interval
CUA	Cost-utility analysis
DSA	Deterministic sensitivity analysis
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicine Agency
ER	Estrogen
EQ-5D	EuroQoL-5Dimension
HER2	Human epidermal growth factor receptor 2
HTA	Health technology assessment
HR	Hazard Ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ITT	Intention to treat
LY	Life year
MBC	Metastatic breast cancer
NHS	National Health Service
NICE	The National Institute of Health and Care Excellence
OS	Overall survival
PARP	Poly (ADP-ribose) polymerases
PFS	Progression-free survival
PgR	Progesterone
PSA	Probabilistic sensitivity analysis
PSS	Prescribed Specialized Services
QALY	Quality-adjusted life year
SD	Standard deviation
SE	Standard error
SLR	Systematic literature review
TEAE	Treatment-emergent adverse events
TNBC	Triple negative breast cancer

Introduction

Breast cancer is the most common cancer affecting women in the UK with 54,700 women diagnosed alone in 2017 (*Breast Cancer Statistics*, n.d.). Out of all diagnosed women, less than 10% are carriers of a mutation in the key tumour suppressor genes, also called the BRCA genes. (Armstrong et al., 2019; *BRCA The Breast Cancer Gene*, 2020). Without a mutation, the BRCA genes would normally play a large role in preventing the development of cancer by helping to repair DNA breaks that otherwise can lead to cancer and tumour growth. However, mutated BRCA1/2 genes are unable to work properly in repairing damaged DNA through homologous recombination (Akram et al., 2017; *BRCA The Breast Cancer Gene*, 2020; Diéras et al., 2020b). This malfunctioning of the BRCA1/2 genes is associated with an increased risk of developing breast and ovarian cancer (Sharma et al., 2014). According to the National Breast Cancer Foundation (2020), 55-65% of women with a BRCA1 and 45% with a BRCA2 mutation are estimated to develop breast cancer before the age of 70 (*BRCA The Breast Cancer Gene*, 2020). Furthermore, patients with a BRCA mutation, especially a BRCA1 mutation, are more likely to have a triple-negative breast cancer (TNBC). Women with this rare type of breast cancer do not have the common receptors Oestrogen (ER) and Progesterone (PgR), and do not produce the protein human epidermal growth factor receptor 2 (HER2), which makes them not suitable for therapies targeting hormone receptors (*BRCA The Breast Cancer Gene*, 2020; *What Is Breast Cancer*, 2020). In contrast to BRCA1, BRCA2 carcinomas are often ER- and PgR- positive and are therefore called hormone receptor-positive (HR+). Most cases of HR+ breast cancers, however, do not express HER2 receptors (HER2-negative) (Diéras et al., 2020a, p. 119).

Despite recent advances in potential treatment options for advanced or metastatic, TNBC or HER2 negative breast cancer, additional options are needed, especially for patients that progressed after their previous therapy line. Currently, NICE does not state any specific

recommendations for the treatment of BRCA-mutated cancer for patients that progressed after first line therapy. However, a systematic review by Armstrong et al. (2019), identified several European guidelines, recommending treatment with platinum agents as carboplatin, for BRCA-mutated cancer types (Armstrong et al., 2019).

In addition, the combination therapy of the platinum compound carboplatin and the antimicrotubular agent paclitaxel, demonstrated good response rate, for highly active breast cancer (Diéras et al., 2020a, p. 121, 2020b). Further, data indicates that BRCA-mutated tumours are sensitive towards the combination of both agents due to carboplatin's DNA-damaging effect and paclitaxel's potential platelet-sparing effect (Diéras et al., 2020a, p. 121, 2020b).

A different treatment approach to chemotherapy, are poly (ADP-ribose) polymerases (PARP) inhibitors, which target PARP proteins in the body. PARP proteins are nuclear enzymes, which help in repairing damaged DNA leading to the replication of BRCA-mutated cells (Livraghi & Garber, 2015; Turk & Wisinski, 2018).

However, some patients treated with chemotherapy or PARP inhibitors experience reversion mutations that restore the BRCA function, leading to concerns about cross-resistance (Diéras et al., 2020b). Therefore, new treatments that maximise the therapeutic benefits in BRCA mutated breast cancer are needed. A new approach to improve treatment outcomes is combining platinum therapy with PARP inhibitors. The orally administered PARP inhibitor veliparib is following this approach and has shown antitumour activity in tumours defective in DNA damage repair. The treatment was tested in combination with carboplatin and paclitaxel in the BROCADE3 clinical trial (Diéras et al., 2020b).

With several new cancer treatments currently under National Institute of Health and Care Excellence (NICE) development and the high costs associated with such treatments, it is important to evaluate those regarding their effectiveness and cost-effectiveness from a National

Health Services (NHS) and Prescribed Specialized Services (PSS) payer perspective in order to guarantee a balance between high costs and potential health benefits. (*Methods for Development of NICE Guidance*, 2012). Veliparib is seeking market authorization in the UK as combination therapy with carboplatin and paclitaxel, for patients with BRCA-positive, HER2 negative advanced breast cancer, who received up to two chemotherapy regimens for advanced disease (*Veliparib NICE Appraisal*, 2019). By conducting an economic evaluation of veliparib in comparison to carboplatin and paclitaxel for advanced breast cancer in the UK, this paper will contribute to the reimbursement discussion around veliparib. Therefore, the research question of this paper reads as follows:

"What is the cost-effectiveness of veliparib in combination with carboplatin and paclitaxel, compared to carboplatin with paclitaxel only, for patients with BRCA-positive, triple-negative, or HER2-negative, advanced breast cancer, who received up to two chemotherapy regimens for advanced disease, in the UK?"

Theoretical Background

In this section the rationale behind using a decision analytic modelling approach for the economic evaluation of veliparib will be elaborated considering the NICE reference case, determining the methodology of the economic evaluation conducted in this study. In addition, the BROCADE3 clinical trial as the key source for clinical parameters in the model will be described. Lastly, previous health economic evaluations of veliparib for BRCA-mutated, advanced breast cancer will be discussed.

Economic evaluation and the role of decision analytic modelling

Due to the high financial burden of cancer for national health care systems, it is crucial to evaluate treatments grounded on evidence-based research. One element of such evidence-based decision making in the UK is conducting economic evaluations for new treatment alternatives (Hall et al., 2015; *Methods for Development of NICE Guidance*, 2012). In the UK,

NICE is analysing new treatments based on their clinical- and cost-effectiveness to make decisions between different alternatives (*Guide to the Methods of Technology Appraisal*, 2013). To guarantee a consistent approach when evaluating new health interventions, NICE defined a reference case, describing the methods that are considered appropriate by the institute for the performance of economic evaluations (*Guide to the Methods of Technology Appraisal*, 2013). The following section will elaborate why an economic evaluation is an important tool for the evaluation of a new health intervention and how the NICE reference case defines methodological elements for such an evaluation.

In an economic evaluation several health alternatives are compared against each other regarding their costs and health outcomes, to estimate how scarce health care resources should be allocated to maximise populations health. Outcomes in this context can be described as the effects of an intervention, mainly focusing on the individual's health effects (Briggs et al., 2006, p. 2).

According to the NICE reference case, the preferred type of health economic evaluation is a cost-effectiveness analysis, using a generic measure of health to capture the consequences of two or more alternatives (Briggs et al., 2006; *Guide to the Methods of Technology Appraisal*, 2013). In practice an often-used generic health measure is the quality-adjusted life-year (QALY). A QALY takes two key aspects of a health intervention's effect into account, the impact on a patient's length of life and the impact of a patient's health-related quality of life (Drummond et al., 2015, p. 8,9; *Guide to the Methods of Technology Appraisal*, 2013). To obtain patient's quality of life, several types of measurements can be used. NICE, however, recommends the use of the generic EQ-5D questionnaire, compiling five dimensions of health (mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression) in which the patients' health-related quality of life is assessed directly by the patient (*Guide to the Methods of Technology Appraisal*, 2013). After the patient's self-

assessment, a sample of the UK population, representing public-preferences, evaluates the utilities (on a scale of 0-1) of the quality-of-life changes, via a choice-based method such as the time trade-off method (Drummond et al., 2015, p. 8; *Guide to the Methods of Technology Appraisal*, 2013).

Cost-effectiveness analyses using QALYs as a measure of health effects and a monetary value as a measure of costs, are referred as cost-utility analyses (Drummond et al., 2015, p. 8,9; *Guide to the Methods of Technology Appraisal*, 2013). A cost-utility analysis combines the costs and health effects of two comparing interventions, therefore, differences in these parameters can be determined and a decision regarding resource allocation can be made (Briggs et al., 2006, p. 5). To what extend costs and effects are included in the analysis is depending on the evaluation's perspective. Economic evaluations for NICE should include all direct health effects for patients, if relevant also for other people such as caregivers, and all costs affecting the NHS and PSS as the public payers in the UK (*Guide to the Methods of Technology Appraisal*, 2013).

An intervention that is less costly and yields more health effects compared to the alternative is considered dominant over the comparator (Briggs et al., 2006, p. 5). However, typically new health interventions have higher health benefits than their predecessor but at the same time also show higher costs (Briggs et al., 2006, p. 5). In such cases it is important to determine whether an intervention is still considered cost-effective despite higher costs. A decision element used for these situations is the calculation of an incremental cost-effectiveness ratio (ICER) (Briggs et al., 2006, p. 5).

$$\text{ICER} = \frac{\text{Costs(A)} - \text{Costs(B)}}{\text{Benefits(A)} - \text{Benefits(B)}} \qquad \text{Equation 1}$$

The ICER takes the difference in costs and the difference in effects of compared interventions into account and determines the additional costs of gaining one extra QALY from the treatment that is considered more effective. In order to make a valid statement about the

cost-effectiveness of an intervention, the ICER needs to be compared to a given threshold value (Briggs et al., 2006, p. 5). For NICE, the threshold value used for decision-making reflects the opportunity costs of financing one health alternative over the other. The reference case does not state a precise threshold value for decision making, however, it is mentioned that technologies with an ICER of more than £30,000 per QALY need to deliver strong arguments supporting their case. Relevant elements to argue in favor of an ICER above £30,000 per QALY might be the innovative nature of the technology, treatments that are extending patients life, or treatments accruing in the end-of-life stage (*Guide to the Methods of Technology Appraisal*, 2013).

Using the ICER to compare different alternatives and to decide, regarding their cost-effectiveness comes always with conditions of uncertainty. To deal with uncertainty in decision making, an economic evaluation in health care predominantly uses decision analytic modelling (Briggs et al., 2006, p. 6). Analytic modelling "uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated. Based on the inputs into the model, the likelihood of each consequence is expressed in terms of probabilities, and each consequence has a cost and an outcome." (Briggs et al., 2006, p. 6). To estimate the inputs used in the model, extracting and synthesizing evidence from several sources is a crucial part of the analysis, according to the NICE reference case (*Guide to the Methods of Technology Appraisal*, 2013). Especially, the clinical trial of the evaluated health intervention is an important source for the input parameters used in the model (Briggs et al., 2006, p. 8; *Guide to the Methods of Technology Appraisal*, 2013).

Additionally, a considerable influence on the uncertainty of decision making in health care is the time horizon in which the treatment has been observed and analyzed. In order to make an informed decision it is crucial to know, how differences in costs and effects will develop in the future. Therefore, a sufficiently long time-horizon needs to be adopted in the

economic evaluation. NICE recommends the adoption of a life-time horizon so all costs and effects over a life-time are included in the analysis (*Guide to the Methods of Technology Appraisal*, 2013). However, the availability of long-term data is often limited. This is especially true for health outcomes measured via a clinical trial with a given follow-up period. A modelling approach offers a framework to deal with this issue by allowing to extrapolate relevant clinical data from a given clinical trial (Briggs et al., 2006, p. 7-8; Drummond et al., 2015, pp. 317, 339).

This study will use a modelling approach for the economic evaluation of veliparib in combination with carboplatin and paclitaxel compared to carboplatin and paclitaxel alone and will incorporate the methodological elements described in the NICE reference case in the model. As described above this allows relevant evidence from multiple sources to be synthesized into estimates of the costs and effects for the two compared treatments. The strategy used to identify estimations for costs and benefits and how these values were incorporated in the model of veliparib will be elaborated in chapter three of this paper.

As briefly mentioned above, the clinical trial of a treatment is of great importance for the extraction of relevant health outcomes. This also applies for the economic evaluation of veliparib, in which the BROCADE3 clinical trial was used as the main source for clinical outcomes such as overall survival (OS), progression free survival (PFS), adverse events (AEs), but also the cycle length for the model. Therefore, the BROCADE3 clinical trial will be described in detail in the next section of this chapter.

The BROCADE3 clinical trial

BROCADE3 is a randomised, double-blind, placebo-controlled, phase 3 clinical trial comparing veliparib in combination with carboplatin and paclitaxel against carboplatin and paclitaxel only. Patients with confirmed metastatic or locally advanced, unresectable, triple-negative or HER2-negative breast cancer, with germline BRCA1 or BRCA2 mutations, and up

to two previous lines of chemotherapy and up to one previous line of platinum therapy, were included in the trial (Diéras et al., 2020b). Further inclusion criteria were an Eastern Cooperative Oncology Group (ECOG) performance status between 0-2 and no progression within 12 months of completing previous line of platinum therapy. Excluded were patients that had a previous treatment line with a PARP inhibitor. Patients were randomly assigned (2:1) to either the treatment group with a combination therapy of veliparib, carboplatin and paclitaxel or the control group, receiving chemotherapy with carboplatin and paclitaxel only. Patients received veliparib or placebo, orally, twice daily at a dose of 120mg, on day 1 to 7 of each 21-day cycle. Additionally, 6 mg/ml per min intravenously of carboplatin on day 3 of each cycle and 80 mg/m^2 intravenously of paclitaxel on day 3, 10, and 17 within each cycle, was administered. This treatment schedule was followed until disease progression or unacceptable toxicity. The dose of any of the three medications could have been reduced or discontinued individually during treatment. Patients discontinuing treatment with carboplatin and paclitaxel because of reasons other than disease progression, received veliparib or placebo monotherapy, twice daily at a starting does of 300mg with the possibility to escalate up to 400mg. In case of disease progression patients in the control group were unblinded and could switch to the veliparib monotherapy treatment. (Diéras et al., 2020a, pp. 180-183, 2020b).

Primary endpoint of the trial was PFS (time from randomisation to disease progression or death from any cause within 63 days of the last tumour assessment). Secondary endpoints were OS, clinical benefit rate (progression-free rate at 24 weeks), objective response rate (proportion of patients with confirmed partial or complete response per RECIST 1.1), and PFS 2 (time from randomization to disease progression on first subsequent therapy or death from any cause) (Diéras et al., 2020b).

Patient-reported outcomes questionnaires were administered at the beginning of each cycle, at final visit, and at the follow-up visit. Outcome questionnaires included the cancer-specific EORTC-QLQ-C30/BR23 and the generic EQ-5D-5L questionnaire (Diéras et al., 2020b).
In order to calculate the proportion of patients alive and progression free at 24 and 36 months, the trial used the Kaplan-Meier method to illustrate time-to-event curves.

In the trial, the intention-to-treat (ITT) population comprises 337 patients in the veliparib arm and 172 in the control arm. In both treatment arms roughly 50% of patients had a TNBC and 50% a HR+/HER2-negative cancer. A similar distribution was observed regarding the BRCA1 or BRCA2 mutation status. In around 50% of the patients a BRCA1 mutation was observed and in the other 50% a BRCA2 mutation. Most patients (70%) received previous chemotherapy in the neoadjuvant or adjuvant setting and 65% of patients with HR+ breast cancer had received previous endocrine therapy in any setting.

Median PFS was 14.5 months (95% CI 12.5-17.7) in the veliparib arm and 12.6 months (10.6-14.4) in the control arm. Median OS was 33.5 months (95% CI 27.6-37.9) in the veliparib arm and 28.2 months (24.7-35.2) in the control group.

Previous health economic evaluations for veliparib

In order to find previous cost-effectiveness analyses for veliparib in BRCA-positive, TNBC and/or HER2-negative advanced breast cancer, a database search was conducted in Embase, PubMed, and Google Scholar. Several search terms were used to identify relevant economic evaluations for veliparib in the described indication. The search in the three databases did not yield relevant cost-effectiveness analyses of veliparib for advanced breast cancer. However, one publication by Gonzalez et al., (2020) was identified studying the cost-effectiveness of several PARP inhibitors, including veliparib, in ovarian cancer from an US perspective. Gonzalez et al., (2020) compared patients receiving veliparib plus chemotherapy

to patients receiving chemotherapy only in a three state Markov model. Due to missing price information for veliparib a price of $13,000 was assumed for a one-month supply of veliparib. The analysis reported by Gonzalez et al., (2020) showed an ICER of $1,512,495/quality adjusted progression-free year (QA-PFY) for veliparib. Considering, the willingness to pay threshold of $150,000/QALY in the US, veliparib was not cost effective for the treatment of ovarian cancer from an US perspective. The paper highlights the benefits of PARP inhibitors in PFS but also stated the substantial high prices for this treatment approach, leading to the high ICER value (Gonzalez et al., 2020).

The lack of evaluations conducted for the use of veliparib in BRCA-mutated breast cancer suggests that this cost-utility analysis of veliparib in combination with chemotherapy for BRCA mutated, triple-negative and HER2-negative, advanced breast cancer from a UK healthcare perspective, may be the first economic evaluation in this indication.

Methods

This section of the paper will elaborate, how the decision analytic model for veliparib was constructed based on the NICE reference case described above (*Guide to the Methods of Technology Appraisal*, 2013). Further, it will be discussed, how the OS and PFS data from the BROCADE3 trial were extrapolated to achieve a longer time-horizon in the model and how input parameters regarding costs and health effects were researched and used in the model. Lastly, this section will describe, how the model deals with uncertainty.

Type of Economic Evaluation

The cost-utility analysis of veliparib in combination with carboplatin and paclitaxel compared to carboplatin and paclitaxel only, was conducted based on the recommendations on economic evaluations given by the NICE reference case (*Guide to the Methods of Technology Appraisal*, 2013). The economic evaluation is a cost-utility analysis hence, monetary values were used as a measure of costs and QALYs were used to capture health effects for people

using the treatment. In order to attain the QALYs, the time being in each health state was multiplied with utilities (on a scale of 0 to 1) attached to the specific health state (Drummond et al., 2015, p. 8; *Guide to the Methods of Technology Appraisal*, 2013). Since patients suffering from an oncological condition are predominantly treated by healthcare professionals, spill over effects, due to the impact of the disease and treatment on the quality of life of informal care givers, was not included in the analysis since only a limited impact was assumed (Brouwer, 2019; Diéras et al., 2020b).

The cost-utility analysis was conducted from a NHS and PSS perspective, including direct and indirect medical costs. A 20 year life-time horizon was implemented in the analysis, as recommended by NICE (*Guide to the Methods of Technology Appraisal*, 2013). A 20-year time horizon in this population was considered sufficient based on the patient's cancer characteristics. Patients in the clinical trial were in an advanced cancer stage, meaning that the cancer spread from the breast to other regions of the body. When a cancer reaches this stage, cure is no longer possible (*Advanced Breast Cancer*, n.d.; Diéras et al., 2020b). As reported by Johansson et al., (2020), advanced breast cancer in the two cancer subtypes included in the clinical trial, HER2-negative and triple-negative, are associated with a high mortality, once the cancer spreads (Johansson et al., 2021). This observation is also reflected in the median OS data obtained from the trial, in which median OS in the veliparib arm was 33.5 months (2.7 years) and 28.2 months (2.3 years) in the control arm (Diéras et al., 2020b).

Population

The target population for the economic evaluation of veliparib in this study was based on the scope of veliparib submitted to NICE and the BROCADE3 clinical trial (Diéras et al., 2020b; *Veliparib NICE Appraisal*, 2020). The scope targets BRCA-positive, HER2-negative advanced breast cancer patients for the treatment in first, second, or third line. However, the BROCADE3 clinical trial, used as the main source for clinical outcomes in this study, not only

included patients with a HER2-negative breast cancer but also with a triple-negative breast cancer in the analysis. Since the OS and PFS Kaplan-Meier curves in the trial incorporated both patient groups, the analysis in this study not only included HER2- negative advanced breast cancer patients, but also patients with advanced TNBC (Diéras et al., 2020b).

Intervention

The intervention of interest in the economic evaluation of this study is veliparib as combination therapy with carboplatin and paclitaxel. As described in the last chapter, veliparib was tested in the BRCOADE3 clinical trial in which patients were randomly assigned to the treatment group or the comparator group. In the treatment group patients received veliparib twice daily at a dose of 120mg, on day 1 to 7 of each 21-day cycle. Additionally, 6 mg/ml per min intravenously of carboplatin on day 3 of each cycle and 80 mg/m^2 intravenously of paclitaxel on day 3, 10, and 17 within each cycle. This treatment schedule was continued until disease progression (Diéras et al., 2020b). According to the study protocol, patients could discontinue treatment with carboplatin and paclitaxel before disease progression and receive single agent veliparib at 300mg, twice daily. The mean duration of monotherapy in the veliparib arm was 350 days (Diéras et al., 2020b). The treatment schedule, dosage, and maximum duration of each treatment agent in the treatment group of the model was based on the treatment schedule of the clinical trial.

Comparator

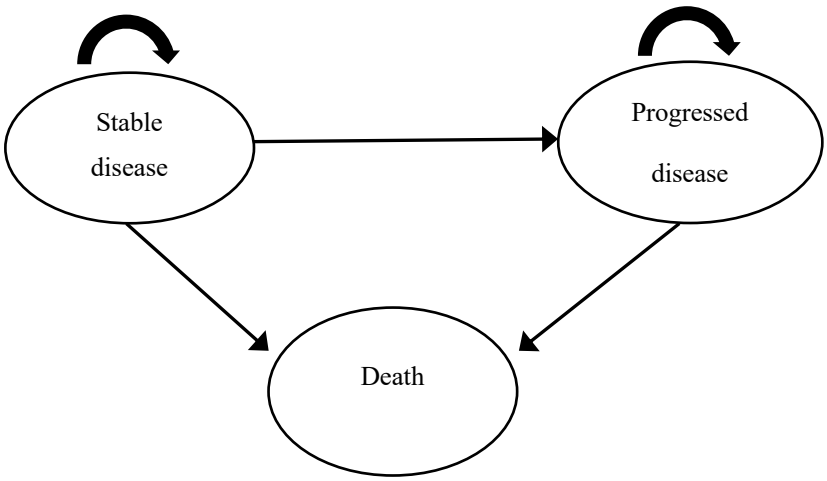
As mentioned in the introduction of this paper, NICE does not state specific recommendations for the treatment of BRCA-mutated breast cancer. However, Armstrong et al., (2019) identified several European guidelines, recommending treatment with platinum agents such as carboplatin (Armstrong et al., 2019). Further, the combination therapy of carboplatin with paclitaxel demonstrated good response rate for highly active breast cancer (Diéras et al., 2020a, p. 121, 2020b).

Therefore, the comparator in this economic evaluation was carboplatin with paclitaxel. The combination of both agents was administered to the control group in the clinical trial. Each cycle, patients in the trial received 6 mg/ml per min intravenously of carboplatin on day 3 of each cycle and 80 mg/m^2 intravenously of paclitaxel on day 3, 10, and 17 (Diéras et al., 2020b). This schedule was followed until disease progression. Like in the treatment schedule with veliparib, patients in the trial could receive blinded monotherapy with placebo thus, carboplatin and paclitaxel were discontinued before disease progression. The mean duration of monotherapy in the control group was 252 days (Diéras et al., 2020b). The treatment schedule, dosage, and maximum duration of each treatment agent in the comparator arm of the model was based on the treatment administered to the control group of the clinical trial.

Model Structure

For the cost-utility analysis of veliparib a Microsoft Excel based Markov cohort decision analytic model was constructed. A Markov model is structured around different disease or health states that are mutually exclusive and that represent the potential consequences of the treatment and the comparator. Transition probabilities between the health states over a certain period, referred as a cycle, were used to reflect the possible consequences. For the model in this study, the three following health states were included: (1) Stable disease/Progression free (SD), (2) Progressed disease (PD), and (3) Death (Fig. 1). This model structure aligns with previous appraisals for HER2- negative, advanced breast cancer submitted to NICE and is a common model structure for cost-effectiveness studies in oncology (*Abemaciclib NICE Appraisal*, 2019; *Ribociclib NICE Appraisal*, 2019).

Figure 1: Diagrammatical representation of the model structure



As illustrated in Figure 1, all patients begin in the stable disease state. From stable disease, patients can either stay progression free, transition to progressed disease, or directly to the death state. Patients in the progressed state can continue in this health state or transition to the death state. The cycle length for the model was based on the treatment schedule of the BROCADE3 trial in which one cycle was 21-days long (Diéras et al., 2020b). To include all relevant costs and effects of treatment and comparator a life-time horizon of 20 years (time point in which < 0.01 of population is alive) was implemented in the model.

Survival data to obtain transition probabilities between the states were retrieved from the OS and PFS Kaplan-Meier (KM) curves illustrated in the BROCADE3 trial. The procedure of extracting the data from the KM curves will be described in more detail in the next section of this chapter. Due to missing individual patient data in the clinical trial, the model for veliparib used a cohort simulation with a cohort size of 1000 patients to calculate how long patients stay in a certain health state (Briggs et al., 2006, p. 33).

The following calculations were done to obtain the number of patients in each health state at a certain point in time t:

Patients in stable disease (t) = 1000 * $PFS_{(t)}$; (If OS > PFS) (Equation 2)

Patients in progressed disease (t) = 1000 – Patients in stable $disease_{(t)}$ – Patients in $death_{(t)}$ (Equation 3)

Patients in death state (t) = 1000 * (1 – $OS_{(t)}$) (Equation 4)

The calculated number of patients in each state and at a certain point in time were used to determine the costs incurred, as well as the QALYs and LYs yielded in each cycle in order to calculate the mean total costs and health effects and subsequently to obtain the ICER of the intervention (Briggs et al., 2006, p. 30).

Survival Analysis

The essence of a Markov cohort model is to simulate the pathway of a patient cohort across the different health states of the model. To determine the number of patients in a particular health state at a certain point in time, a survival analysis, as described by Hoyle & Henely (2011), was conducted, using the original OS and PFS KM curves from the BROCADE3 trial and by extrapolating them with parametric functions. This method allows the estimation of the number of patients affected by an event, such as death, in each time interval and permits the estimation of future events not captured in the clinical trial (Diéras et al., 2020b; Hoyle & Henley, 2011).

OS in the KM curves was observed for 56 months after randomization, PFS for 52 months (Diéras et al., 2020b). Both KM graphs were uploaded in WebPlotDigitizer version 4.4 to retrieve the X and Y coordinates (*WebPlotDigitizer*, n.d.). Via the semi-automated approach, the coordinates for OS and PFS for either the treatment- or the control-group were exported into Excel spreadsheets. The number of patients at risk (R(t)) were given in the clinical trial for

certain points in time (t). With the survival probability (S(t)) extracted from the curves, the number of patients at risk at intermediate times (½ t) were estimated to improve the curve fitting. This step was repeated for further intermediate times (¼ t and ¾ t) to further increase the fitting of the curve. Obtaining the number of patients at risk for several moments in time permits to fit survival curves to the estimated patient numbers by using the method of maximum likelihood (Hoyle & Henley, 2011). This step was conducted via the statistical software "R studio" version 1.4.1103 using a code provided by the Hoyle & Henly (2011) paper (Appendix A1). The parametric distributions Weibull, exponential, log-logistic, and lognormal, were taken into consideration for the selection of the best fitting distribution. The assessment of the different distributions for OS and PFS was based on the DSU technical support document 14 (2011) and included visual inspection, AIC/BIC tests and clinical validity with external data (N. R. Latimer, 2013).

The first assessment method was the inspection of the parametric curves regarding their visual fit compared to the given KM curve. This method, however, is considered rather uncertain and was therefore only used to get a first impression of the different distributions and how closely each follows the KM curves for OS and PFS.

The visual inspection for OS and PFS indicated that all distributions follow the original KM curves closely. The exponential curve was the least accurate, with an underestimation of the OS and PFS probability in the first months of observation (first 20 months for OS in veliparib- and control- group, first 8.5 months for PFS in veliparib group, and first 13 months for PFS in control group), followed by an overestimation until the end of the observation period. Due to the very similar courses of the Weibull, lognormal, and log-logistic curves no clear ranking could be made neither for OS nor for PFS after visual inspection (Figures 2-5).

Figure 2: Kaplan-Meier curve and parametric distributions for OS in the veliparib arm

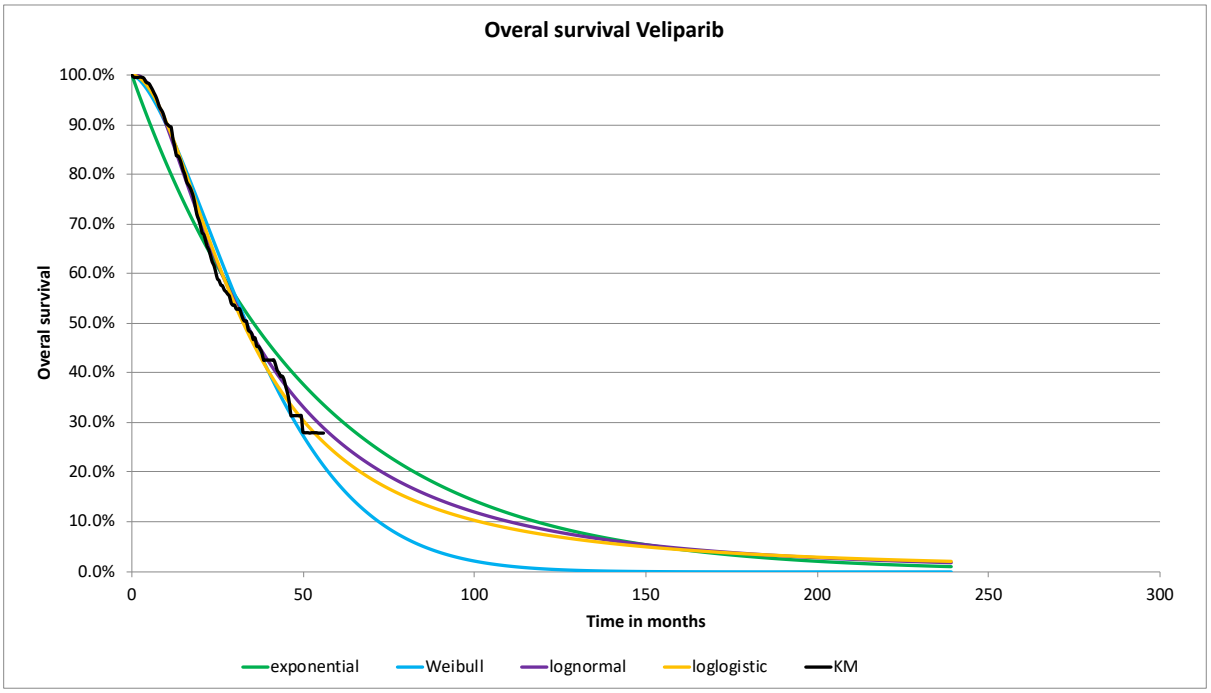


Figure 3: Kaplan-Meier curve and parametric distributions for OS in the control arm

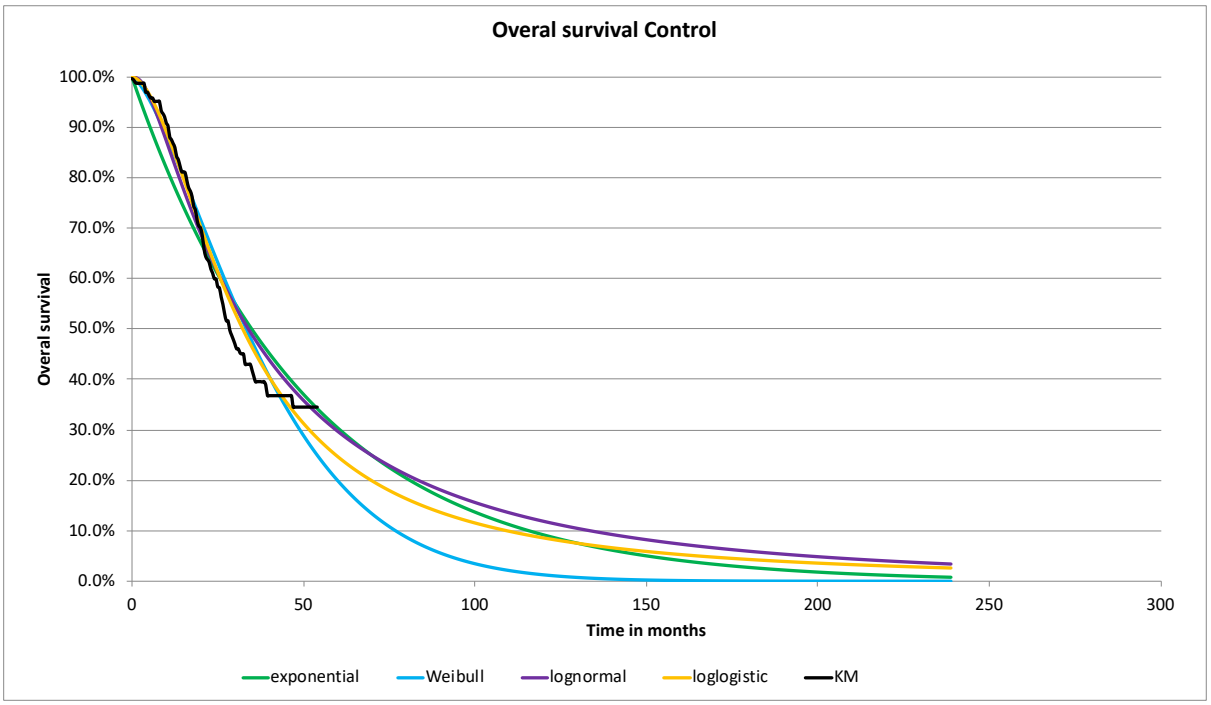


Figure 4: Kaplan-Meier curve and parametric distributions for PFS in the veliparib arm

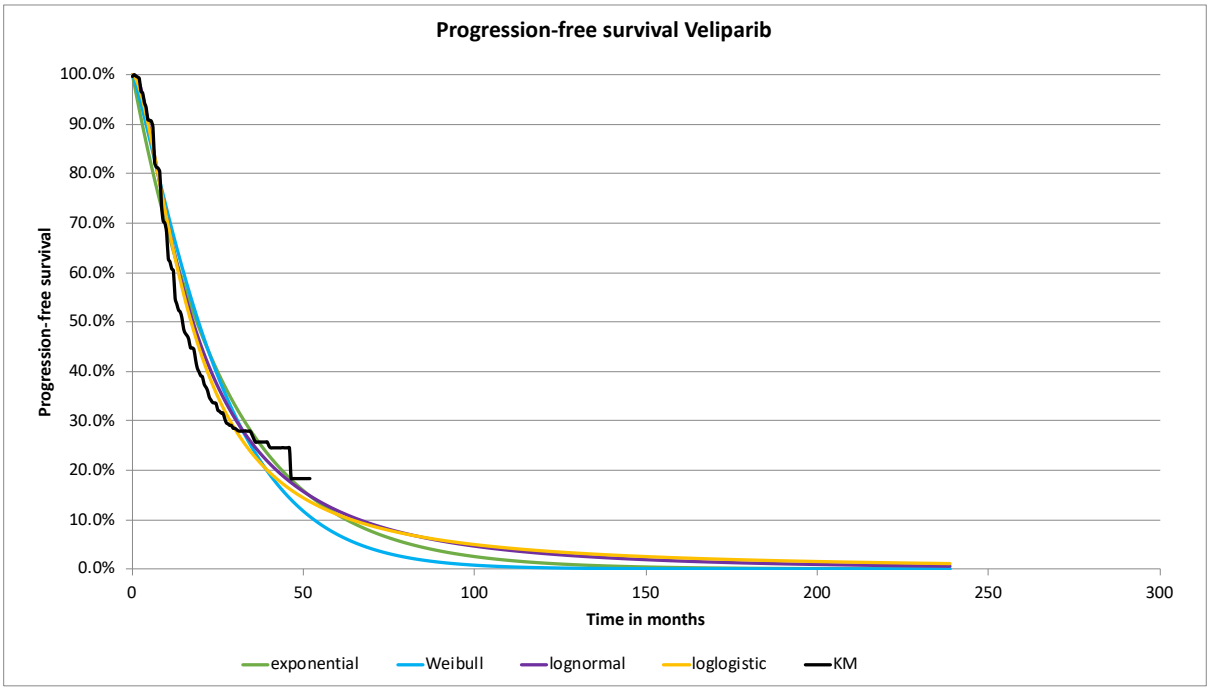
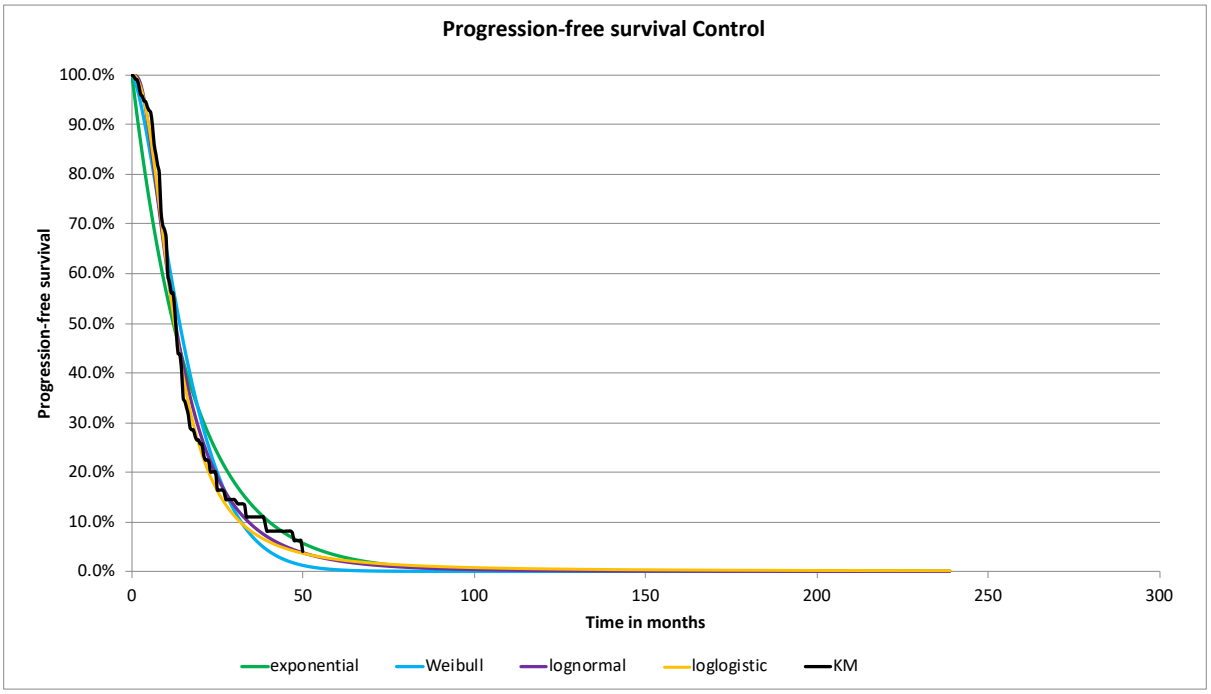


Figure 5: Kaplan-Meier curve and parametric distributions for PFS in the control arm



Statistical assessment was carried out using the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), which provide the relative fit of different parametric distributions (N. R. Latimer, 2013).

The AIC value was reported as an outcome in "R-studio" and did not need any further calculation. For OS in the veliparib- and control group the log-logistic distribution yielded the lowest AIC and was therefore considered to have the best statistical fit (Table 1). The same result was found for PFS in the control group, in which the log-logistic distribution had the lowest AIC (Table 2). In the veliparib group, however, the lognormal distribution had the lowest AIC. For both groups the exponential distribution had the highest AIC in OS and PFS and therefore, the worst statistical fit. This is in accordance with the visual inspection described above.

The BIC values were not given by "R-studio" or any other statistical software and had to be calculated algebraically with the following formulas (Brownlee, 2019):

$$\begin{cases} \mathrm{AIC} = 2\mathrm{k} - 2\ln(\hat{\mathrm{L}}) \\ \mathrm{BIC} = \ln(\mathrm{n})\,\mathrm{k} - 2\ln(\hat{\mathrm{L}}) \end{cases} \qquad \text{(Equation 5)}$$

The two variables needed for the equation are n, the number of data points on the KM curve, and k, the number of parameters estimated by the model. In all cases the BICs were lowest for the distribution with the lowest AIC (Tables 1 and 2).

In conclusion, according to the statistical fit, the log-logistic distribution has the best fit for OS in both treatment groups and the best fit for PFS in the control group. For PFS in the veliparib arm lognormal is statistically seen the best fit. For both arms in OS and PFS the exponential distribution can be considered as the worst fit, which aligns with the visual inspection of the curves.

Table 1: Statistical assessment of the OS parametric distributions using AIC and BIC

	Veliparib arm		Control arm	
	AIC	BIC	AIC	BIC
Weibull	1812.57	1816.622	956.6578	960.636
Lognormal	1811.061	1815.112	962.7886	966.767
Loglogistic	1806.375	1810.426	952.644	956.622
Exponential	1848.224	1850.249	967.8008	969.790

Table 2: Statistical assessment of the PFS parametric distributions using AIC and BIC

	Veliparib arm		Control arm	
	AIC	BIC	AIC	BIC
Weibull	2131.86	2135.762	1151.561	1155.385
Lognormal	2093.592	2097.494	1134.70	1138.524
Loglogistic	2098.263	2102.165	1125.969	1129.793
Exponential	2138.758	2140.709	1175.695	1177.607

An essential limitation of the methods described so far, is that they only assess the fit of parametric models to the already observed data from the KM curves. Neither the visual inspection, nor the AIC/BIC approach describes how accurate a parametric model is for the period after the time observed in the clinical trial. Since the goal of a cost-effectiveness analysis is to estimate long-term costs and health effects of a treatment beyond the follow-up period, it is essential to find a parametric model that plausibly estimates the extrapolated portion of the curve (N. R. Latimer, 2013).

Therefore, an important argument for the choice of distribution is the use of clinical plausibility and external data (N. R. Latimer, 2013). The BROCADE3 trial reports a median OS of 33.5 months (95% CI 27.6-37.9) in the veliparib arm and of 28.2 months (95% CI 24.7-35.2) in the

control arm (HR 0.95, [95% CI 0.73-1.23; p=0.67]), and a median PFS of 14.5 months (95% CI 12.5-17.7) in the veliparib arm and of 12.6 (95% CI 10.6-14.4) months in the control arm (HR 0.71[95% CI 0.57-0.88], p=0.0016). For both groups the Weibull distribution shows a median OS and PFS that is the closest to the trial data (OS: 35.6 months in veliparib arm, 36.5 months in control arm; PFS: 23.2 months in veliparib arm and 15.4 months in control arm), however, a slight overestimation can still be observed. Lognormal, log-logistic, and exponential distribution, estimate median OS and PFS higher than the Weibull distribution and are therefore, less suitable (Appendix A2).

In addition, the Weibull distribution is the only curve, indicating that after 20 years no patient would be alive or in a progression free health state anymore. The two breast cancer subtypes included in the clinical trial, HER2-negative and triple-negative, are associated with a high mortality, especially in the metastatic setting (Johansson et al., 2021). Therefore, the assumption that no patients would be alive, 20 years after treatment begin, aligns with survival data for patients in the indication. This assumption was supported with the life expectancy of breast cancer patients at the mean age of patients when they get diagnosed, compared to the life expectancy of women not having a breast cancer diagnosis at this age. The mean age of patients in the trial was 47 (39-54). According to Botta et al., (2019) patients getting a diagnosis for breast cancer at the age of 47 have a life expectancy of around 27 years compared to 35 years in a healthy population (Botta et al., 2019). However, the study results by Botta et al., (2019) did not distinguish between different cancer stages or subtypes. As already mentioned, the advanced setting of the cancer, as well as the two subtypes included in the trial, HER2-negative and TNBC, are associated with a higher mortality compared to lower stages of breast cancer or with other subtypes. As stated in the BROCADE3 trial, the 5-year survival rate for patients with metastatic breast cancer is 27% and only 11% for patients with a metastatic triple-negative breast cancer (Diéras et al., 2020b). Therefore, the Botta et al., (2019) results present

an overestimation of the expected life expectancy of patients included in the trial, leading to the assumption that when only advanced breast cancer patients and with the relevant subtypes were evaluated, the life expectance would be lower than 27 years as seen by the Botta et al., (2019) paper and closer to 20 years.

These observations led to the conclusion that from a clinical point of view the most plausible estimation for the future course of the curves was achieved via the Weibull distribution. Since clinical plausibility is the key assessment element for determining a parametric model, the Weibull distribution was used for the extrapolation of OS and PFS curves in the veliparib and control group (Drummond et al., 2015, p. 374). However, the described process of selecting the distribution shows that depending on the type of assessment (visual, statistical, or clinical) different distributions might be chosen. Therefore, this decision comes with uncertainty, which will be addressed in a later section of this chapter.

Adverse Events

Patients in the BROCADE3 clinical trial were evaluated for AEs during the whole study period. Results show that serious treatment-emergent AEs (TEAEs) were more often observed in the veliparib arm than in the chemotherapy arm (34% versus 29%). TEAEs are defined as those events appearing during treatment, which were absent before or which worsened relative to the pre-treatment state (*Segen's Medical Dictionary*, 2012). The same observation was made for study drug-related serious AEs in treatment- versus comparator- arm (12% versus 4%). The most common grade 3 or worse AEs were neutropenia (81% versus 84%), anaemia (42% versus 40%), and thrombocytopenia (40% versus 28%) (Diéras et al., 2020b). The model of veliparib incorporated AEs to include the utility decrements- and the costs- related to them. Therefore, AEs of grade 3 or higher with a total incidence of five percent or higher, were integrated in the model (Table 3).

Table 3: Grade ≥ 3 AEs with an incidence ≥ 5% incorporated in the model

	Veliparib arm (%)	Control arm (%)
Neutropenia	81	84
Anaemia	42	40
Thrombocytopenia	40	28
Leukopenia	29	26
Fatigue	7	-
Nausea	6	-
Diarrhoea	5	-
Peripheral sensory	-	5

Note: Cumulative percentage number of grades ≥3 AEs reported in the clinical trial (Diéras et al., 2020b).

Health-related Quality of Life

Health-related quality of life outcomes were measured during the trial period via several questionnaires, however, they were not published (Diéras et al., 2020b). Therefore, the needed HRQoL data, expressed using utility values, for the calculation of QALYs in the progression free and progressed health states were identified via a systematic literature review (SLR) in the database Embase and via a search of relevant NICE technology appraisals.

Systematic literature review

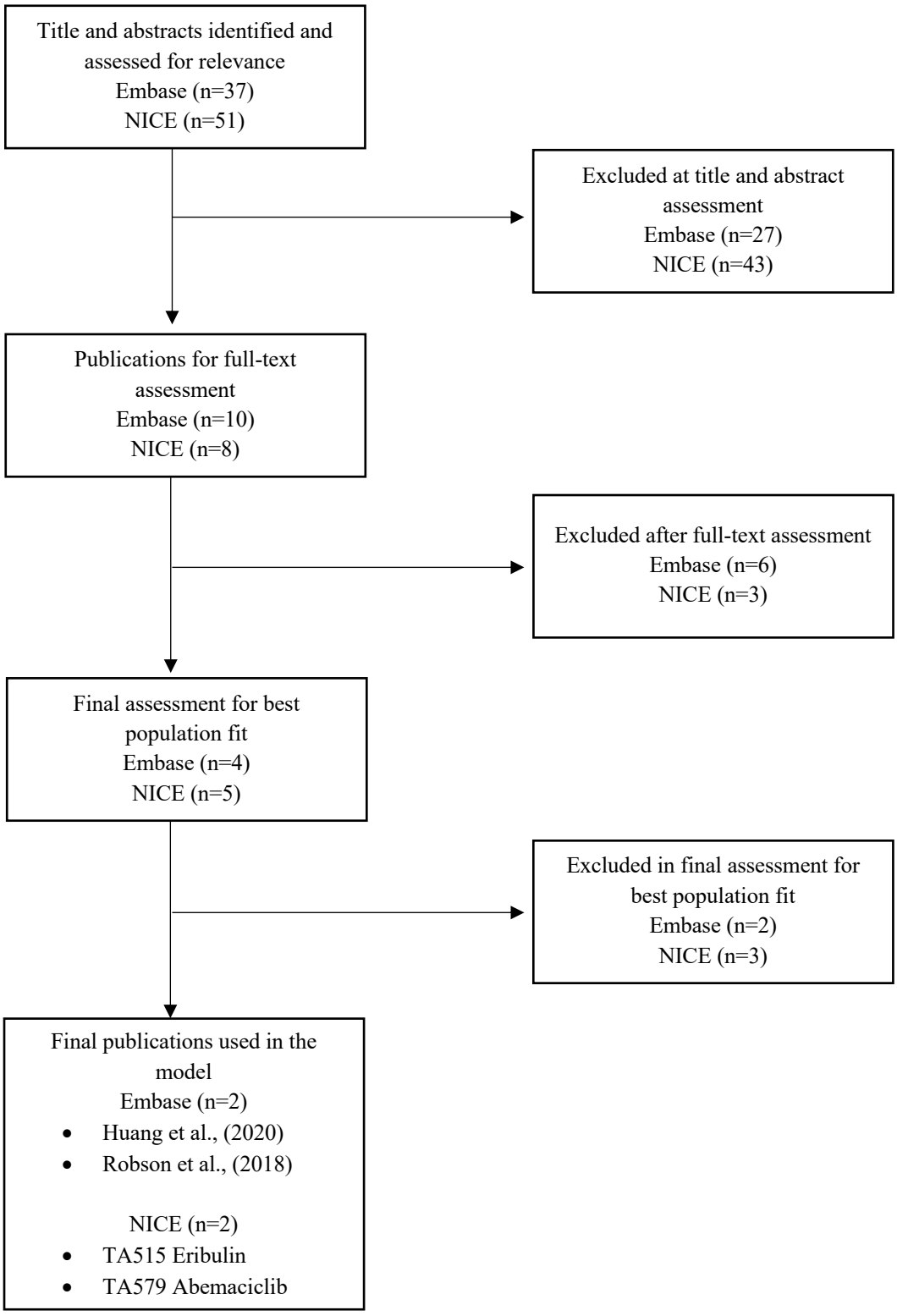
The SLR on Embase was conducted during March 2021, using disease specific search terms (Appendix B1). The population of interest included adult patients, with HER2-negative or triple-negative advanced breast cancer, with or without a BRCA mutation (*Veliparib NICE Appraisal*, 2020). Due to an expected limited number of studies that would include patients with a BRCA mutation, results were not restricted to BRCA-mutated cancers only. The preferred measure to obtain HrQoL data from patients was the EQ-5D as recommended by NICE (*Guide to the Methods of Technology Appraisal*, 2013). However, publications using a different measure of QoL were also included if the population of interest criteria was met. Only English papers were involved for further evaluation. Additional inclusion and exclusion criteria of the SLR can be found in the Appendix B2. The search via Embase yielded a total of 37

results, containing 33 conference abstracts and 4 articles (Figure 6). In the first stage of evaluation the results were judged based on title and abstract. After the first evaluation, 10 results preceded to the second stage of assessment in which the full text of the remaining studies was examined for utility values in the target population. Out of the 10 results, four reported relevant utility values (Huang M. et al., 2020; Niyazov et al., 2019; Robson M. et al., 2018; Rugo et al., 2018) However, only the utility values by Huang et al., (2020) for patients with metastatic TNBC randomised to pembrolizumab or chemotherapy and by Robson et al., (2018) for patients with HER2 negative gBRCA positive, metastatic breast cancer (MBC) randomised to olaparib or single-agent chemotherapy, were used in the model of veliparib due to more similarities between their treatment population and the population of interest in this study.

In addition to the SLR conducted in Embase, already submitted NICE appraisals were reviewed for relevant HrQoL data, in April 2021. The search in NICE focused on health state related utility values but also on utility decrements due to AEs and the duration of AEs. Out of 51 appraisals for triple-negative or HER2-negative, advanced breast cancer, eight were included for further assessment (Figure 6). The decision whether an appraisal would be further evaluated was based on the study population and treatment line described in the title and in the NICE guidance of each appraisal. Out of the eight-remaining appraisals, five reported health state utilities and utility decrements due to adverse events for a study population similar to the one used in the model of veliparib. However, only the values from the TA515 eribulin (2017) appraisal for patients with MBC or advanced breast cancer (ABC) and HER2-negative breast cancer following one prior chemotherapy line and from the TA579 abemaciclib (2019) appraisal for patients with hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy were used in the model, due to better fitting patient populations (*Abemaciclib TA579 Committee Papers*, 2019; *Eribulin TA515 Committee Papers*, 2017). A

detail list and description of the appraisals used for the input parameters in the model can be found in the appendix B3.

Figure 6: PRISMA flow chart for SLR conducted in Embase and NICE for HrQoL



In total, three sets of utility values from three different sources were identified via the systematic literature review and used for either the base-case analysis or the scenario analyses (Table 4).

Utilities in the base-case analysis were taken from Huang et al., (2020). The conference abstract evaluated the health state utility of previously treated metastatic triple-negative breast cancer patients (second- or third- treatment line) via the EQ-5D-3L questionnaire and converted them to population-based utility values using published algorithms. The method and country of the value set used to obtain the population-based utility values was not described in the paper. Patients in the study received either pembrolizumab (antineoplastic agent) or chemotherapy, however, no statistical difference in utility values were detected between the two arms. Therefore, utilities from the pooled treatment groups were reported. The mean utility scores for the total patient population in the progression free state and progressed state reported in the abstract were 0.715 (95% CI 0.701, 0.730) and 0.601 (95% CI 0.571, 0.631) (Huang M. et al., 2020).

Further, for the scenario analyses conducted in the model of veliparib the utility values from Robson et al., (2018) and from the NICE TA515 (2017) appraisal of eribulin were used. Robson et al., (2018), studied the health state utility values for patients with HER2-negative and germline BRCA-mutated breast cancer, receiving olaparib (PARP inhibitor) or chemotherapy in the OlympiAD clinical trial. Treatment specific utility values obtained via the cancer specific EORTC QLQ-C30 questionnaire were mapped to EQ-5D utility values using an algorithm from women with locally advanced breast cancer. To incorporate the utility values from the abstract in the model the average of the two reported treatment specific baseline and progressed disease state values were used. Mean health state utility at baseline for patients treated with olaparib and chemotherapy was 0.827 and 0.810, resulting in an average value of 0.815. Mean health state utility in the progressed disease state was 0.812 and 0.753, resulting

in an average value of 0.783 (Robson M. et al., 2018). The values from Robson et al., (2018) were not chosen for the base-case analysis since they were treatment specific. Only by taking the average of the two values it was possible to incorporate them in this model. However, this method is not as accurate as directly measuring a health state specific utility value for the whole population. Further, the utility values were considered rather high for the target population in this study. This could have been the case because EQ-5D utility values were mapped using an algorithm from women with locally advanced breast cancer not advance breast cancer (Robson M. et al., 2018).

The utility values reported in the eribulin TA515 (2017) appraisal were health state utilities for patients with HER2-negative metastatic breast cancer, following one prior chemotherapy regime. Like Robson et al., (2018) the appraisal mapped QLQ-C30 values to EQ-5D utility values, but via a UK tariff. Utility values in the appraisal were stated for each treatment arm and for the total population of the study. Mean utility values for the total population in the progression free and progressed health state were 0.697 and 0.679 (*Eribulin TA515 Committee Papers*, 2017). Even though the values from TA515 (2017) appraisal were the only utilities gained via a UK tariff, they were not used in the base-case analysis since the utility difference between stable disease and progressed disease was considered too small for patients in the indication.

Table 4: Health state utilities

	Huang et al., (2020)	Robson et al., (2018)	TA515 eribulin (2017)
Population	Patients with metastatic TNBC randomised to pembrolizumab or chemotherapy	Patients with HER2 negative gBRCA+, MBC randomised to Olaparib or single-agent chemotherapy	Patients with MBC or ABC and HER2-negative breast cancer following one prior chemotherapy line
Questionnaire; Direct valuation method	EQ-5D-3L questionnaire converted to population-based utility values with	EORTC QLQ-C30 mapped to EQ-5D with algorithm from women	QLQ-C30 mapped to EQ-5D with UK tariff; NA

	published algorithms; NA	with locally advanced BC; NA	
Progression free health state utility value	0.715	Baseline value for Olaparib and chemotherapy arm: 0.827, 0.802 Average: 0.815	0.697
Progressed health state utility value	0.601	Progressed disease value for Olaparib and chemotherapy arm: 0.812, 0.753 Average: 0.783	0.679
Utility decrement from progression free to progressed disease	(-) 0.114	(-) 0.032	(-) 0.018
Use in the decision model	Base-case analysis	Scenario analysis	Scenario analysis

Beside the utility values for the progression free and progressed health state, utility decrements due to grade ≥ 3 AEs were incorporated in the model and adjusted to their duration (Table 5).

Utility decrements were retrieved from the eribulin TA515 (2017) appraisal and from the abemaciclib TA579 (2019) appraisal (*Abemaciclib TA579 Committee Papers*, 2019; *Eribulin TA515 Committee Papers*, 2017). Both appraisals reported the same utility decrements for AEs, however, they cited two different papers by Hudgens. While the TA515 (2017) appraisal cited Hudgens et al., (2014), the TA579 (2019) appraisal referred to a later version of the Hudgens et al. paper published in 2016 (Hudgens et al., 2014, 2016). In both papers' health state utilities and utility decrements obtained from the QLQ-C30 questionnaire, for patients with advanced breast cancer, were mapped to EQ-5D estimates using published regression algorithms. The EQ-5D utility decrements were obtained using a UK tariff (Hudgens et al., 2014, 2016). The utility decrement for thrombocytopenia was not stated in either of the two

appraisals nor the Hudgens et al. (2014/16) papers. Therefore, a manual search was conducted in the NICE database extending the previous search to treatments for advanced ovarian cancer. Here, the NICE TA673 (2021) appraisal of niraparib for advanced ovarian, fallopian tube and peritoneal cancer was identified and the utility decrement for thrombocytopenia reported in the appraisal was used for the model in this study (*Niraparib TA673 Committee Papers*, 2021).

Lastly, breast cancer specific durations of AEs were not identified through the SLR. However, the TA579 (2019) appraisal included durations of AEs cited from the single technology appraisal ID414 (2012) of pixantrone for adults with relapsed or refractory aggressive B-cell non Hodgkin lymphoma which were incorporated in the model (*Abemaciclib TA579 Committee Papers*, 2019; *Pixantrone ID414 Single Technology Appraisal*, 2012).

Table 5: Utility decrements and durations of adverse events

	Utility decrement	Duration (days)
Neutropenia	0.007	15.10
Thrombocytopenia	0.090	23.30
Anaemia	0.010	16.10
Nausea	0.021	6.00
Fatigue	0.029	31.50
Diarrhea	0.006	6.00
Leukopenia	0.003	14.00
Peripheral Sensory	0.014	35.30

Note: Duration of peripheral sensory was obtain from ID414 pixantrone (2012) grade 2 Neuropathy and assumed to be the same as for grade ¾. To improve readability, detailed sources of the implemented input values from table 5 can be found in the appendix B4.

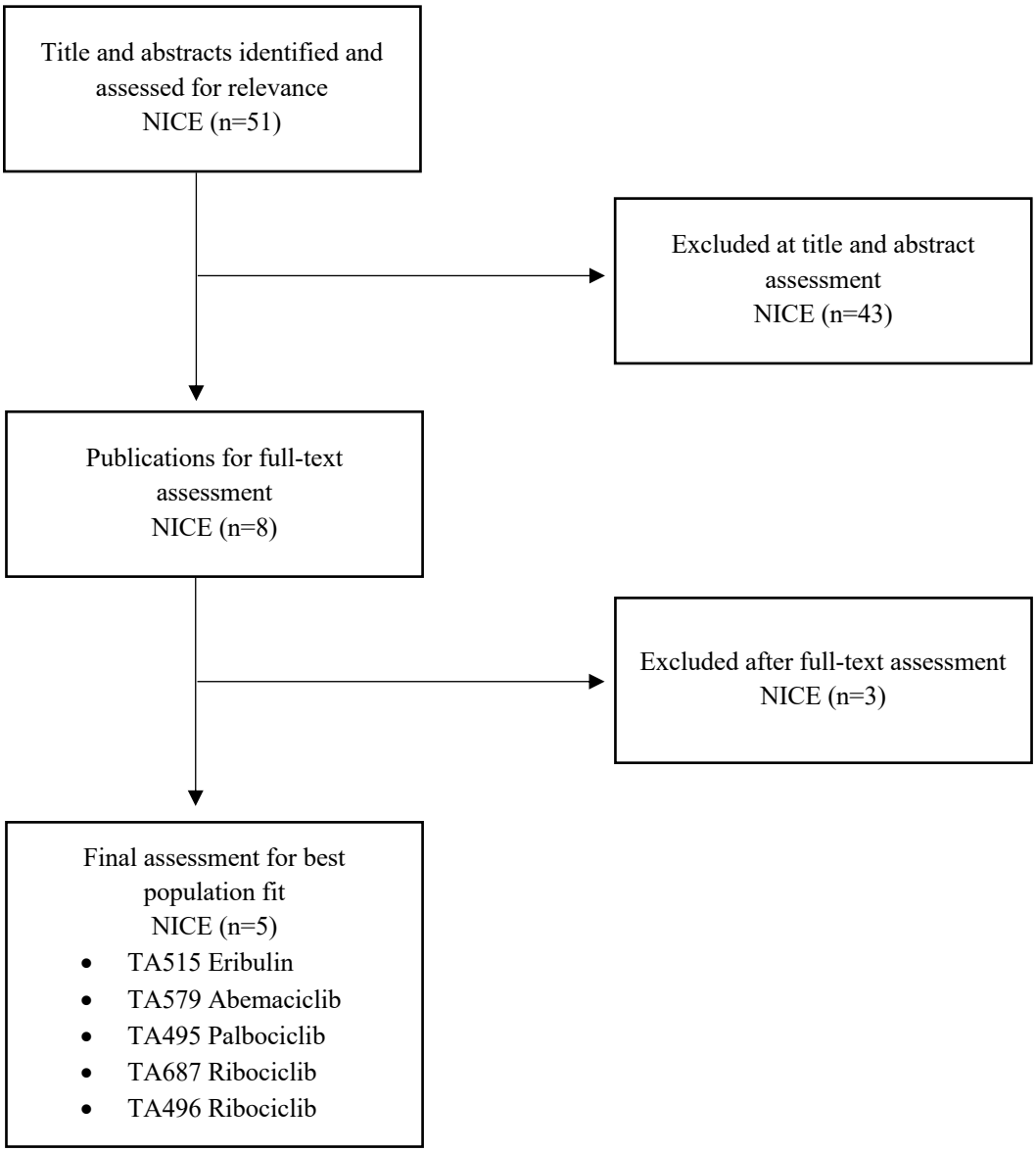
Costs

Systematic literature review

To identify the relevant cost and resource use items, submitted NICE appraisals were reviewed in April 2021. The same search strategy as for HrQoL was used to identify appraisals for advanced or metastatic TNBC or HER2-negative breast cancer. The assumption was made,

that a mutation in one of the two BRCA genes would not influence the resource use of patients. This assumption was validated by the study from Biskupiak et al. (2017), which concluded that the mutation status was not associated with higher breast cancer charges (Biskupiak et al., 2017). Therefore, NICE appraisals for HER2-negative or triple-negative, advanced breast cancer, with or without a BRCA mutation, were included in the review. Out of 51 available submissions in this indication, eight passed the first evaluation stage based on their patient population and treatment line (Figure 7). In the second step, the committee papers of each appraisal were reviewed for relevant health state-, and treatment line-dependent resource use items. This search focused mainly on identifying healthcare resource use for the progression free and progressed health state, monitoring costs, costs related to adverse events, BSC costs and end-of-life costs. Five appraisals were identified containing relevant data inputs used for the model in this study (*Abemaciclib TA579 Committee Papers*, 2019; *Eribulin TA515 Committee Papers*, 2017; *Palbociclib TA495 Committee Papers*, 2016, p. 687; *Ribociclib TA496 Committee Papers*, 2017; *Ribociclib TA687 Committee Papers*, 2021).

Figure 7: PRISMA flowchart for SLR conducted in NICE for costs and resource use



The search in the NICE website was expanded with an additional manual search conducted in May 2021. This search focused on identifying NICE recommendations for subsequent therapy lines in HER2-negative or triple-negative, advanced breast cancer. Once the specific treatments were known, the previously identified appraisals were reassessed to identify input parameters needed for modelling the subsequent treatment lines in the progressed health state. In addition, the appraisal TA639 (2020) for atezolizumab for patients with untreated PD-L1-positive, locally advanced, or metastatic, triple-negative breast cancer was

manually found and used to model subsequent treatment lines (*Atezolizumab TA639 Committee Papers*, 2020). All identified costs were expressed in UK pounds (£).

Drug acquisition costs

Based on the treatment regimens in the BROCADE3 clinical trial, patients in the progression free state could either receive combination therapy with veliparib, carboplatin, and paclitaxel or chemotherapy with carboplatin and paclitaxel only. 41% of patients in the veliparib group of the trial and 34% in the control group discontinued chemotherapy before disease progression and received blinded veliparib or placebo monotherapy. Blinded monotherapy was administered for a mean duration of 350 days (17 cycles) in the veliparib arm and 252 days (11.8 cycles) in the control arm (Diéras et al., 2020b). The model accounts for the fact that a percentage of patients in treatment- and comparator- arm of the trial switched to veliparib or placebo monotherapy before disease progression. The time of transitioning in the model was implemented by determining the cycle in which 50% of the patients, that transitioned during the total trial period, switched to monotherapy. This information was taken from the appendix of the BROCADE3 clinical trial. According to the appendix this time was achieved in cycle 9 for both treatment arms (Diéras et al., 2020a, p.8). Since no information was given in the trial regarding the maximum duration of the monotherapy, the mean duration of monotherapy in each treatment arm was considered as the maximal duration in the model. Therefore, starting in cycle 9 in the stable disease state and for a duration of 17 cycles in the veliparib arm and 11.8 cycles in the control arm, a proportion of patients received either veliparib or placebo monotherapy in the model. Since the treatment with placebo was not considered to include any costs, no additional drug acquisition costs were implemented for the 34% of patients in the control group receiving placebo monotherapy.

Drug acquisition costs for carboplatin and paclitaxel were applied by determining the dose in mg per vial and calculating the vials needed per cycle. Then the number

of vials needed was multiplied with the price per vial. Dosage and frequency of administration were obtained from the clinical trial. Package -price, -size and -dose were identified via the electronic market information tool (eMIT) (Table 6) (Diéras et al., 2020b; *EMIT Database*, 2020). Carboplatin was administered once per cycle at a dose of 900mg intravenously (Diéras et al., 2020b). A package containing one 450mg vial was used in the model with a price per package of £13.74 (*EMIT Database*, 2020). Paclitaxel was administered three times per cycle at a dose of 80mg/m^2 intravenously (Diéras et al., 2020b). In order to calculate the paclitaxel dose in mg, an average body-surface area (BSA) of 1,73m^2, obtained from the BROCADE3 clinical trial, was used in the model (Diéras et al., 2020b). The package of paclitaxel was containing a 150mg vial for a price of £12.41 per package (*EMIT Database*, 2020).

No official price for veliparib was found during the period of conducting this study. The price was due for publication during the study period, however, on the 6th of April 2021 the company decided to delay the veliparib application for marketing authorization in the UK (Veliparib NICE Appraisal, 2020). This indicates that the manufacturer may want to position the product differently or attempts to determine a price for veliparib that would be acceptable for NICE before seeking marketing authorization. Therefore, this study focused on identifying a price for veliparib that would be acceptable for NICE, resulting in the treatment being cost-effective in comparison to the national willingness to pay threshold. For doing so, the price for veliparib for research use was obtained from a third-party website, containing several package sizes (*ABT-888 (Veliparib)*, n.d.). The cheapest option per mg was identified by calculating each price per mg. By doing so, a package size of 200mg with a price of £315.00 was considered as the best option and used in the base-case analysis (Table 6). Given the small size of the package, it can be assumed that the bulk price of veliparib would be lower when entering the market. Therefore, this price was used as a starting-point and then varied in several scenario analyses. Hence, this study not only focused on the question whether veliparib is cost-effective

compared to chemotherapy from a UK payer perspective, but also which price needs to be assigned to veliparib by the manufacturer to be considered cost-effective by NICE.

Table 6: Treatment dosing, administration, and drug acquisition costs stable disease

	Veliparib combination therapy	Veliparib monotherapy	Carboplatin	Paclitaxel
Label information				
Administration route	Oral	Oral	Intravenous	Intravenous
Dose per administration (mg)	120	300	900	80mg/m^2*
Administration frequency per cycle	14	42	1	3
Package information				
Formulation (mg)	200	200	450	150
Pack size	1 unit	1 unit	1 vial per pack	1 vial per pack
Cost per pack (£)	315.00	315.00	13.76	12.41

Note: *Paclitaxel dosing in mg was calculated by multiplying with the average BSA of 1,73m^2

Anti-cancer treatments administered in the progressed health state were retrieved from the list of first subsequent therapies administered in the clinical trial, given in the appendix of the trial (Diéras et al., 2020a, p. 26). The most common subsequent treatments in the veliparib arm were endocrine therapy (14.2%), cytotoxic chemotherapy (30.6%), and platinum chemotherapy (5.3%) (Table 7). In the control arm patients received commonly cytotoxic chemotherapy (19.2%) as first line subsequent treatment and were eligible to receive crossover open label veliparib monotherapy at 300 mg. At the time of analysis, 44% of control group patients received open label veliparib after progression (Diéras et al., 2020a, p. 26). Only subsequent treatments provided to five percent or more of patients in the trial were included in the model. For doing so, the percentages of patients receiving anticancer treatment and patients receiving no further anticancer treatment were reweighted to sum up to 100 percent.

Table 7: Proportion of patients receiving anticancer subsequent therapy

			Reweighted percentages	
Subsequent treatment	Veliparib N(%)	Control N(%)	Veliparib N(%)	Control N(%)
Unblinded veliparib	0	75 (43.6)	-	75 (51.72)
Other PARP inhibitors	2 (0.6)	1 (0.6)	-	-
Platinum chemotherapy	18 (5.3)	3 (1.7)	18 (6)	-
Other cytotoxic chemotherapy	103 (30.6)	33 (19.2)	103 (37)	33 (22.76)
Endocrine therapy	48 (14.2)	6 (3.5)	48 (17)	-
CDK4/6 inhibitor	15 (4.5)	1 (0.6)	-	-
Targeted biologics	4 (1.2)	5 (2.9)	-	-
Other	39 (11.6)	11 (6.4)	-	-

The BROCADE3 clinical trial did not state specific subsequent anti-cancer treatments administered to patients in the progressed state. Therefore, specific treatments were identified via the NICE recommendations for managing advanced breast cancer (Managing Advanced Breast Cancer, 2021). The following treatments were assumed to be clinical practice in the NHS: carboplatin as platinum-based chemotherapy, letrozole as endocrine therapy, and capecitabine as cytotoxic therapy (Table 8) (Managing Advanced Breast Cancer, 2021). For the treatment with capecitabine and letrozole, dosing information was identified through the appraisal TA579 (2019) obtained via the SLR. Capecitabine was administered orally at a dose of 1250mg/m^2, with a frequency of 28-times per cycle. Letrozole was also administered orally at a dose of 2.5mg and with a frequency of 21-times per cycle (*Abemaciclib TA579 Committee Papers*, 2019). For treatment with carboplatin no dosing information was available in the literature from the SLR. Therefore, a manual search was conducted resulting in identifying the abemaciclib TA639 (2020) appraisal. Carboplatin was administered intravenously at a dose of 400mg/m^2, once per cycle (*Atezolizumab TA639 Committee Papers*, 2020). The maximum duration of each subsequent treatment alternative was not given in the clinical trial and had to be identified via external literature. For the treatment with carboplatin and letrozole the cost-effectiveness study by Galve-Calvo et al., (2018) was used, stating a mean duration of 3.10

months for the treatment with carboplatin and 4.90 months for the treatment with letrozole, for patients with HER2-negative advanced or metastatic breast cancer (Galve-Calvo et al., 2018). For the duration of capecitabine the product characteristics report by the EMA (European Medicine Agency) was identified, stating 6 months as recommended maximum time of administration (*Xeloda Product Information*, n.d.). Subsequent veliparib monotherapy was implemented in the model with a maximum duration of 11.8 cycles, based on the mean duration of monotherapy before progression (Diéras et al., 2020b).

Drug acquisition costs in the progressed disease were obtained by calculating the vials or pills needed per cycle and then the number of packages needed to meet the demand. For the treatment with carboplatin the same package -size and -price was used as in the stable disease state. For capecitabine a package, containing 60, 500mg pills with a price per package of £25.02 was used in the model. Letrozole was included in the model by using a package size of 28, 2.5 mg pills with a package price of £1.56 (*EMIT Database*, 2020). For veliparib monotherapy the same package -price and -size was used as in the stable disease state (*ABT-888 (Veliparib)*, n.d.). Costs were applied as a one-off cost to newly progressed patients by subtracting the number of patients in SD in time t from the number of patients in SD in t-1.

Table 8: Treatment dosing, administration, and drug acquisition costs progressed disease

	Carboplatin	Capecitabine	Letrozole	Veliparib monotherapy
Label information				
Administration route	Intravenous	Oral	Oral	Oral
Dose per administration (mg)	400mg/m^2*	1250mg/m^2*	2.5	300
Administration frequency per cycle	1	28	21	42
Duration (months)	3.1	6.00	4.90	11.8 cycles
Package information				
Formulation (mg)	450	500	2.5	200
Pack size	1 vial per pack	60 pills	28 pills	1 unit
Cost per pack (£)	13.76	25.02	1.56	315.00

Note: *Carboplatin and Capecitabine dosing in mg was calculated by multiplying with the average BSA of 1.73m^2

Chemotherapy administration costs

Chemotherapy administration costs were applied to carboplatin, paclitaxel, and capecitabine (Table 9). The costs were obtained via the NHS reference cost sheet (2018/2019) (*Reference Costs Sheet*, 2018). For the treatment with carboplatin and paclitaxel the HRG codes needed for the NHS reference costs sheet were obtained from the TA515 (2017) appraisal (*Eribulin TA515 Committee Papers*, 2017) A distinction was made between costs for complex chemotherapy such as paclitaxel, due to the one hour of administration time and between simple parenteral chemotherapy for carboplatin, due to an administration time of 30 minutes. This distinction was also based on the eribulin TA515 (2017) NICE appraisal (*Eribulin TA515 Committee Papers*, 2017). Further, the assumption from the TA515 (2017) appraisal was implemented, considering all chemotherapies as part of ongoing therapy and therefore, no separation between initial and subsequent therapy had to be applied (*Eribulin TA515 Committee Papers*, 2017). These assumptions resulted in costs per chemotherapy administration of £370.68 for paclitaxel and of £241.06 for carboplatin. For capecitabine the costs of delivery of an oral chemotherapy were used. This assumption was based on the TA579 (2019) abemaciclib appraisal (*Abemaciclib TA579 Committee Papers*, 2019). The HRG code was obtained from the TA579 (2019) appraisal, resulting in costs of administration for the treatment with capecitabine of £195.44 (*Reference Costs Sheet*, 2018).

Table 9: Chemotherapy administration costs

	Paclitaxel (SD)	Carboplatin (SD)	Capecitabine (PD)
Administration costs			
Description of chemotherapy	IV complex with infusion	Simple parenteral chemotherapy	Deliver exclusively oral chemotherapy
HRG code	SB14z	SB12z	SB11z
Costs per administration (£)	370.68	241.06	195.44

Premedication

The BROCADE3 clinical trial stated for the treatment with paclitaxel, premedication with corticosteroids, diphenhydramine, and H_2 antagonists (Table 10) (Diéras et al., 2020a, p. 121). The appendix of the trial mentioned that 20mg of orally administered dexamethasone was used as the corticosteroid agent and that 50 mg of intravenously ranitidine was used as H_2 antagonist (Diéras et al., 2020a, p. 145). The package -size, -dose, and -price for these two agents were obtained from the eMIT database (2020), resulting in a price per package of £27.21 for 30, 4 mg pills of dexamethasone and of £8.16 for 5, 50 mg vials of ranitidine (*EMIT Database*, 2020). However, the eMIT database (2020) did not include diphenhydramine in the list of drugs used in the NHS. Therefore, chlorphenamine 10mg IV was included in the model as alternative to diphenhydramine. This assumption was based on the electronic medicines compendium (EMC) website for the prescription of paclitaxel (*Paclitaxel*, 2020). Cost per package, including 5 vials with a dosage of 10 mg each, were £8.52 (*EMIT Database*, 2020).

Premedication costs were incorporated in the model by calculating the pills or vials needed per cycle and then identifying how many packages are required to meet the demand.

Table 10: Premedication administration, frequency, and costs

	Dexamethasone	Chlorphenamine	Ranitidine
Label information			
Administration route	Oral	Intravenous	Intravenous
Dose per administration (mg)	20	10	50
Administration frequency per cycle	3	3	3
Package information			
Formulation (mg)	4	10	50
Pack size	30 pills per pack	5 vials per pack	5 vials per pack
Cost per pack (£)	27.21	8.52	8.16

Healthcare resource use

Healthcare resource categories and the corresponding frequency of use were health state and treatment line specific and were obtained from the palbociclib TA495 (2016) appraisal for patients with previously untreated, hormone receptor-positive, HER2-negative, locally advanced or metastatic breast cancer (Table 11) (*Palbociclib TA495 Committee Papers*, 2016). The frequency of use reported in the TA495 (2016) appraisal was given for a 28-day cycle length and was therefore, adjusted to 21-days. Monitoring-resources during the progression free state included hematology tests and blood tests and were retrieved from the clinical trial (Diéras et al., 2020b).

Table 11: Healthcare resources used

	Frequency per 28 days	Frequency per 21 days	Length of stay (h)	Travel time (h)*	Source
Stable disease					TA495 (2016)
Community nurse home visit	0.30	0.23	0.30	0.50	
Consultant visit (oncologist) follow-up	0.20	0.15	1.00	-	
GP Contact	1.00	0.75	-	-	
Clinical nurse specialist	1.00	0.75	1.00	-	
Social worker	0.50	0.38	0.50	0.50	
Palliative care	0.50	0.38	0.30	-	
CT scan	0.30	0.23	-	-	
Monitoring resources in SD					Diéras et al., (2020b)
Hematology test	-	3	-	-	
Blood chemistry test	-	3	-	-	
Progressed disease anticancer treatment					TA495 (2016)
Community nurse home visit	0.70	0.53	0.30	0.50	
Consultant visit (oncologist) follow-up	0.50	0.38	1.00	-	
GP Contact	1.50	1.13	-	-	
Clinical nurse specialist	2.00	1.50	1.00	-	
Social worker	0.50	0.38	0.50	0.50	
Palliative care	1.00	0.75	0.30	-	
CT scan	0.30	0.23	-	-	

Therapist	0.50	0.38	0.50	-
Physiotherapist	0.50	0.38	0.50	-

The costs linked to a specific resource item were retrieved either from the PSSRU report (2020), for hourly wages of healthcare professionals, or through the NHS reference cost sheet (2018/2019) and were found via the TA495 (2016) appraisal (Table 12) (Curtis & Burns, 2020; *Reference Costs Sheet*, 2018; *Palbociclib TA495 Committee Papers*, 2016). Costs for therapist and physiotherapist visit were not found in the PSSRU report (2020) or the NHS reference cost sheet (2018/2019) and were therefore, inflated from the TA495 (2016) appraisal to their current value (2020). To identify the costs related to monitoring-resources the TA496 (2017) appraisal for patients with untreated, hormone receptor-positive, HER2-negative, locally advanced, or metastatic breast cancer, was used (*Ribociclib TA496 Committee Papers*, 2017).

Table 12: Healthcare resource costs

	Unit costs (£) (2020/2021)	Unit	Description	Source
Community nurse	40.00	Salary per hour	Average of unit cost per hour, with and without qualification	TA495, PSSRU Report (2020), Table 10.1
Consultant visit (oncologist) follow-up	142.73	Salary per hour	Oncology (Previously Radiotherapy) Non-Admitted Face to Face Attendance, Follow-up	TA495, NHS reference cost sheet (2018/2019), WF01A Service code 800
GP visit	36.00	Per visit	GP unit costs per surgery consultation lasting 9.22 minutes: Average of unit costs with and without qualifications	TA495, PSSRU Report (2020), Table 10.3b
Clinical nurse specialist	50.00	Salary per hour	Cost per working hour of hospital-based nurse band 6	TA495, PSSRU Report (2020), Table 13
Social worker	48.00	Salary per hour	Social worker adult services: Average of unit costs with and without qualifications	TA495, PSSRU (2020), Table 11.1
Palliative care	40.000	Salary per hour	Community nurse salary: Average of unit costs with and without qualifications	TA495, PSSRU Report (2020), Table 10.1

CT scan	105.00	Per Scan	Computerized Tomography Scan of Two Areas, with Contrast	TA495, NHS Reference Cost Sheet (2018/2019): Code RD24Z
Hematology test	2.79	Per test	-	TA496, NHS Reference Cost Sheet (2018/2019): Code DAPS05
Blood chemistry test	1.10	Per test	Clinical biochemistry test	TA496, NHS Reference Cost Sheet (2018/2019): Code DAPS04
Therapist	42.38	Salary per hour	Inflated from £39.00 (2014/15) to 2020 with NHSCII "pay"	TA495
Physiotherapist	39.12	Salary per hour	Inflated from 36.00 (2014/15) to 2020 with NHSCII "pay"	TA495

Best supportive Care

A total of 68% of patients in the veliparib arm and 78.5% of patients in the control arm received further anticancer treatment after progression (Diéras et al., 2020a). However, no further information was given for patients that progressed, but did not receive further anticancer treatment. Therefore, from the percentages mentioned above, it was estimated that the remaining 32% of patients in the veliparib arm and 21.5% of patients in the control arm would have received best supportive care. This assumption was based on NICE recommendations for advanced breast cancer and on the TA495 (2016) appraisal (*Managing Advanced Breast Cancer*, 2021; *Palbociclib TA495 Committee Papers*, 2016). To implement the proportion of patients receiving BSC in the model, the percentages were reweighted with the number for patients receiving anticancer treatment as described above. This resulted in 39% of patients in the veliparib arm and 25.52% of patients in the control arm receiving BSC in the model. The resource use items of patients receiving BSC in the progressed health state were obtained from the palbociclib TA495 (2016) appraisal (Table 13) (*Palbociclib TA495 Committee Papers*, 2016).

Table 13: Best-supportive care resource items

	Frequency per 28 days	Frequency per 21 days	Length of stay (h)	Travel time (h)	Source
Community nurse home visit	3.00	2.25	0.30	0.50	TA495 (2016)
GP Contact	2.00	1.50	-	-	TA495 (2016)
Clinical nurse specialist	3.00	2.25	1.00	-	TA495 (2016)
Social worker	1.00	0.75	0.50	0.50	TA495 (2016)
Palliative care	3.00	2.25	0.25	-	TA495 (2016)
Therapist	0.50	0.38	0.50	-	TA495 (2016)
Physiotherapist	1.00	0.75	0.50	-	TA495 (2016)
Lymphoedema nurse	1.00	0.75	0.30	0.50	TA495 (2016)

As described above, costs linked to a specific resource use were retrieved either from the PSSRU report (2020) or through the NHS reference cost sheet (2018/2019) (Table 14).

Table 14: Best-supportive care costs

	Unit costs (£) (2020/2021)	Unit	Description	Source
Community nurse home visit	40.00	Salary per hour	Average of unit cost per hour, with and without qualification	TA495, PSSRU Report (2020), Table 10.1
GP Contact	36.00	Per visit	GP unit costs per surgery consultation lasting 9.22 minutes: Average of unit costs with and without qualifications	TA495, PSSRU Report (2020), Table 10.3b
Clinical nurse specialist	50.00	Salary per hour	Cost per working hour of hospital-based nurse band 6	TA495, PSSRU Report (2020), Table 13
Social worker	48.00	Salary per hour	Social worker adult services: Average of unit costs with and without qualifications	TA495, PSSRU (2020), Table 11.1
Palliative care	40.000	Salary per hour	Community nurse salary: Average of unit costs with and without qualifications	TA495, PSSRU Report (2020), Table 10.1
Therapist	42.38	Salary per hour	Inflated from £39.00 (2014/15) to 2020 with NHSCII “pay”	TA495
Physiotherapist	39.12	Salary per hour	Inflated from 36.00 (2014/15) to 2020 with NHSCII “pay”	TA495
Lymphoedema nurse	40.00	Salary per hour	Assumed to be same salary as for community nurse home visit	TA495, PSSRU (2020)

Adverse Events Costs

Costs related to the treatment of grade ≥ 3 AEs, as presented above, were obtained from the eribulin TA515 (2017) appraisal and from the ribociclib TA687 (2021) NICE appraisal for patients with hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy (Table 15). Values from the TA515 (2017) appraisal were inflated to their current value with the NHS inflation indices for "pay & prices" presented in the PSSRU (2020) report. Costs were calculated as a one-off cost in the model (Curtis & Burns, 2020; *Eribulin TA515 Committee Papers*, 2017; *Ribociclib TA687 Committee Papers*, 2021).

Table 15: Costs related to adverse events

	Cost per event (£)	Year of cost in previous appraisal	Cost used in the model 2020 (£)
TA687 (2021)			
Anemia	526.26	2019/2020	526.26
Diarrhea	432.62	2019/2020	432.62
Fatigue	475.29	2019/2020	475.29
Nausea	566.07	2019/2020	566.07
Thrombocytopenia	521.82	2019/2020	521.82
TA515 (2017)			
Leukopenia	127.70	2014/2015	138.43
Neutropenia	127.70	2014/2015	138.43
Peripheral Sensory	146.33	2014/2015	158.63

Note: For the costs obtained from the TA687 appraisal no inflation was needed

End-of-life costs

Lastly, end-of-life care was divided in the three different care facilities in which patients could remain during their end of life (Table 16). Costs of hospital care, hospice care or home care, as well as the proportion of patients in each facility were retrieved from the abemaciclib TA579 (2019) NICE appraisal and inflated to their current value (2020) with the NHS inflation indices for "pay & prices" from the PSSRU report (2020) (*Abemaciclib TA579 Committee Papers*,

2019; Curtis & Burns, 2020). Costs per cycle were incorporated in the model by multiplying each end-of-life care facility costs with the proportion of patients in each care facility.

Table 16: End-of-life care costs

End-of life facility	Patient proportion	Cost (£)	Year of cost in appraisal	Cost inflated to 2020 (£)
Hospital	40%	5,695.20	2016/2017	6,024.61
Hospice	10%	7,100.06	2016/2017	7,510.73
Home	50%	2,938.29	2016/2017	3,108.24

Outcome of interest

The outcome of interest in the decision model for veliparib is the Incremental Cost Effectiveness Ratio (ICER) (Drummond et al., 2015, p. 54). Therefore, results were displayed as total and incremental costs, QALYs and LYs. The ICER was calculated by dividing the incremental costs by the incremental health effects of treatment and comparator (Drummond et al., 2015, pp. 8-9). Life Years, QALYs, and costs that would not necessarily occur at the start of a cycle were half-cycle corrected. All costs and health outcomes were discounted with a 3.5% rate as recommended by NICE (*Guide to the Methods of Technology Appraisal*, 2013). Beside the base-case analysis, several DSAs, scenario analyses and a probabilistic sensitivity analysis were conducted which will be described in the next section of this chapter.

Sensitivity analysis

Deterministic sensitivity analyses and scenario analyses

Based on the NICE reference case a distinction was made between uncertainty related to individual input parameters chosen for the model, and uncertainty regarding the structural choices and assumptions for the construction of the model (*Guide to the Methods of Technology Appraisal*, 2013).

In order to determine the sensitivity of the results towards individual parameters, one-way deterministic sensitivity analyses (DSAs) and scenario analyses were conducted.

In the DSAs the following inputs were increased and decreased individually: the utility decrements due to AEs and the duration of AEs, the maximum duration of subsequent therapy, and the average BSA used in the model to calculate drug acquisition costs (Table17). To test the impact of more extreme values, especially considering the utility decrement and the duration of AEs, these two input parameters were increased and decreased by 30%. The duration of subsequent therapy parameter was varied by 20% and the average BSA by 10%.

Table 17: Deterministic sensitivity analyses for several input parameters

	Base-Case	Upper limit	Lower limit
Utility decrements due to AEs	As reported in table 5	+30%	-30%
Duration of AEs	As reported in table 5	+30%	-30%
Duration of subsequent therapy (mo.)			
Carboplatin	3.1	+20%	-20%
Capecitabine	6.00	+20%	-20%
Letrozole	4.90	+20%	-20%
Veliparib	12.00	+20%	-20%
Average BSA (m^2)	1,73	+10%	-10%

Further, a scenario analysis was conducted to identify the impact of the chosen utility values on the results. Therefore, the two utility value sets by Robson et al., (2018) and from the TA515 (2017) appraisal were implemented in the model.

Additionally, the price for veliparib was varied to identify a price in which veliparib would be below the WTP threshold of £30,000. Since no official package price for veliparib was available, varying this input parameter individually and determining its effect on the results is of great interest. In order to do so, several price options were tested and the impact on the results evaluated. One price option being the list price per mg for the PARP inhibitor olaparib, currently available in the UK for the treatment of BRCA-mutated ovarian cancer. The price was identified via its technology appraisal guidance by NICE (*Olaparib Technology Appraisal Guidance*, 2019). To calculate the price per mg of olaparib the list price for a 14-day supply

(£2,317), as stated in the NICE recommendation, was used, and divided by the pills such a package would need. The number of pills per package was not given in the recommendation by NICE. However, since olaparib is administered twice daily and requires two 150mg pills per administration, the number of pills needed for a 14 day supply were assumed to be 56 pills (*Olaparib Technology Appraisal Guidance*, 2019).

Lastly, parameters subject to structural uncertainty were varied to determine the effect on the overall results. This included varying the used parametric distributions for OS and PFS.

In addition to the DSAs and scenario analyses, the 20-year life-time horizon included in the base-case was changed to different horizons (15-, 10-, 5-years) and the discount rate of 3.5% was changed to 1.5%. These parameters were not subject to uncertainty, since they were defined by the NICE reference case, however, varying these parameters and identifying changes in results were assumed to be of interest for the later discussion of the paper.

Probabilistic sensitivity analysis

In order to deal with uncertainty around the input parameters used in the decision analytical model, a probabilistic sensitivity analysis (PSA), in which all parameters were varied simultaneously, was conducted (Briggs et al., 2006, p. 87). The following parameters were included in the analysis: health state specific utilities and utility decrements due to AEs, probabilities, duration of AEs, duration of subsequent treatments, drug acquisition costs, drug administration costs, healthcare resource use and costs, end-of-life costs, and patient characteristics such as body surface area. Drug package size and package dose retrieved from the eMIT database (2020), as well as treatment dosing and frequency of administration for all used treatment agents, were considered fixed.

For the performance of the PSA a probability distribution was assigned to each parameter reproducing its mean, its standard error (SE), and the shape of the data around the mean. Gamma distributions were allocated to cost parameters, due to their constraint to be

positive. To obey with the constraint of probabilities and utilities to only take values between zero and one, a beta distribution was assigned. The probability to receive a certain subsequent treatment line was divided into several categories, since patients could receive either chemotherapy, endocrine therapy, cytotoxic therapy, veliparib monotherapy, or no anticancer treatment at all. For these probabilities a Dirichlet distribution was used (Briggs et al., 2006, p. 88). If provided, SEs were directly adopted from the original source. However, in general no SEs were available in the literature and had to be calculated. For cost parameters obtained from the eMIT (2020) database, standard deviation (SD) and quantities (n) were given and used to determine the associated SE using the following formula:

$$\mathrm{SE} \approx \frac{\mathrm{SD}}{\sqrt{\mathrm{n}}} \qquad \text{(Equation 6)}$$

The SEs for the probabilities of receiving a certain subsequent therapy were calculated via the *gamma.inv* syntax in Microsoft Excel using the number of patients in each subsequent treatment arm as alpha. For parameters with no reported SEs, three different percentages of the mean were used to calculate the SEs. Drug acquisition costs for veliparib were considered to have a high uncertainty since no official package price was available in the time of conducting the research. Therefore, 30% of the mean were applied in the PSA analysis. For parameters considered to have a medium uncertainty, 20% of the mean were applied in the analysis. This was used for cost parameters, duration of AEs, as well as duration of subsequent therapies. For the remaining parameters, including probabilities, 10% of the mean were used to calculate the SEs since only a low uncertainty was expected in these values.

After assigning a probability distribution, determining a SE, and calculating an alpha- and beta-value for each uncertain parameter, probability values were generated, and the PSA was conducted by running 1000 Monte-Carlo simulations. The generated results of the PSA were depicted on a cost-effectiveness-plane plotting the difference in effectiveness against the

difference in costs for the treatment with veliparib against chemotherapy (Briggs et al., 2006, p. 122; Drummond et al., 2015, p. 55).

Results

In the following chapter the deterministic ICER, the outcomes of the numerous scenario analyses, the results of the PSA analysis, as well as the graphical representation of the results, are reported.

Base-case analysis

Over a life-time horizon of 20-years, the total costs per patient was £202,591.09 associated with the treatment with veliparib, and £155,583.49 related to the treatment with carboplatin and paclitaxel (Table 18). QALYs per patient yielded with veliparib were 1.99 and 1.95 with the comparator. Total LYs gained with veliparib were 2.94 compared to 3.00 in the treatment with carboplatin and paclitaxel. The incremental costs, QALYs, and LYs of veliparib versus the comparator were £47,007.60, 0.03 QALYs, and -0.06 LYs. The ICER was £1,355,064.49. Since the ICER value is above the national WTP threshold of £30,000, veliparib would not be considered cost-effective by NICE.

Table 18: Results of the base-case analysis

	Veliparib	Carboplatin + Paclitaxel
Total discounted costs (£)	202,591.09	155,583.49
Total discounted QALYs	1.99	1.95
Total discounted LYs	2.94	3.00
Incremental costs		47,007.60
Incremental QALYs		0.03
Incremental LYs		-0.06
Incremental costs/LY (£)		-759,703.54
Incremental costs/QALY (£)		1,355,064.49

Note: Results were discounted, and half-cycle corrected

The disaggregated results of the base-case analysis are shown in table 19. The table illustrates that the high total costs of the veliparib treatment were due to the drug acquisition cost of veliparib in the SD state. The results further demonstrate that the high total costs of the comparator arm were mainly occurring from the drug acquisition costs in the PD state. This is because a proportion of patients in the control group received veliparib monotherapy after progression. Therefore, both treatment arms received the high priced veliparib drug, leading to a substantial increase in costs in both arms. The issues arising from this cross-over treatment, regarding the interpretation of the results will be discussed in more detail in the discussion part of this paper. In addition to the high drug acquisition costs of veliparib, the chemotherapy administration costs in the veliparib arm in SD and PD were higher compared to the control arm. Higher chemotherapy administration costs in the SD can be attributed to the fact that patients in the veliparib arm stayed longer in the progression free state. In the PD state a higher proportion of patients in the veliparib arm received cytotoxic therapy with capecitabine (37% vs. 22.76%). While the chemotherapy administration costs per unit of capecitabine might be smaller compared to other chemotherapy administration costs used in the model, the high frequency of administration (28x per cycle) led to a high total administration cost per cycle. In addition, 52% of patients in the control group had veliparib monotherapy and were therefore not receiving chemotherapy administration costs.

Regarding the LYs and QALYs gained in treatment and comparator arm, the disaggregated results show that treatment with veliparib was beneficial in the stable disease state in which more LYs and QALYs have been gained compared to the treatment with carboplatin and paclitaxel. However, after progression more LYs and QALYs have been gained in the control arm of the model, leading to only a small but positive total difference in QALYs gained but a negative difference in LYs gained. How the cross-over treatment plays into these results will be elaborated in the discussion.

Table 19: Disaggregated base-case results

	Veliparib	Carboplatin + Paclitaxel	Increment
Stable disease (£)			
Drug acquisition costs	161,842.49	1,207.90	160,634.60
Premedication costs	1,091.75	820.66	271.09
Chemotherapy administration costs	15,183.99	11,413.68	3,770.31
Healthcare resources	5,393.89	3,540.93	1,852.96
AEs costs	683.52	530.22	149.84
Progressed disease (£)			
Drug acquisition costs	251.85	121,727.21	-121,475.36
Chemotherapy administration costs	17,705.18	10,793.57	6,911.61
Healthcare resources	2,951.65	6,182.49	-3,230.84
BSC	2,575.26	2,891.75	-316.43
End of life costs	4,815.00	4,814.96	0.03
LYs			
LYs accrued in SD state	2.09	1.38	0.71
LYs accrued in PD state	1.11	1.90	-0.79
QALYs			
QALYs accrued in SD state	1.50	0.99	0.51
QALYs accrued in PD state	0.67	1.14	-0.48
QALYs lost due to AEs	0.0029	0.0023	0.006

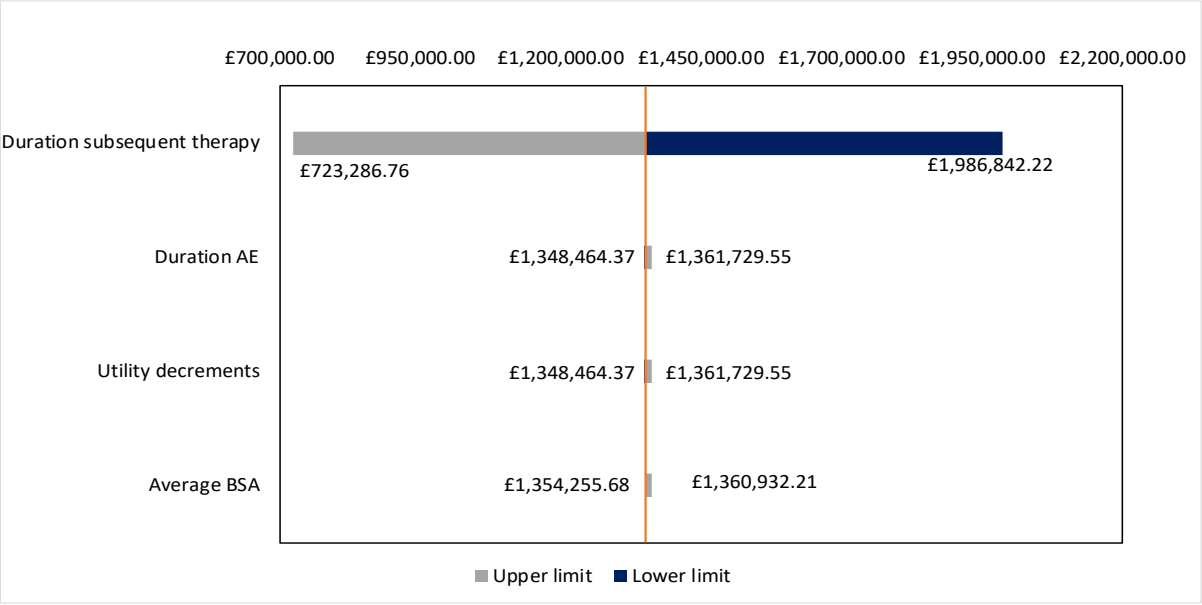
Note: Disaggregated results were not discounted, nor half-cycle corrected

Deterministic sensitivity analyses

The results of the DSAs concerning the parameter uncertainty are illustrated in the tornado diagram in figure 8, including an orange line representing the ICER of the base-case analysis. Varying the average BSA, the utility decrements, and the duration of AEs, only had a small effect on the outcome, as can be obtained from the figure. However, when looking at the effect of the change in duration of subsequent treatment lines on the ICER, the influence of the cross-over treatment is noticeable. When reducing the duration of subsequent treatment lines, the ICER increased, while an increase in duration led to a decrease in ICER. This observation can be explained because with an increase of the treatment duration, the costs of the control group increased substantially, due to longer administration of veliparib

monotherapy after progression. This increase in costs in the control group led to a reduction of the total incremental costs of veliparib and the comparator, resulting in a reduced ICER since incremental health effects were unchanged.

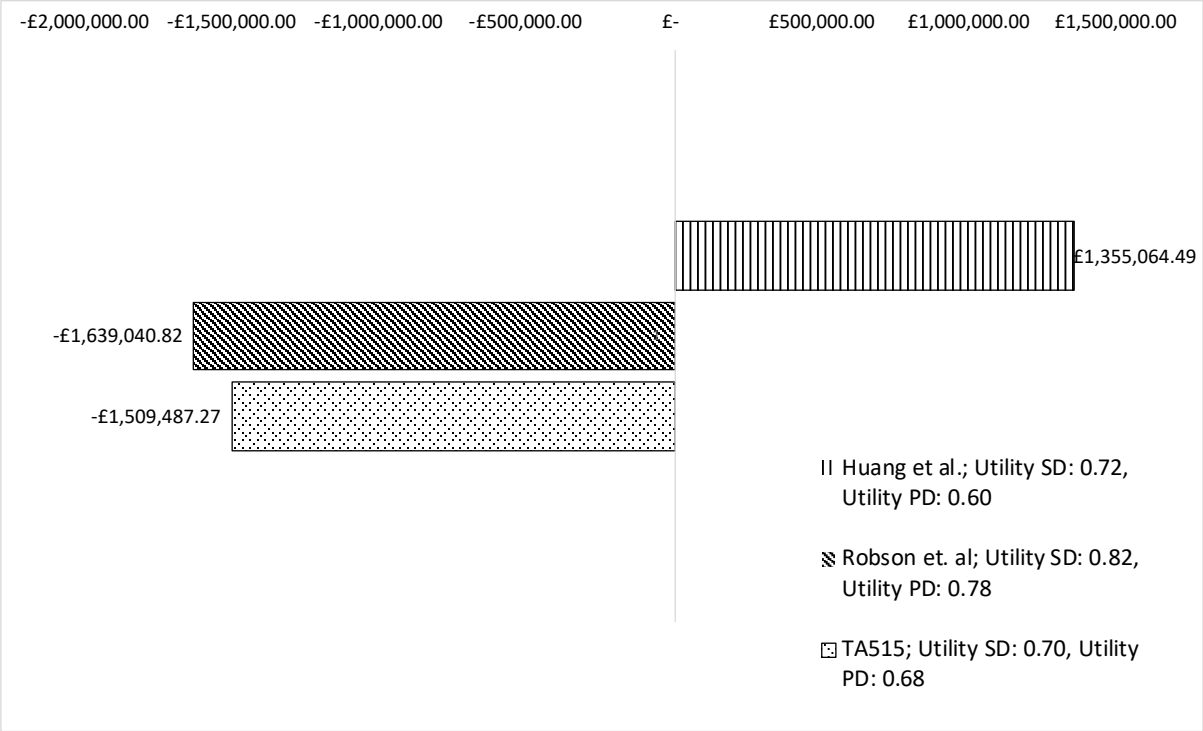
Figure 8: Tornado diagram illustrating ICER change when varying individual parameters



Scenario analyses

In the first scenario analysis, the change in utility values had a substantial influence on the ICER of veliparib (Figure 9). When using the values from the TA515 (2017) eribulin appraisal or the Robson et al., (2018) paper, the ICER turns negative (*Eribulin TA515 Committee Papers*, 2017; Robson M. et al., 2018).

Figure 9: Scenario analysis illustrating ICER change when varying utility values



Patients with a triple negative breast cancer from the Huang et al., (2020) paper had the lowest utility value in PD compared to the values from the TA515 (2017) appraisal or Robson et al., (2018) (0.60 vs. 0.68 vs. 0.78). Since the control group yielded more LYs in the progressed state, compared to the veliparib arm (1.90 versus 1.11), increasing the utility values in this state resulted in putting more weight on the LYs yielded in PD and therefore more QALYs gained in the control group (Table 20). Therefore, when implementing the values from the Robson et al., (2018) paper, the control group yielded the most QALYs in PD since the utility value was the highest compared to the other two papers (*Eribulin TA515 Committee Papers*, 2017; Huang M. et al., 2020; Robson M. et al., 2018) At the same time, the Huang et

al., (2020) values were the lowest in PD, leading to fewer QALYs gained in the PD state of the control group. Therefore, the base-case analysis was the only one achieving positive incremental QALY gains and a positive ICER.

Table 20: QALYs gained in SD and PD when changing utility values

	Veliparib group	Control group
Robson et al., (2018)		
Stable disease	1.70	1.13
Progressed disease	0.87	1.90
TA515		
Stable disease	1.46	0.96
Progressed disease	0.75	1.29

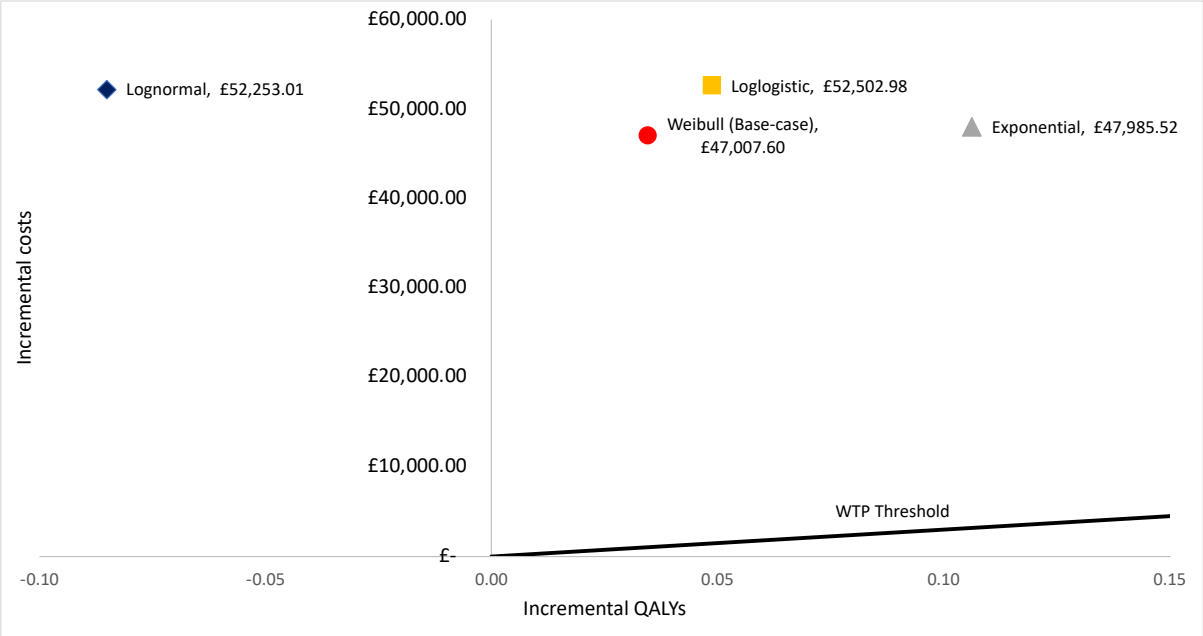
As expected, a reduction of the veliparib price led to a reduction of the ICER as illustrated in figure 10. The price of veliparib used in the base-case (£315.00) was perceived as the maximum price and used as starting point to vary the price and detect the impact on the ICER. Hence, in each scenario the price was reduced by 20% from the price in the previous scenario. In addition, scenario 7 used the price of olaparib (£56.00), resulting in an ICER of £452,904.53 and therefore, still above the WTP threshold in the UK. In fact, even with a price of £0, the ICER (£257,842.91) would still be above the WTP threshold and not be considered cost-effective. While the incremental costs between the veliparib arm and the control arm reduced substantially to £8,944.65, the small incremental QALYs (0.03) stayed constant. Therefore, even when the costs for veliparib are low, or even zero, the ICER remains too high, due to only small incremental QALYs. How the cross-over treatment plays into this observation and the implications of this result for policy makers and future researchers will be elaborated in the discussion part.

Figure 10: Scenario analysis illustrating ICER change when varying veliparib price

Lastly, the results when varying the parametric distributions are illustrated in figure 11. As the figure displays, the incremental costs for all four distributions are around the same range (£47,000 – £53,000). However, the incremental QALYs gained vary greatly between the different distributions (-0.08 – 0.11). This observation can be linked to the fact that in the lognormal, Weibull, and loglogistic distributions the survival probability of the control arm exceeded the survival probability of the veliparib arm at a certain point in time. In the lognormal distribution this moment was already seen after 32 months, leading to the lowest incremental LYs gained. In the exponential distribution however, the survival probability of the control group never exceeded the survival probability of the veliparib group considering the 20-year time horizon. Thus, higher incremental QALYs were achieved compared to the other distributions. Based on these results, the loglogistic and exponential distributions would both have been valid alternatives to the Weibull distribution in the base-case and would have also yielded lower ICER results (£1,074,515.10 and £450,526.24). Yet, as seen in the survival

analysis, both distributions overestimated the median OS and PFS for patients in the indication, compared to the clinical trial data. The implication of these results will be discussed in the next chapter. All scenario results were above the national WTP threshold of £30,000.

Figure 11: Scenario analysis changing the parametric distribution



Further variations were implemented by changing the life-time horizon of 20-years to 15-, 10-, and 5-years. While the first two variations only had a small impact on the ICER, implementing a 5-year time horizon reduced the ICER up to 50% (£646,510.71). While the incremental costs after 5 years only reduced by £2856.72 compared to the total costs after 20 years, the incremental QALYs increased from 0.03 (base-case) to 0.07.

Changing the discount rate to 1.5% impacted the ICER only marginally (£1,504,816.03).

Probabilistic sensitivity analysis

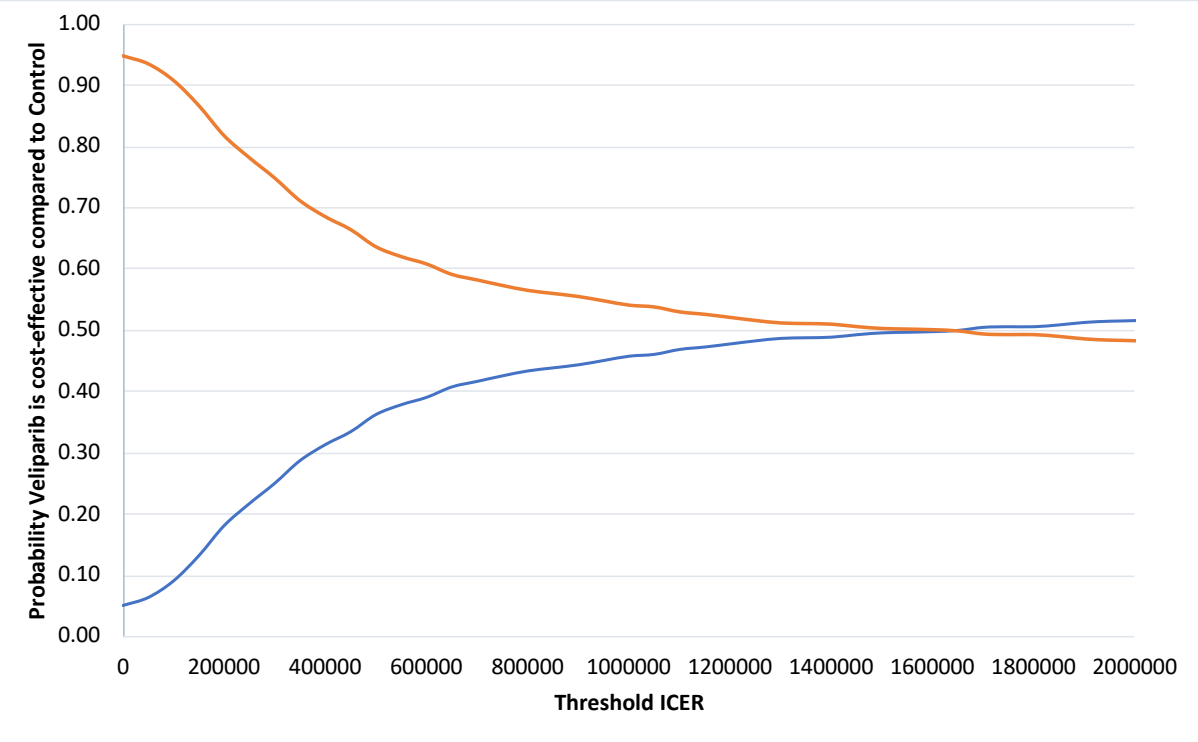
The results from the PSA, in which 1000 Monte-Carlo simulations were performed, showed that the mean ICER of all simulations was £1,449,891.01. Figure 12 shows the CE-plane, in which each point reflects the outcome of one Monte-Carlo simulation and the red line

reflects the national WTP threshold in the UK of £30,000. As can be obtained from the illustration, the outcomes of the PSA were widely spread, with most outcomes being in the northern two quadrants, meaning higher costs related to veliparib in comparison to the treatment arm. Outcomes were almost equally divided between the north-west and north-east quadrant so incremental health effects were either negative or positive. Only 4.2% of outcomes were below the WTP threshold and with positive incremental QALYs (outcomes in the eastern quadrants) and would therefore, be considered cost-effective. Some outcomes were also suggesting that veliparib is less costly than the comparator (southern two quadrants). However, this observation was probably impacted by the high price of the comparator arm due to the cross-over treatment.

Figure 12: CE-plane illustrating the PSA results

The CEAC in figure 13 showed that at a WTP threshold of £30,000, the probability of veliparib being cost-effective was around 5%. When the WTP threshold approaches a value of £2,000,000 the chance of veliparib being cost-effective was 51%. However, these results were also impacted by the high costs and treatment outcomes in PD of the veliparib cross-over treatment in the control group and will therefore, be discussed in the next chapter.

Figure 13: Cost-effectiveness acceptability curve



Discussion

Key findings

This study evaluated the cost-effectiveness of veliparib in combination with carboplatin and paclitaxel compared to carboplatin and paclitaxel alone for BRCA-mutated, HER2-negative, and triple-negative breast cancer patients, after one prior treatment line, by performing a cost-utility analysis with an Excel-based, three health state, Markov cohort model. The analysis was conducted based on guidelines described in the NICE reference case. During the period of conducting the study, the manufacturer suspended the market authorization

application for veliparib and therefore, no official price for veliparib was published. Hence, this study took the veliparib price for research purposes into the base-case analysis and evaluated if veliparib would be considered cost-effective by NICE, considering a WTP threshold between £20,000 to £30,000.

Overall, the treatment with veliparib yielded slightly higher QALYs compared to carboplatin and paclitaxel (1.99 versus 1.95). However, total LYs gained were lower with veliparib in comparison to the control group of the model (2.94 versus 3.00). The costs related to the veliparib arm are slightly higher than in the comparator arm (£202,591.09 versus £155,583.49). Yet, it is important to note that the high costs in the control arm of the model are mainly related to the veliparib monotherapy administered after progression, which will be discussed in more detail later in this section. The analysis led to an ICER of £1,355.064.49, making veliparib not cost-effective considering a WTP threshold of £30,000 in the UK.

As described in section two of this paper, only the study by Gonzalez et al., (2020) was identified evaluating the cost-effectiveness of veliparib. The study focused on the economic evaluation of several PARP inhibitors for the treatment of BRCA-mutated ovarian cancer from an US perspective. Equivalent to the study in this paper, no official veliparib price was identified by Gonzalez et al., (2020), therefore, a price of $13,000 (2018) for a monthly supply of veliparib was assumed by the authors. After correction for inflation and purchasing power, this price corresponds to a current monthly value of £9,598 (£6667.92 per cycle) (*Conversion Rates - Exchange Rates - OECD Data*, n.d.; *Tom's Inflation Calculator*, n.d.). Further, the paper did not calculate the costs per QALY gained, but the costs per QA-PFYs, due to missing survival data. Additionally, a short time-horizon of 44 months was used in the study. By doing so, did the study not only neglect additional costs due to future treatment lines but also failed to incorporate future LYs and QALYs, gained.

Depending on the way Gonzalez would have modelled the subsequent treatment lines, the costs of the comparator arm would either increase to a high level by including the cross-over monotherapy of veliparib or would probably stay moderate if the model would have been adjusted for the cross-over treatment.

Based on the results of the study in this paper, QALYs and LYs gained with veliparib were higher in the PFS state and lower in the progressed state when compared to the control group. If these results hold for the study by Gonzalez et al., (2020) the analysis proportionally overestimated the incremental QALYs and LYs gained with veliparib, by only including PFS in the analysis. Unfortunately, no gained QALY or LY values were given in the paper, making a direct comparison not possible.

Overall, Gonzalez et al., (2020) yielded an ICER of $1,512,495 (£1,115,668.73) making veliparib for ovarian cancer not cost-effective from an US perspective considering a willingness to pay threshold of $150,000/QALY. The several structural differences between the two models, as well as the different indications between the studies, make a direct comparison of the ICERs not meaningfulness.

However, for this discussion the model adopted the assumptions made by Gonzalez et al., (2020) by increasing the price of veliparib, only taking the costs and QALYs from the PFS/SD state into the ICER calculation and implementing a shorter time-horizon (5-years). The ICER obtained from this analysis was £970,403.09/QA-PFY. The analysis shows a reduction in the ICER, while the incremental costs (£384,363.52) and incremental QALYs gained (0.40) between veliparib and its comparator increased substantially. Although, an evaluation only based on costs, QALYs and LYs gained from PFS neglects to include important future costs and health effects, it is interesting to incorporate these assumptions in the analysis of this paper, since it helps to understand how substantial the impact of the cross-over treatment was on the results. This will be further elaborated in the following section.

Strengths and Limitations

In the economic evaluation conducted in this study several strengths can be identified. First, the results contribute to the discussion regarding the implementation of BRCA-mutated specific breast cancer treatment pathways in the UK. As mentioned in the paper, NICE does not define specific treatment recommendations for BRCA-mutated breast cancer. Therefore, evaluating treatment alternatives targeting patients in this indication is of great importance for decision makers. The performed economic evaluation of veliparib is the first one conducted from an NHS and PSS payer perspective. Hence, this study not only evaluates veliparib as potential new treatment for patients in the UK but also carboplatin and paclitaxel as already existing medications in the UK, however, not yet recommended for patients with BRCA-mutated breast cancer. Further, this paper contributes to a still scarce number of health economic literature regarding treatment with PARP-inhibitors for breast cancer patients in the UK.

Secondly, this study highlighted the high price of veliparib and its effect on the cost-effectiveness of the treatment. Considering the manufacturers market authorization application withdrawal, this study contributes to the pricing discussion of veliparib once the manufacturer decides to reapply for market authorization.

An advantage of the design of the model is that it included the administration of monotherapy in the stable disease state. By doing so, the model portrays more accurately the clinical practice of the treatment with veliparib, as described in the clinical trial. Therefore, a more realistic picture of the total costs was shown in the model. In addition, several potential subsequent treatment lines were included in the evaluation, representing more accurate different treatment pathways that can vary greatly between patients, based on the individual patient's needs. Lastly, the model has been designed in a way that several scenarios can be

easily implemented by choosing from different drop-down lists. Hence, assumptions and parameters can be varied freely to see the effect on the final outcomes.

However, the analysis in this evaluation also bears several limitations regarding the structure of the model, the assumptions made, and the parameters used.

Firstly, not adjusting for the cross-over treatment is one of the key structural limitations in this assessment and requires further discussion. The implementation of a cross-over treatment poses an issue in an economic evaluation by not reflecting the relevant treatment pathway for the decision maker. In other words, in an economic evaluation a not yet existing treatment is compared to the current standard of care, however, with a cross-over treatment the not yet existing treatment is part of the already existing treatment pathway, making a comparison and interpretation of results problematic (N. Latimer, 2012, pp. 7–8). A cross-over treatment influences two main elements of an economic evaluation. First, the true difference in OS between treatment and comparator arm cannot be evaluated since patients in the control group also received the new treatment. Therefore, survival benefits in the comparator arm could have been achieved due to the comparator, the cross-over treatment, or a combination of both. However, as described by Latimer (2012), it can be assumed that the actual OS difference between veliparib and its comparator would be larger as seen in this study if patients would not have received cross-over treatment, (N. Latimer, 2012, pp. 7–8). Secondly, if the costs of the cross-over treatment are included in the model no valid statement can be made regarding the total cost difference between treatment and comparator since both include costs of the new treatment. Methods to adjust for cross-over include *naïve*- and more sophisticated- methods (N. Latimer, 2012, pp. 9–10). While naïve methods such as, modelling based only on PFS, as seen by Gonzalez et al., (2020), or censoring or excluding patient data often leads to bias, more sophisticated methods are more difficult to implement and can require additional data (N. Latimer, 2012, pp. 33–43). In this paper the model of veliparib was not adjusted for the cross-

over treatment since insufficient data was available for censoring or to implement a more sophisticated adjustment method. Further, it was considered more accurate to model the treatment over a patient's lifetime instead of only including costs and health effects occurred in the progression free state. Especially, if the survival outcomes of the control group were impacted by the cross-over treatment it would be only right to also include the impact of the cross-over treatment to the costs of the control group. However, due to this decision, the interpretation of the results in the study must always consider that a cross-over treatment has been implemented. To explore how the implementation of a *naïve* method would influence the results, the model was adjusted to only include costs and effects gained in the stable disease state as already done above. However, when using the base-case price (£315.00) and the 20-year time-horizon the ICER further decreases to £351,896.91/QA-PFY. While the ICER was still above the WTP threshold, a substantial reduction was observed compared to the base-case. This analysis might not be as accurate, since no future costs and health effects were included, but it illustrates a more realistic total cost difference between veliparib and the comparator (£176,679.81 versus £16,990.01) and can be used to better understand and classify the results. How the exclusion of the cross-over treatment would impact the OS achieved in the control group after progression is difficult to determine and requires additional data. However, based on the findings from Latimer (2012) it can be assumed that the veliparib monotherapy in PD improved the survival rate in the control group. Hence, without veliparib monotherapy the incremental LYs and QALYs gained between veliparib and control arm would be higher, resulting in a small ICER.

Another limitation of the evaluation refers to the assumptions made when designing the model.

First, some uncertainty remains in the choice of the parametric distribution to extrapolate the survival curves. While the reasoning behind choosing the Weibull distribution

for OS and PFS was elaborated in chapter three, the methods used to evaluate the fit of each distribution were limited. The analysis focused on the visual-, statistical -and clinical- fit to identify the best fitting distribution. However, due to the time constraint other methods such as hazard plots were neglected. If the use of additional methods would have changed the final decision on this matter cannot be estimated however, the clinical plausibility criterium used as the main argumentation for choosing the Weibull distribution is a key decision criterion, especially to evaluate whether the extrapolated part of the curve is reasonable. Yet, when changing the parametric distribution, results vary greatly regarding QALYs gained, as seen in the scenario analysis. Taking the observations from the scenario analysis into account, the loglogistic- or exponential-distribution might have also been realistic models for the extrapolation of the survival curves, especially regarding the cross-over treatment since both distributions yielded higher incremental QALYs. However, with both distributions, an overestimation of median OS and PFS, compared to the clinical trial, was observed. This dilemma shows that the decision in this matter came with uncertainty, affecting the results of the model.

Further, due to limited data given by the clinical trial, assumptions were made in order to implement veliparib monotherapy in the model. For veliparib monotherapy in the stable disease, the clinical trial did not state, when on average patients transitioned to blinded monotherapy nor the maximum duration of monotherapy. Therefore, two assumptions were made. First, the cycle in which patients started to transition to monotherapy in the model was taken from the appendix in the clinical trial, in which the proportion of patients switching to monotherapy in each cycle was given. The cycle at which more than 50% of patients had switched was used as the starting point of monotherapy administration in the model (Diéras et al., 2020a, p. 8). Additionally, since no maximum duration of blinded monotherapy was stated in the clinical trial the mean duration of monotherapy observed in the trial was used as the

maximum number of cycles of monotherapy in the model. As mentioned in the results section, costs in the veliparib arm increased substantially due to the veliparib monotherapy administration. Therefore, the assumptions made to implement monotherapy in the model had a considerable impact on the results. For example, when reducing the number of veliparib monotherapy in the stable disease state from 17 cycles (base-case) to 15 cycles, the ICER decreased by £246,471.17 to a value of £1,108,593.33. Further, for the cross-over monotherapy no maximum duration was stated in the clinical trial. Thus, the duration was assumed to be the mean duration of blinded monotherapy administered in the stable disease state (11.8 cycles). Since the uncertainty around this assumption was high, a longer or shorter duration of each subsequent therapy line was implemented in a scenario analysis to see the impact on the results. However, as described above, this scenario was strongly impacted by the cross-over treatment.

Lastly, the choices made regarding the costs- and quality of life- input parameters come with some uncertainties, impacting the final outcomes of the model.

The utility values by Huang et al., (2020) were chosen for the base case of the evaluation. However, those were not obtained according to the NICE reference case since no information was given whether the utility values were valuated from a UK perspective. Further, the utility values included in the base-case analysis were not related to patients with a BRCA mutation. Since the paper did not provide any information on the valuation method and did not include BRCA specific utilities, two additional utility sets were implemented in the scenario analyses. The Robson et al., (2018) paper obtained utilities for BRCA mutated breast cancer and the TA515 (2017) appraisal utility values mapped with a UK tariff, both for HER2-negative breast cancer. It would have been preferred to use utility values in the base-case that were BRCA-specific and obtained according to the recommendations by NICE, however, due to limited available data the scenarios were used to incorporate different valuation methods and perspectives and identify the effect on the outcome. Further, the utility decrement due to

thrombocytopenia, as well as the duration of AEs, were not breast cancer specific. The other utility decrements were disease specific, however, an indirect approach was used to determine the health state utilities, not aligning with NICE recommendations. Due to these limitations, these parameters were varied to a maximum and minimum value in a DSA, resulting in only small changes in the ICER.

The cost parameter with the biggest uncertainty was the missing price information of veliparib. As seen in the base-case, the high price of veliparib led to very high costs per cycle, especially when administered as monotherapy. To deal with this uncertainty and to determine a price in which the treatment would achieve an ICER at least closer to the WTP threshold, several scenario analyses were conducted, varying the 200mg package price of veliparib. As seen in the scenarios, price reductions led to considerable reductions in the ICER value. However, even a veliparib price of £0 would still not achieve a cost-effective ICER (£257,842.91). This aligns with the outcome of the Gonzalez et al., (2020) paper and might be driven by the small incremental QALYs gained in the analysis and the cross-over treatment. To see what incremental QALY value would be needed for veliparib to be considered cost-effective, the incremental QALYs in the model were increased to the point in which the ICER was below £30,000. With the base-case price (£315.00) incremental QALYs would need to be at least 1.6 to achieve an ICER of £30,000. With the calculated price of olaparib (£56.00) QALYs would need to achieve an increment of at least 0.55. What these results mean for future research will be elaborated later.

In addition to the missing veliparib price, the fact that no BRCA-mutation specific cost inputs were used in the analysis, could be perceived as limitation of the evaluation. For some cost items, such as premedication or chemotherapy administration costs, the BRCA-mutation would not have impacted the costs per cycle. However, for healthcare resource use or best-supportive care use the BRCA-status might have resulted in additional resource use items

needed. In example, since a BRCA mutation is a genetic mutation, genetic testing could have been an additional resource use to include in the analysis. Nevertheless, due to the high total costs of the treatment, it is questionable, if the costs related to genetic testing would have a relevant impact on the total costs.

Uncertainty remains around the costs of subsequent treatment lines. The BROCADE3 clinical trial did not give any further information regarding specific subsequent treatment lines administered in the trial. Therefore, specific treatment medications, administration costs, as well as dosage, duration, and frequency of administration of each treatment had to be identified via additional literature, leading to uncertainty around these values. In addition, the assumption was made that patients not receiving further anticancer treatment would receive BSC after progression.

Lastly, the ranges of uncertainty used in the PSA could be perceived as limitation. Treatment dosing and frequency in SD and PD were assumed not to be uncertain. Only dosages depending on the patients average BSA were varied in the PSA, due to the uncertainty assigned to the BSA parameter. All other inputs used in the model were expected to be uncertain. The SEs, needed to vary each parameter, were preferably based on the literature. However, in most cases data was not available and a range between 10% to 30% was applied. If the uncertainty applied to an individual parameter really portraited the potential range of values the parameter can take, cannot be evaluated without additional data. Nevertheless, by implementing lower uncertainty ranges (5%, 10%, 20%) in the model, the CE-plane still shows a wide spread of ICER results, especially in the two northern quadrants.

Policy recommendations and final considerations

Based on the results of this evaluation, the treatment with veliparib for BRCA-mutated advanced breast cancer is not cost-effective considering the UKs WTP threshold. Therefore, veliparib should not be recommended by NICE. As this study identified, veliparib has

substantially higher costs compared to carboplatin and paclitaxel, while only showing moderate incremental health benefits, so that even a reduction of the veliparib price to £0, would still not achieve a cost-effective ICER. Therefore, based on this study, certain commercial agreements, as seen in other expensive oncology treatments, would not be considered useful to achieve a cost-effective result. However, the cost estimates and health effects in the control group in this study were impacted by the cross-over veliparib treatment. Due to this effect, making a concrete policy recommendation only based on the results of this study, is difficult.

Thus, it is important for future studies to further evaluate veliparib and adjust the model for the cross-over treatment to identify whether health effects in the control group change and if so, how it effects the ICER. Beside additional cost-effectiveness studies of veliparib, the focus of the manufacturer should be on further researching veliparib and collecting additional clinical data to identify the real incremental OS between veliparib and the comparator. Further, it could be beneficial to identify patient subgroups that benefit the most from the treatment with veliparib. By doing so, important patient characteristics could be obtained and used to address the uncertainty around the treatment's success.

Beside the influence of the cross-over treatment in this study, the analysis identified first cost estimates for the treatment with veliparib in the UK and showed that veliparib has high costs, especially when administered as monotherapy. In addition, the model illustrated that treatment with veliparib resulted in higher LYs and QALYs gained in the stable disease state, however, in PD veliparib gained less QALYs and LYs than the comparator, resulting in only small incremental QALYs. Further, this study identified which clinical and cost parameters would need to change for veliparib to be considered cost-effective by NICE and how future research should contribute to the evaluation of veliparib. Therefore, the economic evaluation conducted in this paper should be used as a starting point of further research of veliparib for BRCA-mutated, advanced breast cancer in the UK.

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Appendix A: Survival analysis

Appendix A1: R-studio code provided by Hoyle & Henly (2011)

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

library(survival)


#    Step 4.   Update directory name and text file name in line below

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

attach(data)

data


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

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


#  adding times for patients at risk at last time point

times_start <- c(times_start, rep(30,4))

times_end <- c(times_end, rep(10000,4))


#   Step 5. choose one of these function forms

model_exp  <-  survreg(Surv(times_start,  times_end,  type="interval2")~1,  dist="exponential")       #
Exponential function, interval censoring

model_wei  <-  survreg(Surv(times_start,  times_end,  type="interval2")~1,  dist="weibull")     #  Weibull
function, interval censoring

model_logn <- survreg(Surv(times_start, times_end, type="interval2")~1, dist="lognormal")   # Lognormal
function, interval censoring

model_logl <- survreg(Surv(times_start, times_end, type="interval2")~1, dist="loglogistic")   # Loglogistic
function, interval censoring


#   Compare AIC values

AIC_exp<- -2*summary(model_exp)$loglik[1] + 2*1   #  AIC for exponential distribution
```

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


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

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

```
# For the Probabilistic Sensitivity Analysis, we need the Cholesky matrix, which captures the variance and covariance of parameters
cholesky_exp<-t(chol(summary(model_exp)$var))  # Cholesky matrix for exponential
cholesky_exp
cholesky_wei<-t(chol(summary(model_wei)$var))  # Cholesky matrix for weibull
cholesky_wei
cholesky_logn<-t(chol(summary(model_logn)$var))  # Cholesky matrix for lognormal
cholesky_logn
cholesky_logl<-t(chol(summary(model_logl)$var))  # Cholesky matrix for loglogistic
cholesky_logl
```

Appendix A2: Median OS and PFS estimated via different parametric distributions

	Veliparib arm (months)				Control arm (months)			
	Weibull	lognormal	loglogistic	exponential	Weibull	lognormal	loglogistic	exponential
OS	35.6	46.1	44.5	47.3	36.5	51.1	45.9	46.7
PFS	23.2	27.6	27.8	25.4	15.4	16.1	16.0	16.4

Appendix B: SLR

Appendix B1: Utility search strategy Embase

	Search strings	**Results**
	'Breast cancer'	37
AND	(her2 NEAR/2 negative) OR (triple NEAR/2 negative) OR brca OR brca1 OR brca2 OR 'germline mutatio*' OR 'tumo* suppressor gene' OR parp	
AND	quality of life' OR 'health related quality of life' OR utilit* OR disutilit* OR qol OR hrqol OR hr qol OR hql OR h qol OR eq5d OR eq 5d OR eq5d5l OR eq5d3l OR EQ-5D OR EQ-5D-5L OR EQ-5D-3L OR 'European Quality of Life 5 Dimensions questionnaire'	

Appendix B2: SLR inclusion criteria

Domain	Inclusion Criteria	Exclusion Criteria	Rationale
Population	Adult patients, with HER2-negative or triple-negative breast cancer (with or without BRCA mutation; with advanced or metastatic state)	Patients not including adults with HER2-negative or triple-negative breast cancer	Patients relevant for the submission had BRCA-mutated, triple-negative, or HER2-negative, advanced breast cancer; Reasoning why also study population without BRCA mutation is included: 1) Little data available for this sub-population 2) Assumption that BRCA mutation has little influence on the health status of patients;
Intervention	Any or none	NA	-
Comparator	Any or none	NA	-
Outcomes	Original health state utility data obtained using, preferable the EQ-5D questionnaire, but other methodologies were also included;	No relevant health state utilities matching with the state population	Broad approach in case insufficient studies were identified using the NICE recommendation, recommending the EQ-5D questionnaire and time-trade off method
Study design	Experimental studies, including RCTs and non-RCTs, observational studies, economic evaluations	All other	-
Language	English	Any-other language	-

Appendix B3: Sources used for the input values in the decision model

Source	Identified through	Patient population	Input parameters
Literature			
Huang et al. (2020)	SLR	Patients with metastatic TNBC randomized to pembrolizumab or chemotherapy	Utility values
Robson et al. (2018)	SLR	Patients with HER2 negative gBRCA+, MBC randomized to Olaparib or sing-agent chemotherapy	Utility values
NICE appraisals			
TA515 Eribulin	SLR	Patients with HER2-negative breast cancer whose disease has progressed after 1 chemotherapy regimen in the advanced setting	Utility values, Utility decrement due to AEs, Chemotherapy administration costs
TA579 Abemaciclib	SLR	Patients with hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy	Utility decrement due to AEs, Drug acquisition costs (PD)
TA495 Palbociclib	SLR	Patients with previously untreated, hormone receptor-positive, HER2-negative, locally advanced, or metastatic breast cancer	Healthcare resource use (SD, PD) Best-supportive-care resource use
TA687 Ribociclib	SLR	Patients with hormone receptor-positive, HER2-negative advanced breast cancer after endocrine therapy	Costs related to AEs
TA496 Ribociclib	SLR	Patients with untreated, hormone receptor-positive, HER2-negative, locally advanced, or metastatic breast cancer	Monitoring resource use
TA673 Niraparib	Manual search	Patients with advanced ovarian, fallopian tube and peritoneal cancer after response to first-line platinum-based chemotherapy	Utility decrement due to AEs
TA639 Atezolizumab	Manual search	Patients with untreated PD-L1-positive, locally advanced, or metastatic, triple-negative breast cancer	Drug acquisition costs (PD)

Appendix B4: Utility decrements due to AEs

Adverse Event	Utility decrement	Duration (days)	Source: Utility decrement	Source: Duration
Neutropenia	0.007	15.10	TA515 (Table 51)	TA579 appraisal (2019) (Table 33), citing ID414 pixantrone appraisal (2012) (Table 34)
Thrombocytopenia	0.090	23.30	TA673 (Table 35)	ID414 pixantrone appraisal (2012) (Table 34)
Anaemia	0.010	16.10	TA515 (Table 51)	TA579 appraisal (2019) (Table 33), citing ID414 pixantrone appraisal (2012) (Table 34)
Nausea	0.021	6.00	TA515 (Table 51)	ID414 pixantrone appraisal (2012) (Table 34)
Fatigue	0.029	31.5	TA515 (Table 51) and TA579 (Table 32)	ID414 pixantrone appraisal (2012) (Table 34)
Diarrhea	0.006	6.00	TA515 (Table 51) and TA579 (Table 32)	TA579 appraisal (2019) (Table 33), citing ID414 pixantrone appraisal (2012) (Table 34)
Leukopenia	0.003	14.00	TA515 (Table 51) and TA579 (Table 32)	TA579 appraisal (2019) (Table 33), citing ID414 pixantrone appraisal (2012) (Table 34)
Peripheral Sensory	0.014	35.30	TA515	ID414 pixantrone appraisal (2012) (Table 34)

Note: Duration of peripheral sensory was obtain from Pixantrone (2012) grade 2 Neuropathy and assumed to be the same as for grade ¾