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Abemaciclib and Liquid Biopsies: a Guide to Future Early Breast Cancer Treatment

A COST-EFFECTIVENESS ANALYSIS OF ADDITIONAL ABEMACICLIB AND THE USE OF LIQUID BIOPSIES IN HIGH-RISK HORMONE RESPONSIVE, HER2 NEGATIVE EARLY BREAST CANCER TREATMENT

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Summary

Introduction

In the Netherlands, 17,000 women are diagnosed with breast cancer every year. While various subtypes exist, hormone responsive and HER2-negative ($HR^+/HER2^-$) early breast cancer is the most common one. After surgical removal, risk of recurrence remains, and those with a high recurrence risk currently receive five years of endocrine therapy to reduce that risk. Abemaciclib, a CDK4/6 inhibitor that has shown to be effective in the metastatic setting, has shown promising results for these high-risk $HR^+/HER2^-$ early breast cancer patients. However, as abemaciclib is expensive and may cause serious discomfort, liquid biopsies are proposed as a more precise approach to determine who will benefit from extra abemaciclib treatment. While these liquid biopsies may bring extra costs, it is expected that they might save money in the long run. This research aimed to explore the cost-effectiveness of treating all high-risk $HR^+/HER2^-$ early breast cancer patients with abemaciclib, and of using liquid biopsies as a risk assessment tool to better predict who should receive additional abemaciclib.

Theoretical Background

Economic evaluations are increasingly being used to assess the value of new health interventions and to guide decision-making. In these types of evaluations, the costs and the consequences of an intervention are systematically compared. Often by means of Markov models. In the Netherlands, Zorginstituut Nederland (ZiN) decides whether a new drug will be reimbursed.

Methods

A cost-effectiveness analysis (CEA) was performed in which the costs, life years and QALYs gained for three treatment scenarios were compared. Scenario A consisted of current standard treatment. Scenario B consisted of treating all patients that are at high-risk of recurrence according to current risk assessment with additional abemaciclib. Lastly, in scenario C, only patients with a positive liquid biopsy, which were performed every six months, received additional abemaciclib. A societal perspective and a lifetime horizon were taken. Survival curves and utility values derived from literature were used as effect input. Cost inputs were derived from literature, treatment protocols, hospital price lists and ZiN guidelines. Uncertainty was assessed by means of scenario analyses and probabilistic sensitivity analyses (PSA).

Results

With a minimal treatment effect, the ICER of the comparison between scenario A and B was €5,299,623 per QALY gained. The comparison between scenario A and C led to ICERs of €28,031 per life year gained and €31,367 per QALY gained as the costs were lower and the effects were higher. Uncertainty surrounding the treatment effect in scenario B was substantial. In scenario C, the PSA showed that there was certainty that the treatment effect was positive.

Discussion & Conclusion

Under the ICER threshold of €50,000, treatment scenario B was nowhere near cost-effectiveness under any of the scenario analyses. Treatment scenario C was cost-effective and showed an acceptability probability of 92% at the ZiN threshold. These results suggest that with the rise of expensive medicines a more personalised approach in oncology is needed. Finally, research on the exact effect of abemaciclib and the predictive value of liquid biopsies are necessary.

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1. Introduction

1.1 Breast cancer

Breast cancer is a disease caused by uncontrolled growth of cells in the breast tissue (1). In 2018, breast cancer had the highest incidence of all types of cancer worldwide. Amongst women, breast cancer constituted for approximately 25% of all new cancer diagnoses and had an estimated prevalence of more than 7.7 million (2). In the Netherlands, approximately 17,000 people were diagnosed with breast cancer in 2019. While people of both sexes can be affected by breast cancer, 99.2% of these new breast cancer patients were women. Moreover, the vast majority of new diagnoses occur in patients between the age of 50 and 74, making post-menopausal women the group that is most susceptible for the disease (3). Breast cancer composes of several biological subtypes which all have their own behaviour, prognosis and response to treatment. Currently, the distinction of breast cancer subtypes is mainly based on the grade of the tumour, which expresses the extent in which the tumour DNA has differentiated from the patient's healthy DNA (4). Moreover, distinctions are made based on hormone receptor and HER2 expression by the tumours (5). Lastly, Ki-67 levels can be measured to assess the rate of tumour cell growth (6). Of all Dutch breast cancer patients, the majority is hormone responsive and HER2-negative ($HR^+/HER2^-$), as 8987 of newly diagnosed patients in 2019 were $HR^+/HER2^-$ (3).

The prognosis for patients with breast cancer primarily depends on the stage of the disease at diagnosis. The vast majority of patients present with early or locally advanced disease (3,7), which means that the primary goals of treatment are still to cure the patients and to reduce the risk of tumour recurrence. When left untreated, early or locally advanced disease may spread to other parts of the body (i.e. lungs, liver or brain) through the circulatory and lymphatic system. Breast cancer that has spread to other body parts is called metastatic breast cancer (8).

In order to achieve recurrence risk reduction and to improve overall survival (OS), $HR^+/HER2^-$ early breast cancer patients receive adjuvant endocrine therapy. This means that after initial surgical treatment, patients will receive hormonal treatment for a certain period of time. While the combination of surgical removal and adjuvant endocrine treatment makes a significant contribution to recurrence risk reduction, high risk patients still face considerable recurrence rates (9). For example, from the high recurrence risk patient population investigated

by Pan et al., 52% of patients had recurrence after 20 years (10). Therefore, additional therapy for this specific high-risk patient group is often indicated.

In 2018, the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) approved the use of abemaciclib, a CDK4/6 inhibitor, in metastatic $HR^+/HER2^-$ breast cancer (11–13). Recently, the addition of abemaciclib during the first two years of adjuvant endocrine therapy for $HR^+/HER2^-$ early breast cancer has been investigated By Johnston and colleagues. Their study showed that this addition significantly improved the invasive disease-free survival (DFS) in high-risk $HR^+/HER2^-$ early breast cancer patients from 88% to 92% after two years (14). Because of these promising results, the use of abemaciclib for the $HR^+/HER2^-$ early breast cancer indication is expected to be investigated by the FDA in the foreseeable future.

1.2 Current treatment of $HR^+/HER2^-$ early breast cancer

Currently, $HR^+/HER2^-$ early breast cancer is initially treated by surgery and a short period of adjuvant chemotherapy. Subsequently, patients are treated with adjuvant endocrine therapy that consists of five years of tamoxifen for pre-menopausal women or two years of tamoxifen followed by three years of aromatase inhibitors (AI) for post-menopausal women. These five years of adjuvant endocrine therapy are provided to all $HR^+/HER2^-$ early breast cancer patients, irrespective of their recurrence risk. This recurrence risk is determined pre-surgery according to the grade of the tumour, TNM-classification scale, and Ki-67 levels (15).

Tumours can be graded from 1 to 3, with 3 being the worst grade (4). Additionally, the TNM-classification scale assesses certain characteristics of the tumour at presentation. The T refers to the size of the tumour and ranges from T_1 in which the tumour diameter is smaller than 2 cm, to T_3 in which the tumour diameter is larger than 5 cm. The N refers to the number of lymph nodes that are affected by the cancer. The N-status can range from N_0 in which no nodes are involved, to N_3 in which 10 or more nodes are involved. Moreover, the M-status refers to possible metastases. When the cancer has not visibly metastasised yet, an M_0 status is given and when it has metastasised to other organs, an M_1 status is given (16). Lastly, Ki-67 levels indicate the growth rate of the tumour. A Ki-67 level of more than 20% is considered high (6).

Based on one's grade, TNM-classification score and Ki-67 level, the treating physician may decide that the patient has a high risk of recurrence and therefore, adjuvant endocrine therapy may be extended beyond the standard five years (15). In this study, a patient will be

classified as being high risk when they meet the criteria set by Johnston and colleagues (14). This means that high-risk patients either have more than 4 nodes involved, or have 1-3 nodes involved and either a tumour size of more than 5 cm, a grade of 3 or a Ki-67 level of above 20%. An overview of this treatment can be found in Figure 1.1.A.

1.3 Inclusion of abemaciclib in treatment of $HR^+/HER2^-$ early breast cancer

Considering the promising results of adding abemaciclib to standard adjuvant endocrine therapy during the first two years, a new treatment scenario has been proposed. Figure 1.1.B depicts this scenario in which high-risk $HR^+/HER2^-$ early breast cancer patients will receive additional CDK4/6 inhibitors during the first two years of treatment. The last three years of treatment will be finished as described in treatment scenario A.

1.4 Reconsidering risk assessment tools

As was explained before, when one aims to assess a patient's recurrence risk based on the tumour grade, TNM-classification scale and Ki-67 levels, they must perform this assessment prior to surgical treatment at disease presentation. When applying this form of risk assessment according to the criteria by Johnston, 9,8% of patients will be classified as having high risk of recurrence. In the Dutch context, this would mean that approximately 882 patients per year would have a high risk of disease recurrence and could therefore possibly benefit from additional abemaciclib treatment.

The current standard adjuvant endocrine treatment that consists of tamoxifen and/or AIs is relatively cheap and costs €0.21 or €0.88 per day, respectively (17). In comparison to standard treatment, abemaciclib is considerably more expensive costing €93.04 per day (18) and in an ideal situation, it would only be used on those who actually need it. Moreover, it is important to note that abemaciclib use may cause serious discomfort and may lead to a significantly lower quality of life (14,19). This highlights that while abemaciclib has positive clinical value, the decision to prescribe it should not be taken lightly. Taking this into consideration, the oncologists at the Erasmus Medical Center propose to use a more precise risk assessment tool: liquid biopsies. These liquid biopsies are easily obtained from bodily fluids (e.g. blood or urine) and provide real-time information on the tumour in a minimally invasive manner. Moreover, liquid biopsies are expected to make a more precise risk assessment than the current system as only those with a positive biopsy will be classified as

high risk. Thus, liquid biopsies may save costs and prevent patients from receiving unnecessarily harsh treatments.

Examples of tumour derived components which can be detected by liquid biopsies are circulating tumour cells (CTCs) and cell-free tumour DNA (ctDNA). Presence of these components in the adjuvant setting effectively indicates risk of recurrence (20,21). By identification if tumour specific mutations prior to surgery and taking liquid biopsies every six months, one will be able to make a better prediction of the patient's recurrence risk and may prevent high costs and severe discomfort by only providing abemaciclib treatment when appropriate. This scenario is depicted by Figure 1.1.C.

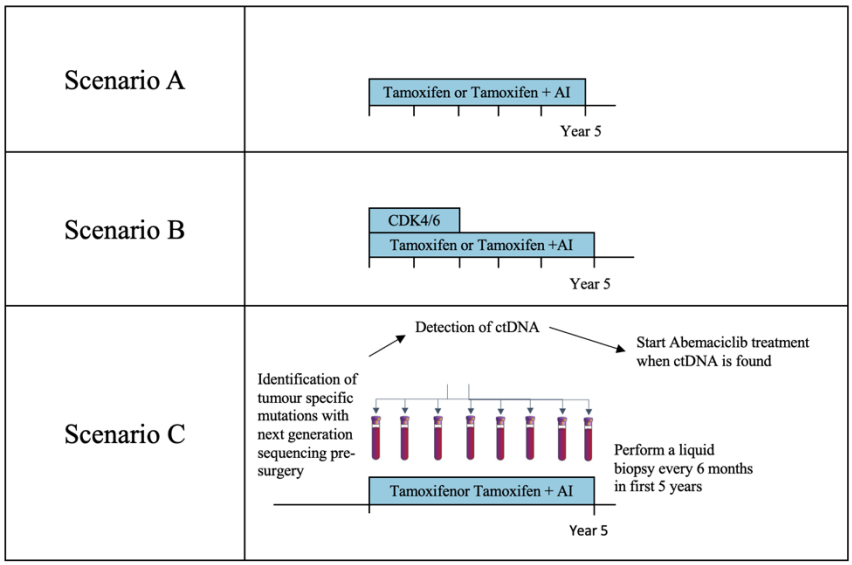

Figure 1.1: Overview of treatment of high risk $HR^+/HER2^-$ early breast cancer. Treatment starts after initial surgery and may be extended beyond the first five years.

1.5 Aim & research question

Literature on the use of abemaciclib and liquid biopsies in $HR^+/HER2^-$ early breast cancer remains scarce. Therefore, the aim of this research is to explore whether providing abemaciclib treatment to $HR^+/HER2^-$ early breast cancer patients could be cost-effective compared to current standard treatment. This will be done by performing a cost-effectiveness analysis (CEA) comparing treatment scenario A and B. Moreover, an additional CEA comparing treatment scenario C to A will be performed to investigate whether the use of liquid biopsies as a risk assessment tool is more cost-effective than using the current system and whether it could save costs and spare patients unnecessarily harsh treatments when compared to treatment scenario B. As this research is issued by the Erasmus Medical Center, it will be performed in the Dutch context. The outcomes may provide insight in which treatment scenario may be preferable for $HR^+/HER2^-$ early breast cancer patients in the Netherlands.

To reach the above-mentioned aims, the following research questions will be answered:

- *Is the addition of abemaciclib to current standard treatment for $HR^+/HER2^-$ early breast cancer patients with high risk of recurrence cost-effective compared to current standard adjuvant treatment?*
- *Is the use of liquid biopsies as a risk assessment tool within $HR^+/HER2^-$ early breast cancer cost-effective compared to using the standard risk assessment system?*

1.6 Overview of thesis

The following chapters provide the required information to answer the proposed research questions and the research aim. The second chapter elaborates on the theoretical foundations of economic evaluations, breast cancer research and treatment, and the theory behind liquid biopsies. In the third chapter, the methodological choices and assumptions made are justified and research inputs are provided. Subsequently, in the fourth chapter the results of the cost-effectiveness analyses are presented, and scenario analyses and probabilistic sensitivity analyses are performed. In the fifth and final chapter, the results, the implications of the assumptions that were made, the strengths and the limitations are discussed within the broader context of breast cancer research and treatment. Based on this discussion, conclusions are drawn and recommendations for reimbursement and future research are provided.

2. Theoretical Background

This chapter contains the theoretical background that is required to reach the proposed research aim. First, a more comprehensive background on $HR^+/HER2^-$ early breast cancer its current and future treatment will be provided. Second, the theoretical basis for health technology assessment and economic evaluations will be discussed. Subsequently, the importance of modelling in health decision-making will be described, followed by an explanation of Markov modelling. Finally, the process of health technology assessment in the Netherlands will be discussed.

2.1 Breast cancer treatment

As was mentioned in the introduction, approximately 17,000 people are diagnosed with breast cancer in the Netherlands per year (3). Symptoms include among others lumps in the breast, change of the breast shape and dimpling of the skin. While some environmental factors including being female, having obesity and high age can increase one's risk of getting breast cancer, genetic predisposition may also play a role. Mutations in several genes, e.g. $BRCA_{1\&2}$, ATM and TP53, have been shown to increase the risk of breast cancer development as they are involved in DNA repair or cell growth (8,22). According to data retrieved from Integraal Kankercentrum Nederland (IKNL), approximately 9,000 out of the 17,000 new yearly diagnoses are classified as invasive $HR^+/HER2^-$ early breast cancer. This type of breast cancer is characterised by the expression of oestrogen and progesterone receptors, and the lack of receptors for HER2, which is a protein that regulates cell growth in healthy cells (22).

When the patient presents with early $HR^+/HER2^-$ breast cancer, meaning that it has not yet spread to other parts of the body, the tumour will be surgically removed. It is possible for patients to receive neoadjuvant systemic treatment prior to surgery to decrease the tumour size and to increase the probability that a breast-saving surgery is possible. Surgical removal, in patients who are not treated by neoadjuvant chemotherapy, is often followed by a short period of adjuvant chemotherapy to decrease the risk on disease recurrence. Moreover, during the first five years after surgery, patients are treated with adjuvant endocrine therapy to reduce recurrence risk and to improve OS. As was explained in the introduction, this therapy consists of either five years of tamoxifen for pre-menopausal women, or it consists of a combination of tamoxifen and AI for post-menopausal women, as both combinations are highly effective (23,24). If deemed necessary, based on risk factors including presence of lymph nodes and a

large tumour at baseline, the treating physician and the patient may decide to extend this adjuvant endocrine treatment beyond those five years (15).

In the metastasised setting, abemaciclib, a CDK4/6 inhibitor is indicated as a treatment option in combination with antihormonal therapy. As metastasised breast cancer is incurable, the primary aim of this treatment is no longer to cure the patient, but it is to prolong progression free survival (PFS) and OS. CDK4/6 inhibitors effectively delay disease progression by inhibition of pathways that are involved in cell cycle progression, and therewith cell division. Currently, palbociclib, ribociclib and abemaciclib are the three CDK4/6 inhibitors that are available, and they are under investigation in the PALLAS, MONALEESA and MONARCH trial respectively. All three have shown significant effect on PFS and OS. Abemaciclib specifically has been shown to prolong OS by 9.4 months (37.3 to 46.7) and to delay progression by 7.1 months (9.3 to 16.4) in second-line treatment of metastasised $HR^+/HER2^-$ breast cancer (19).

Due to the success of CDK4/6 inhibitors in the metastasised setting, investigations on their use in the early $HR^+/HER2^-$ breast cancer setting have been initiated. While palbociclib did not show any desired effect yet, abemaciclib did (19). Johnston and colleagues showed that while abemaciclib causes serious adverse events, it significantly improves PFS from 88.7% to 92.2% after two years (14). Considering that only a fraction of patients benefits in terms of PFS, that abemaciclib may cause serious adverse events and the high treatment costs, it is of great importance to identify a more specific patient group that might benefit from abemaciclib in the early setting.

2.2 Liquid biopsies

Liquid biopsies are non-invasive sample alternatives which could detect material originating from a tumour. Unlike traditional tissue biopsies, liquid biopsies can be obtained in a minimally invasive manner from for example peripheral blood, urine or cerebrospinal fluid. Different materials originating from the tumour, like ctDNA and CTS, can be obtained from these fluids and can provide information on the characteristics of the tumour (20,21).

Compared to CTCs, ctDNA is more easily detectable in early breast cancer patients and only requires standard laboratory equipment. Additionally, an increasing number of studies have been performed specifically on the detection of ctDNA in patients with early breast cancer in the last years (21,25). For these reasons the focus of this thesis will lie on using liquid biopsies to analyse ctDNA as risk assessment tool.

ctDNA is DNA that originates from a tumour and is present in the bloodstream. However, blood also contains DNA from leukocytes. ctDNA can be distinguished from leukocyte DNA by the detection of tumour-specific mutations (25). Several studies have shown that patients with early breast cancer and detection of ctDNA in their peripheral blood have a worse prognosis compared to patients without ctDNA detection. Garcia-Murillas et al. showed that patients with detectable ctDNA during the first 3 years after surgery in patients with all types of breast cancer had a 16.7 fold higher recurrence rate than patients without detectable ctDNA (95% CI, 3.5-80.5) (21). In the study of Coombs et al. non-invasive detection of metastasis by a ctDNA assay predicted breast cancer recurrence earlier than imaging in 16 out of 17 patients experiencing clinical recurrence with a lead time of 2 years (25). More research is needed to find the optimal timeframe in which ctDNA detection by means of a liquid biopsy should take place.

CtDNA can be detected by different methods. These methods have their own strengths and limitations and differ in costs. In general, a trade-off must be made between the costs and the number of genes that are analysed (26). Since breast cancer is a heterogeneous genetic disease, it is important to use a method that analyses a larger number of genes (27). In the studies described above, a panel of multiple genes is used to find mutations in the primary tumour tissue. Based on those results, a single mutation can be tracked to determine whether ctDNA is present in the peripheral blood (21,25).

In this thesis a similar method was applied to determine the presence of ctDNA. At baseline, tumour tissue was sequenced by a panel of mutations and a relatively cheap digital PCR was used to track the detected mutation in the liquid biopsies every six months.

2.3 Health technology assessment & economic evaluation

In order to keep healthcare accessible and affordable for all, available resources must be used as efficiently as possible. Since economic evaluations shed light on the most efficient allocation of the available resources and which interventions would provide the best value for money (28), decisions on which treatments, interventions or technologies to use in practice are increasingly based on these evaluations (29). Drummond and colleagues defined economic evaluations as follows: *'The comparative analysis of alternative courses of action in both their costs and consequences'* (3 p.4). This definition highlights the three basic characteristics of an economic evaluation: costs, consequences and comparisons.

It seems straightforward that in economic evaluations, costs are expressed in monetary value. However, the choice on which costs to include in your analysis is less clear and depends on the perspective chosen. The two most common perspectives are the health care/hospital and the societal perspective. The first perspective only includes costs that are made within the health care sector. This means that only costs like hospital staff labour and the costs of medicines are included (29,30). The healthcare perspective is currently adopted by the National Institute for Health and Care Excellence (NICE) as they choose to assess the maximisation of health benefits from the perspective of the National Health Services (NHS) and their limited budget (31).

The second perspective is broader than the first. Not only does the societal perspective include these costs made in the health care sector, it also includes costs that are made outside of health care. These costs could take the form of patient travel costs to the hospital, out-of-pocket spending, informal care costs and productivity losses (29,30). This societal perspective is preferred by many for several reasons. First of all, some argue that because health economics finds its origin in welfare economics, social welfare maximisation should be the goal of a health economic evaluation (31,32). Moreover, some advocate that the value and benefits of informal care are essential within health economic evaluations. Taking into consideration that populations are ageing, informal care will become an increasingly important aspect of many health interventions and should not be neglected in economic assessments (33). It is important to note that while the societal perspective is preferred by many, it may be difficult to implement (34).

In order to estimate the costs of the treatment options, the quantity of the resources used must be measured and prices must be assigned to these resources. To create an overview of all resources used, data from research trials or treatment protocols can be used. Databases and literature that provide resource unit prices can then be used to assign the appropriate price to the resources used (30).

With regards to the consequences or effects of health interventions, it is less straightforward how to measure and express them. Effects can be expressed in monetary terms, which would make the evaluation a cost-benefit analysis (CBA). Additionally, one could also express effects in natural units (e.g. heart attacks prevented), making the evaluation a cost-effectiveness analysis (CEA). Lastly, effects can be expressed in terms of quality-adjusted life

years (QALYs), which would make the evaluation a cost-utility analysis (CUA)[1] (29,30,35). When performing a CUA, the number of QALYs gained per patient is calculated. This is often done by assigning a utility value to all health states a patient can be in and multiplying that utility value with the life years spent in that health state. Utility values of health states represent the health-related quality of life (HRQoL) of someone that is in that particular state. There are two categories within HRQoL measures: disease-specific measures and generic measures (30). An example of a measure from the first category is the Quality-of-Life Questionnaire C-30 (QLQ-C30) from the European Organisation for Research and Treatment of Cancer (EORTC). This questionnaire is one of the most widely used disease specific HRQoL measures (36). The EORTC QLQ-C30 consists of 30 questions that assess relevant aspects for the HRQoL of cancer patients. Moreover, they have developed extra questions that are cancer type specific. For breast cancer patients, an additional 25 questions contribute to an even more specific HRQoL estimate (37). Within the category of generic measures, the EQ-5D is one of the most popular HRQoL measures (38). EuroQol has developed three EQ-5D measures. One with 3 levels, one with 5 levels, and one specialised in paediatric HRQoL (39). Instead of focussing on the specific impact a certain disease has on patients, it assesses a more general and broad range of aspects that affect the overall perception of HRQoL. While disease-specific measures provide a more accurate description of one's HRQoL, they have a limited use as it is difficult to compare their outcomes to outcomes from other measures for other diseases. Therefore, generic measures like the EQ-5D are preferred by many (35).

Another crucial term in the definition of economic evaluations provided above is them being 'comparative'. This means that the costs and effects of the intervention of interest must be compared to at least one alternative when assessing a new health technology. Usually, the comparator of choice is the standard treatment at the time of analysis, or another newly proposed intervention (28,30). When the comparator is chosen and the costs and effects of both interventions have been calculated, the incremental cost-effectiveness ratio (ICER) can be calculated (40). Equation 2.1 presents the formula used to calculate the ICER.

$$ICER = \frac{Cost\ A - Cost\ B}{Effect\ A - Effect\ B}$$

Equation 2.1: Formula for incremental cost-effectiveness ratio

[1] Cost utility analyses are commonly referred to as cost-effectiveness analyses and from now on, the term cost-effectiveness analysis will be used.

Moreover, a cost-effectiveness (CE) plane is a clear and transparent way to display the additional costs and effects of the new treatment (29). Figure 2.1 shows the CE-plane with its four quadrants. Negative ICERs will either fall in the north-western (NW) or south-eastern (SE) quadrant. The interpretation of an ICER falling in these quadrants is rather straightforward. When the ICER falls in the NW quadrant, the new treatment generates fewer effects with higher costs, so it will not be cost-effective under any circumstances. When the ICER falls in the SE quadrant, the new treatment saves money while generating more effects, which means that it is dominant over current treatment. Positive ICERs could either fall in the north-eastern (NE) and south-western (SW) quadrant. Whether the new treatment is cost-effective or not depends on lambda (λ). λ represents the maximum amount of money one is willing to pay for gaining one QALY. This maximum differs per country. In the SW quadrant, the new treatment saves costs, but does not generate as much effect as the comparator treatment. Whether or not such results are acceptable, must be decided by the policy makers. When the ICER falls in the NE quadrant, the new treatment generates additional effects, but at higher costs. When the ICER falls below λ, the new treatment will be considered cost-effective. When it falls above, it will not (41,42).

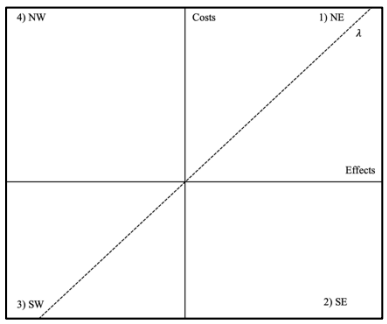

Figure 2.2: Cost-effectiveness plane

2.4 Modelling in economic evaluations

Usually, economic evaluations are based on evidence that is subtracted from a variety of sources. Decision-analytical modelling can be used as a means to bring together all that evidence in one place (30) and provides a systematic way of calculating the costs and probabilities of all possible consequences that are derived from the different intervention options. Additionally, uncertainty and variability are included in decision-analytical modelling (29). Patient data on the treatment, survival, adverse events from clinical trials and costs data can be incorporated into models. Because the time horizon of most clinical trials is insufficient for a long-term economic evaluation, existing data on the costs and effects of the interventions can be extrapolated over a more adequate time horizon.

2.5 Markov modelling

One type of model that is commonly used in economic evaluations is the Markov model. A Markov model typically provides a stochastic and simplified version of the disease discourse and describes the possible effects of the interventions as mutually exclusive health states patients can be in. Transition probabilities show the probability of patients being in a certain health state for a certain time period, called a cycle. By dividing the hypothetical patient population over the existing health stated according to these probabilities, by assigning a utility value and costs to each health state, by multiplying that with the number of patients expected to be in that health state, and by repeating that for all cycles, the total costs and effects per intervention can be calculated (29).

The main assumption made in a Markov model is that the probability of a patient going from one health state to another is solely based on their current health state, and not those they were in during previous cycles. This means that the model has no memory of where patients have come from and how their disease has manifested (29). Tunnel states may be used as a means to include patient history and time-dependency in a Markov model. When survival depends on a certain treatment that was previously received, or on at what time point treatment was initiated, patients can be assigned to separate tunnel states that account for these influences and history. It is important to consider the number of tunnel states that must be added to the Markov model to sufficiently incorporate patient history and time-dependency. If time dependency or history plays a considerable role in the disease simulation process, the number of tunnel states may easily escalate, making programming of the Markov model in a spreadsheet challenging (29).

Furthermore, in oncology, partitioned survival models are most commonly used. These models include the following health states: progression free, progression, death. In these partitioned survival models, transition probabilities of each health state are directly derived from the area under the OS and PFS curves from randomised controlled trials (RCTs). OS data would represent those still being alive and therefore those in the death state can be derived from this curve. Those who remain progression free can be directly derived from the PFS curve. Lastly, the patient group that has progressed disease can be calculated by subtracting the number of patients in the progression free and death states from the total patient population in the simulation. The most important assumption in these models when applied to oncology is that one cannot go back from progression to progression free (43,44).

2.6 Health technology assessment in the Netherlands

Several official and unofficial sources claim that the Dutch healthcare system is among the best and most efficient of the world (45,46). All drugs that wish to acquire market authorisation in the Netherlands must first be approved by the EMA or the 'College ter Beoordeling van Geneesmiddelen'. However, getting approval from one of these authorities, does not automatically mean that a drug is reimbursed. It is estimated that if no government measures would be in place, the total spending on pharmaceutical care in the Netherlands would increase by a minimum of 10% every year. Therefore, Zorginstituut Nederland (ZiN) has been assigned the task to review new health technologies on their cost-effectiveness. Based on information on the costs and the effects, ZiN advises the Minister of Health whether new drugs should be included in the standard health insurance package or not. A threshold differentiation based on disease burden is applied. The cost effectiveness threshold for diseases with a low burden is €20,000. Diseases with a moderate burden are deemed acceptable when their ICER falls below a threshold of €50,000 and for diseases with a very high burden, a threshold of €80,000 applies (35). New drugs are (sometimes temporarily) excluded from the standard package when the technology appraisal shows that it will cost more than €40,000,000 per year nationally or when it costs more than €50,000 per patient and more than €10,000,000 nationally. Especially in oncology, innovative medicines are often extremely expensive, and if that is the case, ZiN needs more information on what causes these prices to be so high and what can be done to reduce them (47). More specific information on the requirements of a review by ZiN will be provided in the next chapter as the rationale behind the chosen methodology.

3. Methods

In this chapter, the methodological choices that were made and their rationale are discussed. The guidelines of ZiN are used as basis. An overview of the input parameters is presented in Table 3.1.

3.1 Audience

As was explained in the previous chapter, ZiN has the authority to decide whether new health technologies and drugs will be reimbursed in the Netherlands (35). Therefore, this research will be directed to ZiN, and the methods used will be in accordance with their preferences.

3.2 Perspective

One of the first choices that must be made when designing an economic evaluation is what perspective will be used. ZiN dictates that their standard analysis procedure has to be followed and therefore, a societal perspective must be used (35). As was explained before, taking a societal perspective is a more holistic approach to estimate costs and effects of the medical interventions of interest. This means that all costs and benefits will be included irrespective of who is paying for them or who benefits (30).

3.3 Framing – PICOT

The next step in the design of an economic evaluation according to ZiN guidelines is the framing of the research aim. The aim of this research was to explore whether the use of abemaciclib is cost-effective compared to standard adjuvant endocrine therapy and whether it would be cost-effective to use liquid biopsies instead of current risk assessment tools and requirements to assess which patients would qualify for additional abemaciclib treatment. To adequately frame the economic evaluation, the following aspects need to be described clearly: population, intervention, comparators, outcomes and time horizon.

3.3.1 Population

The target population of this study consisted of high risk EBC patients that presented with a $HR^+/HER2^-$ primary tumour. This population has undergone surgery and additional chemotherapy to remove the primary tumour and can therefore be classified as disease free. The recurrence risk assessment is initially performed based on the tumour grade, TNM-

classification scale and Ki-67 levels, and the high-risk definition provided by Johnston and colleagues. A patient is classified as high risk if they meet one of the following criteria (14):

- *Four or more positive nodes*
- *One to three positive nodes AND either tumour size ≥ 5 cm, histologic grade 3 or central Ki ≥ 20%.*

3.3.2 Interventions

This study investigated three intervention scenarios which can be found in Figure 3.1. First a comparison between treatment scenario A and B was made. Scenario B involved abemaciclib treatment within the indication of $HR^+/HER2^-$ EBC. In addition to standard adjuvant endocrine treatment, patients in scenario B received 150mg of abemaciclib twice per day across a time span of two years (14).

Intervention C consisted of a scenario in which a liquid biopsy was performed every six months for the first five years after surgery. Patients were treated with standard adjuvant endocrine treatment and only when the liquid biopsy shows presence of ctDNA, patients were classified as having minimal residual disease (MRD). Only when MRD was present, patients received additional abemaciclib treatment.

3.3.3 Comparator

The comparator scenario, treatment scenario A, is the current standard treatment for $HR^+/HER2^-$ EBC. Patients received adjuvant endocrine treatment for a minimum of five years. Pre-menopausal women received five years of tamoxifen treatment in combination with leucrin. Patients received 20mg of tamoxifen per day and a dose of 11.25mg leucrin once every three months. Post-menopausal women received two and a half years of tamoxifen followed by two and a half years of letrozole. Similar to pre-menopausal women, they received 20mg of tamoxifen per day and after two and a half years, they receive 2.5mg of letrozole per day. It is possible or post-menopausal women to receive exemestane or anastrozole instead to letrozole. However, for simplicity and based on expert opinion that the proportions of patients receiving letrozole, exemestane or anastrozole does not differ between the treatment scenarios, the assumption was made that all post-menopausal patients received letrozole. Treatment for both pre- and post-menopausal women is often extended beyond the first five years with the treatment they are receiving at that time (15). However, data on the proportion of patients that get a treatment extension and its duration is scarce. Since experts do not expect the new treatment scenarios to affect the chance of treatment extension, it was excluded from this CEA.

3.3.4 Outcomes

The primary outcomes that have been compared in this analysis are the costs and the QALYs gained for each treatment scenario. Costs were measured by using data from standard treatment protocols, treatment protocols from clinical trials and by consulting experts (30,35). Costs were valued according to the *'Kostenhandleiding'* from ZiN. This manual provides reference prices and links to other databases that can be used to find price values (48). The effects were estimated by using OS and recurrence-free survival (RFS) data from Kaplan-Meijer curves from clinical trials found in literature (35). Based on this data, the best fitting distribution was chosen and the data was extrapolated beyond the measured time period. By combining this data with results from the liquid biopsies, all patients were assigned to certain health states. With these utility values and information on the numbers of patients in each health state at different time points, the total QALYs gained were calculated. The outcomes of this CUA were two ICERs. One that compared treatment scenario A to B, and one that compared treatment scenario A to C. Based on these two ICERs, conclusions were drawn on the cost-effectiveness of both scenarios.

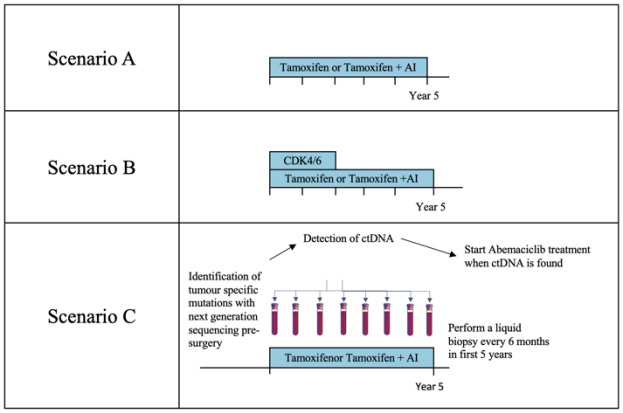

Figure 3.1: Overview of treatment scenario A, B and C as used in the CEA

3.3.5 Time and horizon

The cycle length in this study was three months. Based on the available survival and treatment protocol data, this cycle length seemed most appropriate. According to the data provided by IKNL, the mean age at diagnosis is 57. In accordance with the ZiN guidelines, the time horizon was set at lifetime. A lifetime horizon is reached when less than 0.5% of patients remains alive at the end of the simulation (35). In this study, this meant that the patient population was followed for 163 cycles which corresponds to 40.75 years.

3.4 Type of evaluation

As preferred by ZiN, the evaluation approach was a CUA in which the incremental costs and benefits were compared (35). The CUA will be referred to as a CEA throughout this report.

3.5 Discounting

All economic evaluations analyses take place over different timespans. To ensure that costs made and benefits generated in the future did not have the same weight as those made and generated in the present, discounting was used as a means to reduce their influence on the outcomes proportionally (30,49). Discounting must be applied in all analyses that are performed over a timespan that exceeds one year. All HTA bodies apply different rates, but ZiN dictates that a discount rate of 4.0% and 1.5% should be used to discount costs and effects respectively (35).

3.6 Markov model, partitioned survival & tunnel states

This CEA was performed by means of a Markov model. A visual representation of the health states of the patients is presented below in Figure 3.2. All patients have been previously treated with surgery and a short period of chemotherapy, making them recurrence-free. Therefore, all patients start in the recurrence free (RF) state. In scenario A and B, patients can either move to the recurrent disease (RD) or the death state. As was explained in the previous chapter, in oncology, partitioned survival models are often used, meaning that when one moves from RF to RD, they cannot turn back (43,44).

The target patient population consists of high recurrence risk $HR^+/HER2^-$ EBC patients. In scenario C, liquid biopsies will be performed to assess which patients within this high-risk category, are at even higher risk of disease recurrence. When the liquid biopsy is positive, patients are classified as having minimal residual disease (MRD). This does not necessarily mean that they have recurrence yet, but if not treated adequately, MRD will develop into recurrence. In this scenario, only patients in the MRD state were treated with abemaciclib. Because abemaciclib treatment is time- and patient history-dependent, tunnel states have been incorporated in the model. In accordance with research performed on liquid biopsies in early breast cancer, every six months, after the liquid biopsies are performed, 5.88% of patients in

the RF state, moved to the respective MRD state (21). Eventually, 10 MRD tunnel states have been included.

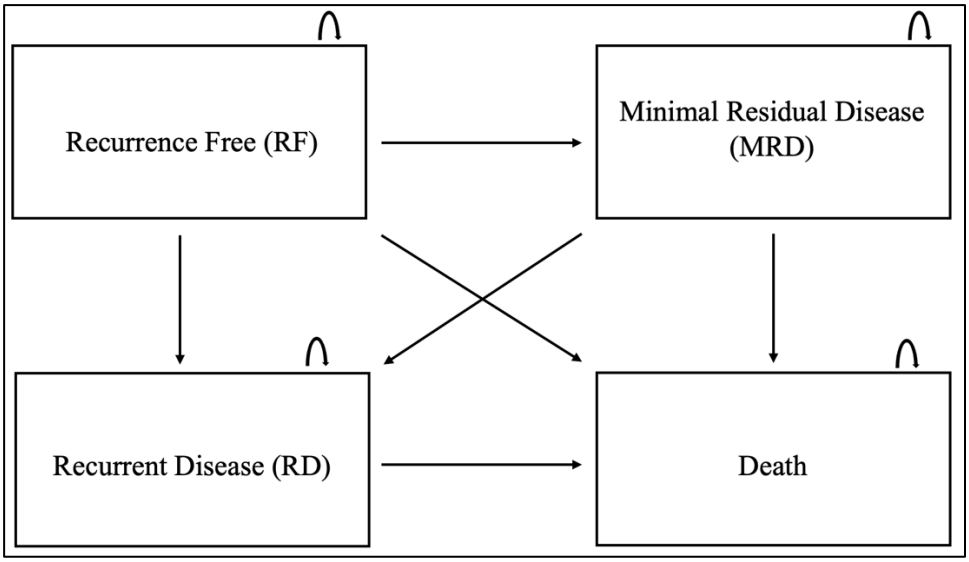

Figure 3.2: Visual representation of the Markov health states.

3.7 Effectiveness input - survival

Treatment effectiveness data was derived from literature. The trial conducted by Johnston et al. was used for RFS data (14). They have reported RFS for both the treatment arm that received only standard adjuvant endocrine therapy and the treatment arm that received additional abemaciclib (14). PFS was observed over a timespan of 2 years and therefore, this data was extrapolated to a lifetime horizon in R. The observed RFS data is presented in Figure 3.3. While the Weibull distribution had the lowest AIC value, the loglogistic distribution was chosen, because it seemed to be the clinically most appropriate distribution.

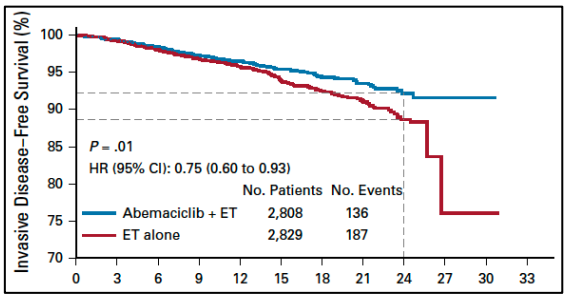

Figure 3.3: Observed RFS data from Johnston et al. (3).

OS data was not reported by Johnston et al., because it was too immature. Therefore, OS data was derived from Pan et al. They collected OS data over 20 years for patients with different risk profiles. They made two high risk categories based on the number of nodes affected at disease

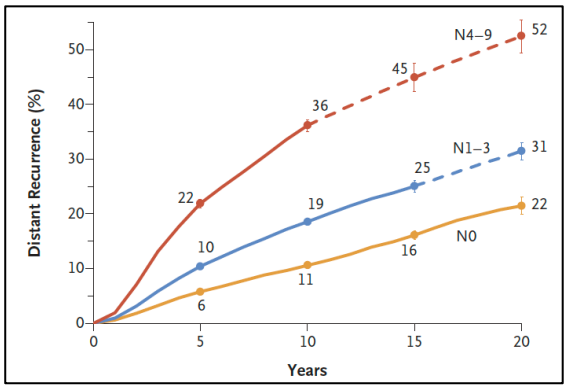

Figure 3.4: Observed OS data from Pan et al. (10).

presentation; 1-3 nodes or 4-9 nodes affected at disease presentation, which correspond to the blue and red lines in Figure 3.4 respectively (10). Neither of these categories directly corresponded to the risk profile defined by Johnston. Therefore, Pan and Johnston's RFS data was compared first to find which risk categories correspond best. Based on that comparison and an expert consultation, the choice was made to use OS data from the highest risk group defined by more than 4 nodes affected at disease presentation. The Weibull distribution was chosen for OS because of its low AIC and good clinical fit. In addition to the OS curves derived from literature, survival of the patient population was adjusted for background mortality. Background mortality was derived from CBS data (50).

Because of the short follow-up of RFS data and absence of mature OS data, assumptions had to be made on the treatment effect and its duration. Firstly, based on expert opinion and the absence of data, the assumption was made that abemaciclib does not have any effect on OS. Therefore, the OS curves were equal for those receiving endocrine therapy only and those receiving additional abemaciclib. Secondly, literature on other CDK4/6 inhibitors shows that their effect duration does not last permanently. A study by Loibl et al. showed that their CDK4/6 inhibitor, palbociclib, had a positive effect on RFS, but that the effect started declining after three years. After a year, so year four of follow up, the RFS curves from palbociclib and standard treatment were equal again (51). Therefore, in consultation with clinical experts, the assumption was made that the effect of abemaciclib lasts for four years. Inclusion of abemaciclib treatment in the MRD tunnel states from scenario C was achieved by restarting the abemaciclib survival curves at the beginning of each MRD state. To ensure that RFS does not exceed OS, the minimum value of OS and RFS was used to calculate the number of patients in the health states throughout time.

3.8 Effect input – quality of life

In order to estimate the effects of the three treatment scenarios, life years spent in all health states were calculated and utility values were assigned to these states. The Markov model used has four health states. Two states in which the patient remains disease free, one where they have recurrent disease, and the death state. The before mentioned RFS and OS data were extrapolated and based on those extrapolations, the number of patients in each health state were calculated for all time points.

A study by Rautalin and colleagues was used as input for the utility scores for the health states. They measured HRQoL of early breast cancer patients irrespective of the subtype using

three different questionnaires: EQ-5D, 15D and EORTC QLQ-30 (52). Their outcomes from the EQ-5D were used as is preferred by ZiN (35). Based on the study by Rautalin, a utility value of 0.87 (0.16) was assigned to both recurrence free health states and a utility value of 0.74 (0.26) was used for recurrent disease (52).

Adverse events and their disutility were considered to differentiate between the different treatment scenarios. Based on research by Johnston, grade III and IV adverse events that were present in at least 5% of patients of one of the treatment arms were included. These adverse events were neutropenia, leukopenia, diarrhoea and lymphopenia. A considerable difference in incidence of adverse events was found as 1.7% and 42.5% of those receiving endocrine therapy and those receiving additional abemaciclib experienced a grade III or IV adverse events respectively (14). No literature could be found on the disutility of these adverse events in the context of early breast cancer. Therefore, disutility values were derived from studies by Uyl-de Groot et al. and Bullement et al. (9, 10). For neutropenia, leukopenia, diarrhoea and lymphopenia these disutility values were -0.0897, -0.0897, -0.046 and -0.09 respectively (53,54). The total disutility values calculated were incorporated as a one off in the first cycle of the model. An overview of all QoL input parameters can be found in Table 3.1.

3.9 Cost input

According to ZiN, costs within and beyond the healthcare system must be included in a CEA (35). With regards to the costs made within the health sector, drug acquisition costs and healthcare resource use costs were included for the RF, MRD and RD states. The costs of the adverse events were included as a one off in the first cycle. The inputs for the cost calculations were derived from treatment protocols, Farmacotherapeutisch Kompas, the Integraal Kankercentrum Nederland (IKNL), hospital price lists and literature. Drug acquisition costs were calculated based on dosage information from treatment protocols, costs of pharmaceutical care provided by ZiN (48) and drug prices extracted from Farmacotherapeutisch Kompas (17). Drug acquisition costs were calculated separately for pre- and post-menopausal patients as they receive different treatment. The mean drug acquisition costs per patient per cycle were calculated based on the proportion of pre- and post-menopausal women provided by IKNL. The use of several healthcare resources was provided by the available treatment protocols that were validated by expert opinion. Prices of these resource units were estimated by taking the mean price provided by two academic and two non-academic hospitals: Erasmus Medical Center, University Medical Center of Groningen, Rijnstate and Diakonessenhuis. The costs for

RD were derived from Braal et al. They derived their estimate from literature and validated it with confidential data from insurers. This estimate included drug acquisition costs and all healthcare resource use (55).

Costs made outside of the healthcare system, were estimated based on the treatment protocols and literature. All costs that were extracted from literature were first indexed to 2021 prices according to the CBS consumer price index when necessary (50). The societal costs included productivity losses and travel costs. Productivity losses were calculated on the short term by multiplying the number of hours of paid and unpaid work with their respective replacement costs. Long-term productivity losses were calculated according to the friction cost method. The assumption was made that when entering RD, patients that were still employed stopped working within 85 days. Data on employment, i.e. the average hours worked per day and the absence from work, was collected according to the iMTA Productivity Cost Questionnaire (iPCQ). Data was available for patients receiving adjuvant endocrine therapy (55). For patients receiving abemaciclib, the available data was combined with the difference in number of hospital visits between the treatment scenarios extracted from treatment protocols, to estimate short- and long-term productivity losses. Moreover, the difference in adverse events experienced between patient receiving endocrine therapy and those receiving additional abemaciclib was large. Expert opinion stated that 7.6% of patients with diarrhoea are hospitalized for approximately 7 days. Therefore, productivity loss of these hospitalisations was included for patients on abemaciclib. Travel costs were based on the number of hospital visits and the mean distances to hospitals and pharmacies provided by ZiN (48).

A summary of the most important cost input parameters is presented in Table 3.1 and an overview off all input parameters is presented in appendix 1. In Table 3.1, cost inputs are presented for patients only receiving adjuvant endocrine therapy and for patients receiving additional abemaciclib. While in scenario B all patients in the RF state received abemaciclib, these costs were only included for patients in one of the MRD states in scenario C. The costs for the RF patients in scenario C were calculated with the input parameters for adjuvant endocrine therapy only.

3.10 Uncertainty & sensitivity analyses

The results from a CUA are subject to uncertainty and in order to address this uncertainty, sensitivity analyses have been performed. These sensitivity analyses can help to make better informed recommendations to ZiN.

According to the ZiN guidelines, several deterministic scenario analyses have been performed in which one input parameter was varied at the time (35). The first scenario analysis assessed the effect of varying the price of abemaciclib on the final ICER results. Additionally, a scenario analysis was performed that investigated the effects of doubling the treatment effect duration or making it life-long. In the later scenario, the effect reached at year four was maintained throughout the entire time horizon. Furthermore, a scenario analysis that investigated the possibility of abemaciclib influencing OS was performed. For this scenario, the effect of abemaciclib on OS in the metastasised setting as investigated by Sledge and colleagues was used. They found a hazard ratio of 0.757 (56) and the same hazard ratio was applied in this scenario analysis. Lastly, the frequency with which the liquid biopsies were performed was varied to once a year, and only once after 2.5 years. When the liquid biopsy was performed once a year, a MRD transition probability of 11.88% was used, and when the liquid was only performed after 2.5 years, a MRD transition probability of 9.8% was used (21).

In addition to this, a PSA was performed in which all input parameters were varied simultaneously. When literature did not provide an SE for an input parameter or the SE could not be calculated, the SE was based on a percentage of the mean value. Based on expert opinion, and SE of 10% of the mean was taken for all parameters except for the treatment costs for adverse events and healthcare resource use parameters. For these parameters a SE of 20% of the mean was used as they are surrounded by more uncertainty. The PSA consisted of running the model 1,000 times while simultaneously varying all input parameters randomly.

3.11 Validity & reliability of results

The internal validity of this research was increased by consulting clinical experts in order to check the model and the assumptions made in it. The external validity and generalisability were increased by using methods that are generally used in other health economic evaluations. Moreover, in order to test the reliability of the model and its results, sensitivity analyses were performed (30).

3.12 Reporting of results

In the next chapter, the results are presented. Total costs, life years and QALYs of the three treatment scenarios are presented, together with their respective ICERs to assess their cost effectiveness. The results of the deterministic scenario analyses are presented by means of comparative tables and CE-planes and CEAS describe the results from the PSA. In the result section, only discounted results are reported. Undiscounted results are presented in Appendix 2.

Table 3.1: Overview of input parameters

Input variable	ET only – Mean value (SE)	Abemaciclib + ET – Mean value (SE)	Distribution	Reference
Age	57	57	-	IKNL
Discount rates				(35)
Costs (%)	4%	4%	-	
Effects (%)	1.5%	1.5%		
Survival				(10,14)
RFS			Loglogistic	
Intercept	0.0942864	0.08173883		
Log(scale)	0.0271629	0.02079744		
OS			Weibull	
Intercept	0.01863041	0.01863041		
Log(scale)	0.01128065	0.01128065		
Utility health states			Bèta	(52)
RF	0.87	0.87		
MRD	0.87	0.87		
RD	0.74	0.74		
Incidence AEs			Bèta	(14)
Neutropenia	0.007	0.189		
Leukopenia	0.004	0.109		
Diarrhoea	0.001	0.076		
Lymphopenia	0.004	0.051		
Disutility AEs			Bèta	(53,54)
Neutropenia	-0.087	-0.087		
Leukopenia	-0.087	-0.087		
Diarrhoea	-0.046	-0.046		
Lymphopenia	-0.090	-0.090		
Costs AEs			Gamma	(53,54)
Neutropenia	€1465.69	€1465.69		
Leukopenia	€2026.97	€2026.97		
Diarrhoea	€2461.60	€2461.60		
Lymphopenia	€1746.33	€1746.33		
Drug acquisition RF			Gamma	(14,15,17,18) Expert opinion
Cycle 1 – 8	€ 93.61	€ 8,560.25		
Cycle 9 – 10	€ 93.61	€ 93.61		
Cycle 11 – 20+	€141.77	€141.77		
Healthcare resource use RF			Gamma	(14,48,57–60) Expert opinion
Cycle 1 – 4	€130.46	€ 495.81		
Cycle 5 – 8	€63.14	€175.25		
Cycle 9 – 20+	€63.14	€63.14		
RD costs	€10050.00	€10050.00	Gamma	(55)
Societal costs RF			Gamma	(14,48,55)
Productivity loss	n.a.	€32.52		
AEs	€686.02	€893.10		
Cycle 1 – 4	€430.02	€518.76		
Cycle 5 – 8	€430.02	€430.02		
Cycle 9 – 20+				
Societal costs RD	€ 5264.56	€ 5264.56	Gamma	(48,55)

4. Results

In this chapter, the results from the CEA are presented. First, the costs for treatment scenario A, B and C are provided and summarised in Table 4.1. Secondly, the effects of the three treatment scenarios are described and presented in Table 4.2, followed by the final ICER results which are presented in Table 4.3. Moreover, the results from both the deterministic scenario analyses and the probabilistic sensitivity analysis are presented by means of comparative tables, CE-planes and CEACs.

4.1 Costs

In the three treatment scenarios, costs were calculated for the RF state (including the MRD states) and the RD state. Costs made in the RF state were made in four categories: drug acquisition, healthcare resource use, treatment of adverse events and societal costs. RD consists of two cost categories: medical costs and societal costs. The following paragraphs explain how the total costs per patient per category were calculated and what the results of these calculations were.

Table 4.1: Overview of the costs per category of the three treatment scenarios

	Scenario A	**Scenario B**	**Scenario C**
Recurrence free			
Drug acquisition costs	€1,667	€63,540	€ 29,160
Healthcare resource use costs	€1,182	€2,999	€ 2,068
Genetic testing & liquid biopsies	n.a.	n.a.	€987
Adverse events medical costs	€30	€774	€455
Societal costs	€6,824	€8,241	€ 7,951
Total recurrence free	**€9,702**	**€75,554**	**€ 40,620**
Recurrent disease			
Medical costs	€157,415	€153,925	€149,432
Societal costs	€3,813	€3,798	€3,645
Total recurrent disease	**€161,228**	**€157,724**	**€153,077**
Total treatment costs	**€170,931**	**€233,278**	**€ 193,697**

4.1.1 RF – Drug acquisition costs

Average drug acquisition costs per cycle for those receiving standard treatment were estimated to be €93.61 in cycle one to ten and €141.77 in cycle eleven to twenty. These differences in drug acquisition costs were caused by the switch from tamoxifen to letrozole by

postmenopausal women after two and a half years of treatment (i.e. cycle ten). For patients receiving abemaciclib, drug acquisition costs per cycle were estimated at €8,560.25, €93.61 and €141.77 for cycle one to eight, nine to ten and eleven to twenty, respectively.

Total drug acquisition costs per patient in scenario A, B and C amounted to €1,667, €63,540 and €29,160 respectively. The differences in costs between the scenarios were caused by the addition of abemaciclib in scenario B and C. Daily costs of abemaciclib were €93.04 versus €0.21 for tamoxifen or €0.88 for letrozole. In scenario B, all patients received additional abemaciclib and in scenario C, only those in one of the MRD states received it. The difference between the treatment protocols explains why drug acquisition costs were higher in scenario B than in scenario C.

4.1.2 RF – Healthcare resource use

In the category of healthcare resource use, the costs for oncology consults, kidney- and lab tests and mammographies were incorporated. For those on standard treatment, healthcare resource use costs per cycle were €130.46 and €63.14 in cycle one to four and cycle five to twenty. Patients receiving abemaciclib made use of more healthcare resources as they had more oncology consults and kidney- and liver lab tests. Their healthcare resource use costs per cycle totalled up to €495.81 for cycle one to four, €175.25 for cycle five to eight and €63.14 for cycle nine to twenty. In scenario C, the costs of genetic testing prior to surgical removal of the tumour and the liquid biopsies were also included. These costs were €450 for the genetic testing and €100 per liquid biopsy.

The average total healthcare resource use costs per patient added up to €1,182 in scenario A, €2,999 in scenario B and €2,068 in scenario C. In addition to this, €987 must be added to the treatment costs because of the genetic tests and liquid biopsies. One might expect that the total healthcare resource use costs would be highest in scenario C, as it included costs for genetic testing and liquid biopsies. However, these extra costs did not exceed the extra healthcare resource use costs when all patients receive additional abemaciclib, making healthcare resource use in scenario B most costly.

4.1.3 RF – Treatment of adverse events

The third category of RF costs were the treatment costs for adverse events. As was stated in the methods, four adverse events have been included in the model: neutropenia, leukopenia, diarrhoea and lymphopenia. The treatment costs for these adverse events were estimated to be €1465.68, €2026.97, €2461.60 and €1746.33 respectively.

Total average treatment costs of adverse events added up to €30 in scenario A, €774 in scenario B and €425 in scenario C. The difference between scenario A and B can be explained by the percentage of patients experiencing one of the included adverse events in grade three or four. For patients receiving standard treatment, this percentage was 1.7%, while 42.5% of patients receiving additional abemaciclib experienced one of these adverse events. The fact that only patients in one of the MRD states in scenario C receive abemaciclib explains the difference between average total costs in scenario B and C.

4.1.4 RF – Societal costs

The last category within the RF state is societal costs. This category contained a combination of travel costs and productivity losses due to treatment in general and the adverse events. For patients receiving standard treatment, societal costs came to €559.33 in the first four cycles and in the remaining cycles, societal costs were €430.02. Patients receiving abemaciclib were expected to have more travel costs and productivity losses. Also, to account for hospitalisation due to their increased risk of grade three or four adverse events, €32.53 is included as a one-off. In the first four cycles, their societal costs were estimated to be €766.16. In cycle five to eight, their societal costs were €518.51 and in the remaining cycles societal costs amounted to €430.02 as they no longer receive abemaciclib and their treatment is equal to that of those receiving standard treatment only.

Average total societal costs per patient in scenario A added up to €6,824. As was expected, societal costs were highest in scenario B, namely €8,241. Moreover, in scenario C, societal costs were higher than in scenario A, but were lower than in scenario B with €7,951.

4.1.5 RD – Medical costs

In RD state, no difference is made in medical costs for those previously receiving standard treatment or additional abemaciclib. The medical costs per patient per cycle were estimated to be €10,050. In this category, average total costs per patient were highest in scenario A, €157,415. In scenario B the average total cost per patient amounted to €153,925

and €149,432 in scenario C. These differences were caused by the fact that the additional abemaciclib treatment prolongs the average time spent in RF and does not prolong OS. This leads to a reduction of time spent in RD and therefore, less medical costs.

5.1.6 – RD – Societal costs

The societal costs in the RD state were based on replacement costs when patients stop working. As all patients leave the RF at some point, the RD societal costs were nearly equal for all treatment scenarios. Average total societal costs in RD for scenario A, B and C were €3,813, €3,798 and €3,644, respectively. The slight differences observed were caused by discounting of costs. As abemaciclib prolongs the time spent in RF, the replacement of patients is delayed in scenario B and even more in scenario C when compared to scenario A. Because costs that were made later in time were discounted more, societal costs in RD were lower for patients in scenario B and C.

4.2 Effects

Table 4.2: Overview of the effects of the three treatment scenarios

		Scenario A	Scenario B	Scenario C
Life years				
	RF	8.251	8.344	9.212
	RD	5.302	5.210	5.153
	Total life years	**13.55**	**13.55**	**14.37**
QALYs				
	RF	7.179	7.259	8.015
	RD	3.923	3.855	3.813
	Lost due to AEs	-0.000009	-0.000234	-0.000129
	Total QALYs	**11.102**	**11.114**	**11.828**

4.2.1 Life years

The average total number of life years gained per patient was equal in the first two treatment scenarios, 13.55. This result was expected because the assumption was made that abemaciclib does not affect OS. However, as both the RFS and OS curves were started again in the beginning of each MRD state, the total life years gained for treatment scenario C were 14.37. Moreover, differences were observed in the number of life years gained in RF and RD. In treatment scenario A 8.251 life years were gained in RF. A slight increase to 8.344 was

observed in scenario B. Patients in scenario C had the highest average life years gained in RF, 9.212.

With regards to the average number of life years generated in RD, patients in scenario A gained the highest number of life years, 5.302. Patients in treatment scenario B and C gained 5.210 and 5.153 life years respectively. Again, these results were expected as abemaciclib prolongs RFS, but not OS and thus shortens the time spent in RD.

4.2.2 QALYs

With regards to QALYs gained, a similar trend as seen in the life years gained was observed. Patients in treatment scenario A generated the least QALYs in RF and patients in scenario C gain the most with 7.179, 7.259 and 8.015 QALYs respectively. In RD the opposite is observed with patients in scenario A had 3.923 QALYs, patients in scenario B had 3.855 QALYs, and patients in scenario C had 3.813.

Additionally, the QALYs lost due to adverse events were included. The average patient in scenario A lost 0.000009 QALYs. In scenario B, the average patient lost the most QALYs to adverse events, 0.000234. Finally, in scenario C, 0.000129 QALYs were lost to adverse events on average.

4.3 Incremental cost-effectiveness ratios

The average total costs for scenario A added up to €170,931 and the total number of life years and QALYs gained were 13.55 and 11.201. The average total costs for treatment scenario B were considerably higher, €233,278, the life years gained were equal, 13.55, and the number of QALYs gained were slightly higher, 11.114. These results lead to an ICER of €5,299,623.

	Increment B - A	**Increment C - A**
Costs	€62,347	€22,766
Life years	0.00	0.812
QALYs	0.012	0.726
ICER (life years)	n.a.	**€28,031**
ICER (QALYs)	**€5,299,623**	**€31,367**

The average total costs for a patient in scenario C were slightly lower than for scenario A, € 193,697. The number of life years gained were 14.37. Additionally, the number of QALYs gained in scenario C were also higher, 11.828. Comparing scenario A and C generates an ICER of € 31,367 per QALY. Additionally, with a life year increment of 0.812, an ICER of €28,031 per life year was calculated.

4.4 Uncertainty and sensitivity analyses

4.4.1 Base case and probabilistic sensitivity analysis

The top row from Table 4.4 represents the base case results from the performed CEAs. As was described before, the comparison of treatment scenario A and B resulted in an ICER of €5,299,623 and the comparison of treatment scenario A and C resulted in an ICER of €31,367.

To assess the uncertainty surrounding these ICERs, a PSA was performed and Figure 4.1.A and 4.2.A show their results. In Figure 4.1.A, PSA results from the comparison between scenario A and B are shown, and in Figure 4.2.A, results from the comparison between scenario A and C are shown. The x-axis in the two figures represents the incremental QALYs while the y-axis represents the incremental costs. Figure 4.1.B and 4.2.B show the CEAC from both comparisons. In these figures, the x-axis represents the ICER threshold value, and the y-axis represents the acceptability probability.

Figure 4.1.A shows that the majority of probabilistic ICER results from the comparison between scenario A and B lay in the NW quadrant and that the minority were in the NE quadrant. Figure 4.1.B confirms this, as the maximum acceptability that could be reached in the scenario A and B comparison was approximately 0.45, meaning that 45% of ICER results lay in the NE quadrant and 55% of ICER results lay in the NW quadrant.

Figure 4.2.A shows that almost all probabilistic ICER results from the comparison between A and C lay in the NE quadrant. The CEA curve shows that at an ICER threshold of €50,000, an acceptability probability of 0.9 is reached.

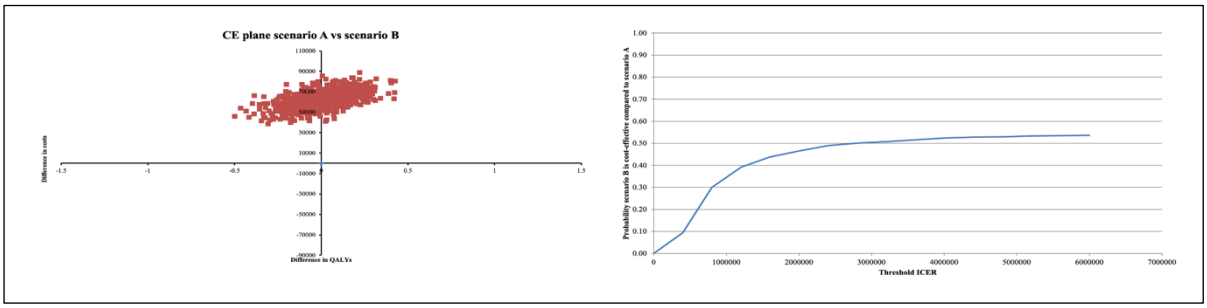

Figure 4.1.A: cost-effectiveness plane scenario A vs B

Figure 4.1.B: cost-effectiveness acceptability curve scenario A vs B

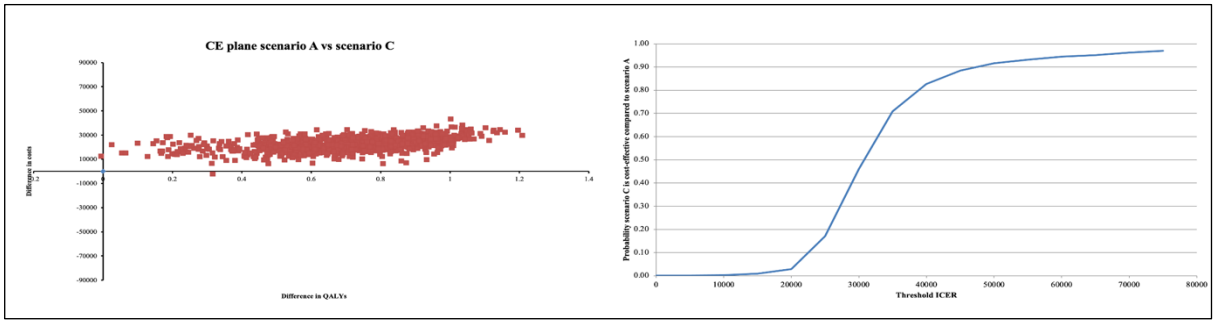

Figure 4.2.A: cost-effectiveness plane scenario A vs C

Figure 4.2.B: cost-effectiveness acceptability curve scenario A vs C

4.4.2 Price variations

In the first couple of scenario analyses, the price of abemaciclib was varied. Table 4.4 shows the results of these scenarios on the ICERs of the comparison of treatment scenario A to B and A to C. Moreover, figures 4.3.A and 4.3.B are visual representations of the impact of these price variations on the ICER results by means of tornado diagrams.

The table and figures below show that in the comparison of treatment scenario A to B, variation in the price of abemaciclib had significant consequences. However, only when the price is decreased by 99%, the ICER fell below €100,000 to €96,309. Table 4.4 shows that in the case of the comparison of scenario A and B, the price variations and their effects on the ICERs were almost proportionally equal. For example, when the price was lowered to 90% of the original price, the ICER decreased to 90.1% of the original ICER.

Similarly, the comparison between A and C also resulted in almost proportionally equal price and ICER increases. Moreover, price decreases below 10% of the original price of abemaciclib resulted in negative ICERs.

Table 4.4: Results from deterministic scenario analyses varying the price of abemaciclib

	ICER scenario A vs. Scenario B	ICER scenario A vs. Scenario C
Base case	**€ 5,299,623**	**€ 31,367**
Abemaciclib price		
199%	n.a.	€ 68,787
190%	n.a.	€ 65,385
150%	n.a.	€ 50,266
130%	n.a.	€ 42,706
110%	n.a.	€ 35,147
90%	€ 4,774,036	€ 27,587
70%	€ 3,722,861	€ 20,027
50%	€ 2,671,687	€ 12,468
10%	€ 569,338	-€ 2,651
1%	€ 96,309	-€ 6,053

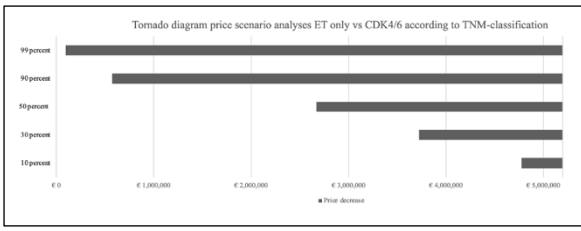

Figure 4.3.A: tornado diagram of price variations on scenario A vs B

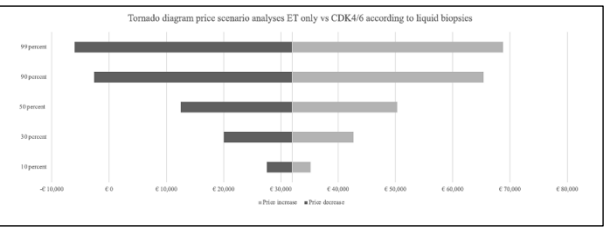

Figure 4.3.B: tornado diagram of price variations on scenario A vs C

4.4.2 Effect variations

Several scenarios in which the duration and nature of the effects of abemaciclib were varied have been investigated as well. The ICER results of these scenario analyses are presented in Figure 4.4 and Table 4.5 and some scenarios will be discussed in more detail. Appendix 3 provides more detailed information on the costs, QALYs and life years gained in the remaining scenarios.

When the assumption was made that the treatment effect of abemaciclib was eight instead of four years, the ICER comparing treatment scenario A to B was lowered to €770,063 and the ICER comparing A to C was lowered to €20,711. In both treatment scenarios, this reduction of the ICER value was caused by both an increase in QALYs and a decrease in costs.

Another scenario that is believed to be plausible is that the effect of abemaciclib reached at four years is maintained throughout the entire time horizon. This scenario yielded an ICER of € 177,245 when comparing treatment scenario A to B because the number of QALYs gained increased from 11.114 to 11.268 and costs decreased from € 233,278 to €200,403 in scenario B. The resulting ICER was considerably lower than the base case of €5,197,764. Furthermore, this treatment effect scenario led to an ICER of €8,311 in the comparison of A to C. Again, this difference was caused by an increase in QALYs gained and a decrease in costs. This time, a QALY increase from 11.828 to 11,906 and a cost reduction from €193,697 to €177,612 was observed in scenario C.

Subsequently, a scenario in which a treatment effect on OS was explored. When an effect with a HR of 0.757 was assumed, the ICER comparing A to B was improved to €2,090,172. In the comparison of treatment scenario A to C, the ICER slightly to € 31,595.

4.4.3 Frequency of liquid biopsies

The last scenario analyses concerned the frequency with which liquid biopsies were performed. When the liquid biopsies were performed once a year, the ICER decreased from €31,367 to €28,494. Moreover, the while cutting the number of liquid biopsies performed by half, the number of QALYs gained only decreased by 0.1 and the total treatment costs were lowered by €4,000.

When the liquid biopsy was only performed at 2.5 years, the ICER increased to €38,691. Moreover, in this scenario the number of QALYs gained decreased from 11.828 to 11.231, which was a substantial decrease compared to the previous scenario analysis.

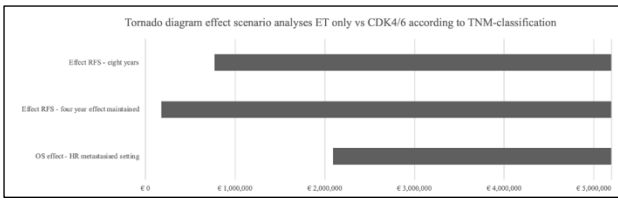

Figure 4.4.A: tornado diagram effect scenarios A vs B

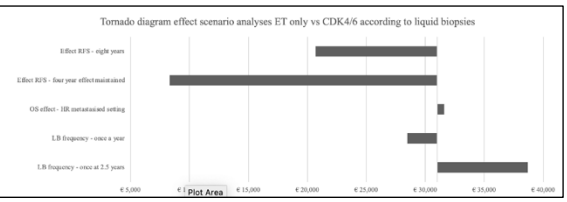

Figure 4.4.B: tornado diagram effect scenarios A vs C

Table 4.5: Results from the deterministic scenario analyses varying the effect of abemaciclib

	ICER scenario A vs. Scenario B	**ICER scenario A vs. Scenario C**
Base case	**€ 5,299,623**	**€ 31,367**
Duration treatment effect		
8 years	€ 770,063	€20,711
Four year effect maintained	€ 177,245	€8,311
Treatment effect on OS		
HR in metastasised setting	€ 2,090,172	€ 31,595
Frequency of liquid biopsies		
Once a year	n.a.	€28,494
Once at 2.5 years	n.a.	€ 38,691

5. Discussion

The previous chapters have presented the CEAs that were performed on the following three treatment scenarios for high-risk $HR^+/HER2^-$ early breast cancer patients; A) Current standard adjuvant endocrine treatment in the form of five years of tamoxifen or a combination of tamoxifen and letrozole for all high risk patients. B) A combination of five years of standard endocrine treatment and two years of abemaciclib for all high-risk patients. C) Current standard treatment as described in scenario A and an addition of two years of abemaciclib for those that have MRD.

In this final chapter, the results from the CEAs will be interpreted. Moreover, the assumptions that were made throughout the research and their effects will be discussed, together with the strengths and weaknesses of this study. Further, the results of this CEA will be placed within the realm of comparable research on other breast cancer drugs, the use of abemaciclib in the metastasised setting and to research advocating for personalised approaches in medicine. Finally, some recommendations on the reimbursement of abemaciclib for the $HR^+/HER2^-$ early breast cancer indication will be made.

5.1 Interpretation of base case results

The results have shown that the comparison of treatment scenario A to B and the comparison of scenario A to C yield substantially different ICERs: €5,197,764 and €31,367, respectively. In order to assess cost-effectiveness, a maximum ICER threshold needs to be established. ZiN uses ICER thresholds that are proportional to the burden of the disease at hand. The disease burden of other forms of early breast cancer have been estimated at 0.34 (61), which would correspond to an ICER threshold of €20,000 per QALY (62). However, since this CEA concerns high recurrence risk population, the disease burden will be higher. According to the formula provided by ZiN, which is presented on the right, and the iMTA burden of disease calculator, the disease burden for this specific patient population is 0.43, which corresponds to an ICER threshold of €50,000 (62,63).

$$\frac{(\textit{remaining QALYs without condition} - \textit{Remaining QALYs with condition but without new treatment})}{\textit{Remaining QALYs without condition}}$$

Equation 5.1: Formula for calculation of disease burden

With its substantial incremental costs of €62,347, and the minimal QALY gain of 0.012 (i.e. 4.4 quality adjusted days), treatment scenario B was nowhere near cost-effective when applying the ICER threshold. Moreover, the sensitivity analysis showed that 55% of PSA results lay in the NW quadrant, meaning that one would pay a higher price, for a loss in effect,

making it not cost-effective under any threshold. For those PSA results that did lie in the NE quadrant to be cost-effective, extremely high thresholds would have to apply to make them cost-effective. As Figure 4.2.a showed, at a threshold of €25 million there would only be a 40% chance that scenario B would be cost-effective.

Scenario C showed more promising results. With its incremental costs of €22,766 and its effect of 0.812 life years (i.e. 296.4 days) and 0.726 QALYs (i.e. 265 quality adjusted days), the final ICERs were €28,031 per life year and €31,367 per QALY. Moreover, the PSA showed that almost none of the PSA results were outside of the NE quadrant, meaning that scenario C almost certainly results in positive effects. While some uncertainty remained surrounding the extent of the effect, the majority of PSA results ranged from 0.4 to 1.0 QALY, and the CEAC showed that at an ICER threshold of €50,000, the acceptability probability was approximately 0.93, which is high.

All of the above would lead to the conclusion that treating all high-risk $HR^+/HER2^-$ early breast cancer patients with abemaciclib, which is a scenario that will be investigated by the FDA in the foreseeable future, is not favourable. Scenario B is expensive and yields very minimal results that are subject to substantial uncertainty. However, introducing personalised medicine by only providing additional abemaciclib to those who have MRD does seem to be favourable. Scenario C did not lead to very high incremental costs and yields good results that are subject to less uncertainty surrounding the effect of abemaciclib.

5.2 Main assumptions

As it was challenging to find sufficient survival and costs data, several assumptions had to be made to perform this CEA. While the rationale behind these assumptions has already been discussed in chapter three, the influence of the most important ones will be discussed further.

The main assumption that had to be made was that abemaciclib did not affect OS. This assumption had to be made, because of immaturity of OS data and was set as a 'worst-case scenario'. The main consequence of this assumption was that when RFS was improved by abemaciclib, the time spent in RD was directly reduced. Considering that treatment costs in RD are significantly higher than the treatment costs in RF during the first five years, and that no costs are made in RF after these initial five years, this assumption indirectly caused a reduction in total costs when RFS was prolonged. Combining literature on the use of abemaciclib in the metastasised setting (56) and expert opinion, the scenario in which

abemaciclib positively affects OS was deemed plausible enough to include it in the scenario analysis. However, it is important to note that the OS data of the use of abemaciclib in the RF setting remains immature that other CDK4/6 inhibitors have not shown any effect on OS either. Therefore, it must be stressed that while this scenario seems plausible, the real clinical value of abemaciclib is not clear yet. More research on the effect of abemaciclib on OS is therefore necessary. Another, yet less significant, consequence is that when time spent in RFS increases and time spent in RD decreases, a slight increase in QALYs gained would be observed. As the difference between utility of patients in RFS and RD only differed by 0.13, this assumption only had limited consequences on the final QALYs gained.

Another assumption that was made was to exclude treatment in RFS beyond the first five years. An exception to this rule was made in the last MRD states in scenario C in which the two years of abemaciclib treatment were finished despite the first five years being over. This assumption is believed not to affect the final ICER results greatly. According to expert opinion, it is too early to assume that treatment will be extended less frequently when a patient has received additional abemaciclib. Moreover, it was argued that having received additional abemaciclib will probably not affect the duration or chance of treatment extension. Thus, as treatment extensions are expected to be equally applied across the three treatment scenarios, the decision to exclude them from this CEA has probably not affected the ICERs much. Moreover, no adequate estimations on the proportion of patients receiving a treatment extension and its duration could be made and thus, including it would have increased uncertainty surrounding the final results. Even though the effect on the ICER expected to be limited, it is advised to do more research on the effect of abemaciclib on treatment extension.

The third major assumption made was the exclusion of exemestane and anastrozole from the analysis. Exemestane and anastrozole are different types of AIs, and the choice was made to only include letrozole as this is prescribed most often. Experts did not expect any differences in AI prescription across the treatment scenarios, and thus, the ICERs will probably not be affected greatly by this exclusion. Nevertheless, future research could investigate the consequences of including all three types of AIs on the cost-effectiveness of scenario B and C.

5.3 Interpretation of scenario analyses

It is important to note, that the assumptions made in the base case model were rather strict and cautious. As some of the required input data was not yet available, assumptions and estimations were made cautiously to ensure that effects or costs were not overestimated or

underestimated. Several scenario analyses have been performed to investigate the cost-effectiveness of treatment scenario B and C under different and more positive circumstances.

The first set of scenario analyses performed concerned the price of abemaciclib. With regards to scenario B, plausible price reductions still did not result cost-effectiveness. When the price of abemaciclib was reduced by 99%, the ICER comparing scenario A and B was €96,309. This means that to reach cost-effectiveness with an ICER threshold of €50,000, the price of abemaciclib must be lowered below 1% of the original price, which is a highly unrealistic scenario. With regards to treatment scenario C, price reductions led to lower ICERs and made it more cost effective. When the price was reduced to 10% of the original price of abemaciclib, treatment scenario C even became cost saving. While this scenario may be unrealistic now, it might be of interest in the future when the patent on abemaciclib has expired and cheaper generics may become available (64,65). Additionally, it is important to note, that even when the price is increased by 50%, treating MRD patients with abemaciclib remains cost-effective at a threshold of €50,000.

As the exact effect of abemaciclib remains uncertainty, the second set of scenario analyses concerned the effect of abemaciclib. When the treatment effect duration was doubled, the ICER of scenario B fell below €1,000,000. This considerable reduction was not only caused by an increase in effect, but also by a decrease in costs. Because the assumption was made that OS was not affected by abemaciclib, an increase in time spent in RF directly leads to a decrease in time spent in RD. As being in the RD state is much more expensive than being in RF, especially after the first five years, this leads to a considerable reduction of average total costs. However, this reduction did not lead to cost-effectiveness as the ICER value became €770,063. The same was observed in scenario C when treatment effect duration was doubled. A minimal improvement in QALYs gained was observed, but this was accompanied by a more substantial reduction in treatment costs in RD, and thus leading to a considerably lower ICER. As only treating MRD patients with additional abemaciclib was cost-effective in the base-case already, this scenario does probably not affect decision-making greatly.

When the assumption was made that the treatment effect reached at year four was maintained throughout the time horizon, the ICER for scenario B was lowered to approximately €180,000. Again, this reduction in the final ICERs was caused by an increase of QALYs gained and a decrease of treatment costs, but the treatment remains not cost-effective under these circumstances. The ICER of treatment scenario C also dropped to €8,311. This change was due to an increase in QALYs.

The scenario analysis regarding the effect of abemaciclib on OS significantly decreased the ICER of scenario B to €2,090,172. However, cost-effectiveness still is not reached. In scenario C, the ICER remained roughly the same and stayed cost-effective. The lack of effect of this scenario is caused by the fact that when an effect on OS is assumed, the time spent in RD is prolonged and therefore, the average treatment costs increase. Thus, the extra QALYs gained are immediately compensated for by increasing treatment costs. As no significant change in the ICER was observed, treatment scenario remained cost-effective under these circumstances.

Lastly, the frequency with which liquid biopsies were performed was varied to investigate the optimal frequency. Cutting the number of liquid biopsies performed in half reduced the ICER value by approximately €3,000. Moreover, the number of QALYs gained only decreased by 0.01 in this scenario. The scenario in which a liquid biopsy was only performed after 2.5 years of treatment led to an ICER increase of roughly €7,000 and a substantial decrease in QALYs gained. This led to the conclusion that this scenario is not favourable. Moreover, while the scenario in which liquid biopsies are only performed once year led to a slight decrease in the ICER, it might not preferred as patients progressing to the MRD state might be missed or observed too late for them to still be treated with abemaciclib to prevent progression into RD. More research on the time spent in MRD and its development is needed to make sufficiently informed decisions on the frequency with which liquid biopsies are taken.

The various scenario analyses performed have shown that the price of abemaciclib had a substantial influence on the ICERs of both treatment scenarios. This was expected as the incremental costs are mainly determined by the extra costs of abemaciclib. The price variations did not lead to cost-effectiveness of treatment scenario B, in which all high-risk patients are treated with abemaciclib. In scenario C, where only those in MRD received additional abemaciclib, the price variations showed that this scenario would even remain cost-effective when the price is increased by 50%, and would become cost saving if the price is decreased to 10% of the original price. Effect duration of abemaciclib had the most substantial influence on the ICERs of B and C. This was mainly due to the fact that prolonging time spent in RF directly causes a reduction in time spent in RD, and therewith lower treatment costs. Moreover, the scenario analyses have shown that treatment scenario C remains cost-effective when an effect on OS is assumed. Finally, the scenario analyses regarding the frequency of the liquid biopsies did not indicate the need to change the frequency assumed in the base case until more research is done on liquid biopsies and the MRD state.

5.4 Comparison to literature

Since no literature on the cost-effectiveness of abemaciclib in early breast cancer is available yet, it may be interesting to compare the results of this current study to CEAs in the metastasised $HR^+/HER2^-$ breast cancer setting. As was explained in Chapter 2, palbociclib, ribociclib and abemaciclib showed similar clinical effects and significantly improved PFS and OS in the metastasised setting (19). In 2019, Zhang and colleagues have performed a CEA of palbociclib and ribociclib in the metastasise setting and from a US healthcare perspective. They found that while both had considerable clinical effect, neither of the two were cost-effective at a threshold of $100,000 per QALY. In the Netherlands, ZiN has evaluated all three CDK4/6 inhibitors. While they all had a positive clinical effect, none of the three was cost-effective given the thresholds that applied. Therefore, they entered the 'sluice for expensive medicines' that that allows temporary inclusion of expensive medicines that are not cost-effective under the normal thresholds under special price agreements (66,67). While these analyses were performed within a different disease indication, this goes to show that abemaciclib is very expensive and is not likely to be considered cost-effective at its current list price, even if it has a significant clinical effect. This is in accordance with the findings of treatment scenario B, in which the entire high-risk population is treated with abemaciclib. Even in the more positive scenarios where the effect of abemaciclib on PFS or OS was more substantial, treatment scenario B did not reach cost-effectiveness at the €50,000 threshold. Moreover, these findings highlights the need for the exploration of more personalised approaches like treatment scenario C, in which abemaciclib is only prescribed to those that have developed MRD.

Literature concerning the cost-effectiveness of liquid biopsies as a risk assessment tool or treatment guidance in breast cancer is currently lacking. One CEA has been performed to assess the cost-effectiveness of liquid biopsies to determine change in treatment in advanced $HR^+/HER2^+$ breast cancer. The researchers concluded that the use of liquid biopsies was not cost-effective in their setting of interest. However, their CEA was performed in a different disease indication, from a medical perspective and with a time horizon of only one year. Moreover, due to a lack of adequate information on the methods and inputs, the quality of the paper was questioned (68). This makes it difficult to compare the results of that study to the current results. Furthermore, no CEAs have been performed on the use of liquid biopsies in other cancer indications either. This could be explained by the fact that research on the clinical utility of liquid biopsies is still at its infancy and clinical data about the effect of decisions based on liquid biopsies is lacking (69). Nonetheless, this does highlight the relevance of this

current study and proves that more research into this topic is needed to create better insight in the benefits of an efficient use of the liquid biopsy technique in guidance of cancer treatment.

Besides the use of liquid biopsies, the role of personalised approaches in breast cancer has been growing over the past years. Breast cancer was long believed to be a singular disease and therefore, it was treated as one (70). However, over the past decades, biological features and genetic profiling have helped to personalise breast cancer treatment and thereby maximised treatment effects, minimised treatment toxicity and prevented excessive medical costs due to overtreatment (70–73). Many examples can be found of studies that have shown the cost-effectiveness of adding gene expression analyses to treatment decision making. An example is the use of Mammaprint, which can identify low-risk early breast cancer patients, and therewith spare them the standard adjuvant endocrine therapy (74). Several CEAs in different country settings including the Netherlands, have shown that this technique is cost-effective (74,75). Moreover, the assessment of HER2 expression has made the use of certain medicines, like trastuzumab, more cost-effective by ensuring that it is only provided to those who are expected to benefit from it (76). The study outcomes described above advocate for a more personalised approach in breast cancer treatment as it can increase the cost-effectiveness of breast cancer treatments. This is in accordance with the findings of the current study.

5.5 Strengths and limitations

The main strength of this research was its scientific relevance. A knowledge gap on the cost-effectiveness of abemaciclib in the $HR^+/HER2^-$ early breast cancer was identified, and this study may therefore contribute to the body of knowledge surrounding this disease indication. Moreover, while the use of liquid biopsies in this setting had been proposed as a topic for future research, by our knowledge, this study has been one of the first to explore the cost effectiveness of their use in early breast cancer. Especially considering the increasing need for personalised medicine approaches, this study has created insight in how liquid biopsies may be used in clinical practice and what their impact on health care spending might be. Thus, this study may be of value for policy makers.

Secondly, the comprehensiveness of the CEA performed has contributed to the strength of this research. Not only has this study created insight on the benefits and costs of providing abemaciclib to all high-risk patients, but it has also investigated a more cost-saving and personalised approach of incorporating abemaciclib into the current treatment standard. Furthermore, costs beyond the medical perspective were included, which has increased its use

in practice. Additionally, a comprehensive set of scenario analyses have been performed to investigate the costs and effects of the treatment scenarios under different and more positive circumstances.

Finally, the collaboration with the Erasmus MC, especially regarding the clinical perspective has contributed to increased internal and external validity as all choices and assumptions made that concerned clinical validity were made in consultation with medical experts.

The challenges mainly lay with the availability of adequate survival data. However, the lack of adequate survival data is common in appraisal of new drugs in oncology and may lead to a delay in availability of life saving drugs (77,78). Because the aim of this CEA was to explore the cost-effectiveness of the proposed treatment scenarios, it is recommended that this CEA is repeated when more comprehensive data is available. Other limitations, including the assumptions made on the exclusion of treatment extensions and some different treatment options that have been discussed above, may have led to a decrease of external validity. However, as was discussed before, the impact of these assumptions is expected to be limited.

Nonetheless, it must be noted that while the results are surrounded by uncertainty, this CEA provided the most realistic representation of the cost-effectiveness of the treatment scenarios possible, considering the available data resources.

5.6 Conclusions and recommendations for future research

This study was one of the first to explore both the cost-effectiveness of abemaciclib in the $HR^+/HER2^-$ early breast cancer indication and of the use of liquid biopsies as treatment guidance. The performed CEA has shown that providing additional abemaciclib to all high-risk $HR^+/HER2^-$ early breast cancer patients does not seem to be cost-effective under the circumstances of this study as it leads to high incremental cost and yields minimal effects. Even when assumptions with positive influecnes on costs and effects of abemaciclib were made, this treatment scenario did not reach cost-effectiveness. In contrast, the treatment scenario in which liquid biopsies are used as guidance in treatment decisions making was dominant over treatment scenario B and current standard treatment. Not only did scenario C save costs compared to scenario B, it also led to a significant increase in effects. Thus, the results of this study advocated for a more personalised approach in breast cancer management, a trend that has increasingly been recognised by experts in the field as it could increase benefits and limits

harm for the patients and consequently reduce the financial burden of new medicines in oncology.

Due to immaturity of data, the results are subject to uncertainty. Therefore, it is recommended to repeat the analyses when more rigorous data is available. To confirm the results of this preliminary CEA, future research could focus on the effects of abemaciclib in the early $HR^+/HER2^-$ breast cancer indication. Moreover, more research is needed on the predictive value of liquid biopsies in this setting and their cost-effective use beyond breast cancer should be explored.

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Appendix 1 – Complete Overview of Parameters

PARAMETER NAME	VALUE	DESCRIPTION	SOURCE
DISCOUNT RATE			
cDR	**0.040**	Discount rate costs	ZiN guideline
oDR	**0.015**	Discount rate effects	ZiN guideline
background mortality	**0.0038**	Background mortality	CBS
CHOICE OF DISTRIBUTION OS AND PFS			
Distribution_OS	**2.000**	Weibull distribution	n.a.
Distribution_PFS	**4.000**	Loglogistic distribution	n.a.
UTILITIES			
uDF	0.87	Utility value for disease-free patients	Health-related quality of life in different states of breast cancer – comparing different instruments
uRD	0.74	Utility value for patients with recurrent disease	
du_neutropenia	0.087	Disutility value for neutropenia	Uyl-de Groot, Al, Zaim (2015) & Bullement et al. (2019)
du_leukopenia	0.087	Disutility value for leukopenia	Uyl-de Groot, Al, Zaim (2015) & Bullement et al. (2019)
du_diarrhoea	0.046	Disutility value for diarrhoea	Uyl-de Groot, Al, Zaim (2015) & Bullement et al. (2019)
du_lymphopenia	0.09	Disutility value for lymphopenia	Bullement et al. (2019)
ADVERSE EVENTS			
p_neutropenia_et_only	0.007	Probability of having neutropenia ET only	Johnston et al. (2020)
p_leukopenia_et_only	0.004	Probability of having leukopenia ET only	Johnston et al. (2020)
p_diarrhoea_et_only	0.001	Probability of having diarhhoea ET only	Johnston et al. (2020)
p_lymphopenia_et_only	0.005	Probability of having lymphopenia ET only	Johnston et al. (2020)
p_neutropenia_CDK4	0.189	Probability of having neutropenia ET + abemaciclib	Johnston et al. (2020)
p_leukopenia_CDK4	0.109	Probability of having leukopenia ET + abemaciclib	Johnston et al. (2020)
p_diarrhoea_CDK4	0.076	Probability of having diarrhoea ET + abemaciclib	Johnston et al. (2020)
p_lymphopenia_CDK4	0.051	Probability of having lymphopenia ET + abemaciclib	Johnston et al. (2020)
p_hospitalisation_AE	0.076	Probability of hospitalisation due to diarrhoea	expert opinion
dur_neutropenia	2	Duration Neutropenia	Bullement et al. (2019)
dur_leukopenia	2	Duration leukoopenia	Bullement et al. (2019)
dur_diarrhoae	7	Duration diarrhoea	expert opinion
dur_lymphopenia	2	Duration lymphopenia	Bullement et al. (2019)
TRANSITION PROBABILITIES MDR			
p_MRD0.5	0.0588	probability of entering MRD at 0.5 years	Garcia-Murrilas et al (2020)
p_MRD1	0.0588	probability of entering MRD at 1 years	Garcia-Murrilas et al (2020)
p_MRD1.5	0.0588	probability of entering MRD at 1.5 years	Garcia-Murrilas et al (2020)
p_MRD2	0.0588	probability of entering MRD at 2 years	Garcia-Murrilas et al (2020)
p_MRD2.5	0.0588	probability of entering MRD at 2.5 years	Garcia-Murrilas et al (2020)

p_MRD3	0.0588	probability of entering MRD at 3 years	Garcia-Murrilas et al (2020)
p_MRD3.5	0.0588	probability of entering MRD at 3.5 years	Garcia-Murrilas et al (2020)
p_MRD4	0.0588	probability of entering MRD at 4 years	Garcia-Murrilas et al (2020)
p_MRD4.5	0.0588	probability of entering MRD at 4.5 years	Garcia-Murrilas et al (2020)
p_MRD5	0.0588	probability of entering MRD at 5 years	Garcia-Murrilas et al (2020)
COSTS			
days_per_cycle	91	number of days in a cycle	
mean_age	57	mean age patients	IKNL
p_pre_menopausal	0.21	proportion of patients that is pre-menopausal	IKNL
p_post_menopausal	0.79	proportion of patients that is post-menopausal	IKNL
Drug acquistion costs			
c_pharmaceutical_care_cycle	6	costs pharmaceutical care per cycle (cycle 2+)	
c_tamoxifen_day	0.21	mean costs tamoxifen per 20 mg	medicijnkosten.nl & farmacoceutischkompas.nl
c_letrozole_day	0.88	mean costs letrozole per 2.5 mg	medicijnkosten.nl & farmacoceutischkompas.nl
c_abemaciclib_day	93.04	mean costs abemaciclib per 300 mg	farmacoceutischkompas.nl
c_leucrin_cycle	293.18	mean costs leucrin per injection	farmacoceutischkompas.nl
c_leucrin_admin	33	mean costs leucrin administration	kostenhandleiding
Healthcare resource use per cycle			
c_oncologist	132	costs oncologist visit	Rijnstate (2020), Universitair Medisch Centrum Groningen (2020), Erasmus Medisch Centrum (2021) & Diakonessenhuis Utrecht (2021)
c_kidneylab	5.28	costs kidney laboratory test	Rijnstate (2020), Universitair Medisch Centrum Groningen (2020), Erasmus Medisch Centrum (2021) & Diakonessenhuis Utrecht (2021)
c_liverlab	10.43	costs liver laboratory test	Rijnstate (2020), Universitair Medisch Centrum Groningen (2020), Erasmus Medisch Centrum (2021) & Diakonessenhuis Utrecht (2021)
c_mammography	110.14	costs mammography	Rijnstate (2020), Universitair Medisch Centrum Groningen (2020), Erasmus Medisch Centrum (2021) & Diakonessenhuis Utrecht (2021)
co_liquid_biopsy	100	costs liquid biopsy	Expert opinion
c_genetic_test	450	costs genetic testing	Expert opinion
A_oncologist_y1	3	Sit A: number of oncologist visits in year 1	Expert opinion
A_oncologist_2/5+	1	Sit A: number of oncologist visits in year 2 - 5	Expert opinion
A_kidneylab_y1	1	Sit A: number of kidney labcontroles in year 1	Expert opinion
A_liverlab_y1	1	Sit A: number of liver labcontroles in year 1	Expert opinion
A_liverlab_y2/5+	1	Sit A: number of liver labcontroles in year 2 - 5	Expert opinion
AB_mammography_y1/5+	1	Sit A: number of mammographies in all years	Expert opinion
C_oncologist_y1	13	Sit C: number of oncologist visits in year 1 for those on CDK4/6	Johnston et al.
C_oncologist_y2	4	Sit C: number of oncologist visits in year 2 for those on CDK4/6	Johnston et al.

C_oncologist_y3/5+	1	Sit C: number of oncologist visits in year 3 - 5 for those on CDK4/6	Johnston et al.
C_kidneylab_y1	10	Sit C: number of kidney labcontroles in year 1 for those on CDK4/6	Johnston et al.
C_kidneylab_y2	4	Sit C: number of kidney labcontroles in year 2 for those on CDK4/6	Johnston et al.
C_liverlab_y1	10	Sit C: number of liver labcontroles in year 1 for those on CDK4/6	Johnston et al.
C_liverlab_y2	4	Sit C: number of liver labcontroles in year 2 for those on CDK4/6	Johnston et al.
C_liverlab_y3/5+	1	Sit C: number of liver labcontroles in year 3 - 5 for those on CDK4/6	Johnston et al.
Societal costs			
c_travel_hospital	4.33	mean travel costs hospital visit	Hakkaart-van Rooijen et al. (2016)
c_travel_pharmacy	0.25	mean travel costs pharmacy visit	Hakkaart-van Rooijen et al. (2016)
proportion employed	0.5	proportion of patients being employed	Braal et al. (2021)
c_productivity_paid_hour	31.6	productivity costs for women per hour for paid work	Hakkaart-van Rooijen et al. (2016)
c_productivity_unpaid_hour	14	productivity costs for women per hour for unpaid work	Hakkaart-van Rooijen et al. (2016)
dur_friction_period	85	duration of friction period	Hakkaart-van Rooijen et al. (2016)
hours_worked_day	1.96	mean number of hours worked per day	Braal et al. (2021)
hours_missed_ETonly_year1	12.58	mean number of hours missed in year 1 ET only	Braal et al. (2021)
hours_missed_ETonly_year2+	9.5	mean number of hours missed in year 2+ ET only	Braal et al. (2021)
hours_missed_unpaid_ETonly_year1	11.23	mean number of unpaid hours missed year 1 ET only	Braal et al. (2021)
hours_missed_unpaid_ETonly_year2+	9.1	mean number of unpaid hours missed year 2+ ET only	Braal et al. (2021)
Adverse events			
c_neutropenia	1465.68	Treatment costs neutropenia	Uyl-de Groot, Al, Zaim (2015)
c_leukopenia	2026.97	Treatment costs leukopenia	Uyl-de Groot, Al, Zaim (2015)
c_diarrhoea	2461.6	Treatment costs diarhhoea	Uyl-de Groot, Al, Zaim (2015)
c_lymphopenia	1746.325	Treatment costs lymphoopenia	Expert opinion
Recurrent disease			
c_RD	10050	Costs recurrent disease per patient per cycle	Braal et al. (2021)

Appendix 2 – Undiscounted Results

Treatment	endocrine therapy only based on TNM-classification scale	abemaciclib + endocrine therapy based on TNM-classification scale	abemaciclib + endocrine therapy based on liquid biopsies
Drug acquisition costs - RF	€ 1,847	€ 66,449	€ 33,553
Healthcare resource use - RF	€ 1,219	€ 3,157	€ 2,295
Genetic testing & liquid biopsies - RF	€ 0	€ 0	€ 1,035
Adverse events medical costs - RF	€ 30	€ 774	€ 455
Societal costs - RF	€ 7,450	€ 8,789	€ 8,777
Medical costs - RD	€ 260,324	€ 256,476	€ 256,866
Societal costs - RD	€ 5,245	€ 5,248	€ 5,245
LYs accrued in RF state	9.350	9.446	10.473
LYs accrued in RD state	6.476	6.380	6.390
QALYs accrued in RF state	8.135	8.218	9.112
QALYs accrued in RD state	4.792	4.721	4.728
QALYs lost due to adverse events	-0.000009	-0.000234	-0.000129
Total costs	€ 276,115	€ 340,892	€ 308,225
Total life years	15.83	15.83	16.86
Total QALYs	12.927	12.939	13.840
ICER life years			**€ 30,952**
ICER QALYs		**€ 5,301,211**	**€ 35,146**

Appendix 3 – Results from Scenario Analyses

Treatment effect on RFS – 8 years

Treatment	endocrine therapy only based on TNM-classification scale	abemaciclib + endocrine therapy based on TNM-classification scale	abemaciclib + endocrine therapy based on liquid biopsies
Drug acquisition costs - RF	€ 1,667	€ 63,600	€ 29,164
Healthcare resource use - RF	€ 1,182	€ 3,025	€ 2,069
Genetic testing & liquid biopsies - RF	-	-	€ 987
Adverse events medical costs - RF	€ 30	€ 774	€ 455
Societal costs - RF	€ 6,824	€ 8,431	€ 7,962
Medical costs - RD	€ 157,415	€ 140,142	€ 142,307
Societal costs - RD	€ 3,813	€ 3,727	€ 3,608
	€ 161,228	€ 143,869	
LYs accrued in RF state	8.251	8.740	9.431
LYs accrued in RD state	5.302	4.813	4.934
QALYs accrued in RF state	7.179	7.604	8.205
QALYs accrued in RD state	3.923	3.562	3.651
QALYs lost due to adverse events	-0.000009	-0.000234	-0.000129
Total costs	€ 170,931	€ 219,700	€ 186,552
Total life years	13.55	13.55	14.37
Total QALYs	11.102	11.165	11.856
ICER life years			**€ 19,234**
ICER QALYs		**€ 770,063**	**€ 20,711**

Treatment effect on RFS – life long

Treatment	endocrine therapy only based on TNM-classification scale	abemaciclib + endocrine therapy based on TNM-classification scale	abemaciclib + endocrine therapy based on liquid biopsies
Drug acquisition costs - RF	€ 1,667	€ 63,588	€ 29,164
Healthcare resource use - RF	€ 1,182	€ 3,020	€ 2,069
Genetic testing & liquid biopsies - RF	-	-	€ 987
Adverse events medical costs - RF	€ 30	€ 774	€ 455
Societal costs - RF	€ 6,824	€ 8,392	€ 7,960
Medical costs - RD	€ 157,415	€ 121,000	€ 133,415
Societal costs - RD	€ 3,813	€ 3,628	€ 3,562
LYs accrued in RF state	8.251	9.532	9.814
LYs accrued in RD state	5.302	4.021	4.552
QALYs accrued in RF state	7.179	8.293	8.538
QALYs accrued in RD state	3.923	2.976	3.368
QALYs lost due to adverse events	-0.000009	-0.000234	-0.000129
Total costs	€ 170,931	€ 200,403	€ 177,612
Total life years	13.55	13.55	14.37
Total QALYs	11.102	11.268	11.906
ICER life years			**€ 8,227**
ICER QALYs		**€ 177,245**	**€ 8,311**

Treatment effect on OS

Treatment	endocrine therapy only based on TNM-classification scale	abemaciclib + endocrine therapy based on TNM-classification scale	abemaciclib + endocrine therapy based on liquid biopsies
Drug acquisition costs - RF	€ 1,667	€ 63,540	€ 29,160
Healthcare resource use - RF	€ 1,182	€ 2,999	€ 2,068
Genetic testing & liquid biopsies - RF		-	€ 987
Adverse events medical costs - RF	€ 30	€ 774	€ 455
Societal costs - RF	€ 6,824	€ 8,241	€ 7,951
Medical costs - RD	€ 157,415	€ 154,868	€ 149,923
Societal costs - RD	€ 3,813	€ 3,798	€ 3,645
LYs accrued in RF state	8.251	8.344	9.212
LYs accrued in RD state	5.302	5.235	5.167
QALYs accrued in RF state	7.179	7.259	8.015
QALYs accrued in RD state	3.923	3.874	3.824
QALYs lost due to adverse events	-0.000009	-0.000234	-0.000129
Total costs	€ 170,931	€ 234,220	€ 194,188
Total life years	13.55	13.58	14.38
Total QALYs	11.102	11.132	11.838
ICER life years			**€ 28,153**
ICER QALYs		**€ 2,090,172**	**€ 31,595**

Frequency of liquid biopsies – once a year

Treatment	endocrine therapy only based on TNM-classification scale	abemaciclib + endocrine therapy based on liquid biopsies
Drug acquisition costs - RF	€ 1,667	€ 26,963
Healthcare resource use - RF	€ 1,182	€ 2,017
Genetic testing & liquid biopsies - RF		€ 1,019
Adverse events medical costs - RF	€ 30	€ 424
Societal costs - RF	€ 6,824	€ 7,934
Medical costs - RD	€ 157,415	€ 149,842
Societal costs - RD	€ 3,813	€ 3,644
LYs accrued in RF state	8.251	9.217
LYs accrued in RD state	5.302	5.165
QALYs accrued in RF state	7.179	8.019
QALYs accrued in RD state	3.923	3.822
QALYs lost due to adverse events	-0.000009	-0.000119
Total costs	€ 170,931	€ 191,844
Total life years	13.55	14.38
Total QALYs	11.102	11.841
ICER life years		**€ 25,218**
ICER QALYs		**€ 28,293**

Frequency of liquid biopsies – only at 2.5 year

Treatment	endocrine therapy only based on TNM-classification scale	abemaciclib + endocrine therapy based on liquid biopsies
Drug acquisition costs - RF	€ 1,667	€ 6,935
Healthcare resource use - RF	€ 1,182	€ 1,354
Genetic testing & liquid biopsies - RF		€ 1,137
Adverse events medical costs - RF	€ 30	€ 110
Societal costs - RF	€ 6,824	€ 7,018
Medical costs - RD	€ 157,415	€ 155,588
Societal costs - RD	€ 3,813	€ 3,781
LYs accrued in RF state	8.251	8.431
LYs accrued in RD state	5.302	5.264
QALYs accrued in RF state	7.179	7.335
QALYs accrued in RD state	3.923	3.896
QALYs lost due to adverse events	-0.000009	-0.000024
Total costs	€ 170,931	€ 175,922
Total life years	13.55	13.70
Total QALYs	11.102	11.231
ICER life years		**€ 34,976**
ICER QALYs		**€ 38,691**