Economic evaluation of enzalutamide and androgen deprivation therapy in men with metastatic hormone-sensitive prostate cancer in the United Kingdom

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Abstract

Introduction: metastatic hormone-sensitive prostate cancer (mHSPC) patients in the United Kingdom (UK) are underrepresented in the treatment guidelines for prostate cancer. They are either treated with first-generation anti—androgens which inevitably leads to the development of hormone-resistance, or they receive no treatment other than symptomatic treatment. Recently, the efficacy and safety of enzalutamide, a second generation anti-androgen, combined with continuous testosterone suppression (cTS) has been assessed in the ENZAMET and ARCHES trials. Enzalutamide proved to extend the overall survival (OS) as well as progression free survival (PFS) of mHSPC when compared to standard of care (SoC). For this option to be included in the National Health Services (NHS) budget of the UK and recommended in the treatment guidelines of the National Institute for Health and Care Excellence (NICE), the cost-effectiveness needs to be assessed to ensure rational use of the healthcare budget.

Objective: To assess the cost-effectiveness of enzalutamide combined with cTS compared to SoC combined with cTS in mHSPC patients in the UK, expressed as the incremental cost-effectiveness ratio (ICER).

Methods: A cost-utility analysis was performed. Survival and utility data were extracted from the ENZAMET and ARCHES trial. The healthcare perspective was used for the inclusion of direct medical cost parameters. The time horizon was 15 years, which is considered as lifetime in this population. A three-state Markov trace model was used for extrapolation of the data to fit the time horizon of the study. The cycle length was four weeks. All patients (n=1000) started in the stable disease state, of which a proportion could enter the serious adverse event state in the first cycle. Patients could then move to progression, to death, or stay in the stable disease cycle. A base case deterministic analysis was performed, as well as deterministic scenario analyses, and a probabilistic sensitivity analysis (PSA).

Results: The Weibull distribution is used for the extrapolation of OS data, and the lognormal distribution is used for the extrapolation of PFS data. In the base case scenario, the deterministic ICER is £125,853 per QALY gained. The PSA showed that around 70% of all possible ICERs resulted in cost-savings as well as loss of QALYs. The scenario analyses addressed this loss of QALYs which was due to the higher incidence of adverse events, and showed that this could lead to enzalutamide being considered as cost-effective.

Conclusion: In the base case scenario, enzalutamide cannot be considered cost-effective. However, treating mHSPC patients with enzalutamide early on could induce cost-savings, though this is often accompanied by a loss of QALYs. The loss of QALYs is due to the higher incidence of adverse events in the enzalutamide group, and should therefore be addressed to provide mHSPC patients with the first targeted treatment for their disease trajectory. Future research is needed to decide what the eventual placement of enzalutamide in the treatment guidelines should be, and whether uptake in the NHS budget is rational.

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List of abbreviations

95% -CI	95%-confidence interval
AAs	Anti-androgens
ADT	Androgen deprivation therapy
AR	Androgen receptor
CE	Cost-effectiveness
CTCAE	Common terminology criteria for adverse events
cTS	Continuous testosterone suppression
DHT	Dihydrotestosterone
FSH	Follicle-stimulating hormone
GnRH	Gonadotropin-releasing hormone
HPG-axis	Hypothalamic-pituitary-gonadal-axis
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
LH	Luteinizing hormone
mHSPC	Metastatic hormone-sensitive prostate cancer
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
OS	Overall survival
PC	Prostate cancer
PD	Progressed disease
PFS	Progression free survival
QoL	Quality of life
rPFS	Radiographic progression free survival
SD	Stable disease
SE	Standard error
SoC	Standard of care
UK	United Kingdom

Chapter 1. Introduction

The prostate is a gland that is part of the male reproductive system. The main function entails the production of liquids that form the vessel for sperm cells which are produced by the testicles. Prostate cancer is a form of cancer that develops in the prostate gland. As with all cancerous growth, prostate cancer is also marked by an uncontrolled malignant growth of cells in the prostate gland. (1) Around 48,500 new cases of prostate cancer are registered annually in the United Kingdom (UK). It is currently the second most common malignancy and leading cause of cancer mortality in men. (2) The causes are largely unknown, but certain factors can increase the risk of developing prostate cancer. Men over 50 years of age, of African or African-Caribbean decent, or who have a brother or father with prostate cancer, are more at risk for developing prostate cancer. (3)

There are different stages of prostate cancer. The early stage is often asymptomatic. Active surveillance is recommended, but no treatment is started yet. (3) In the localised or locally advanced stage, symptoms such as an increased need to urinate, difficulty urinating, and the sense that the bladder is not fully emptied, are present. Treatment in this stage is curative, aiming at removing the tumour through radical treatment and hormone suppression. Finally, there is the metastatic stage, in which the cancer has spread to various parts of the body through lymph nodes. Treatment in this stage is aimed towards prolonging survival and relieving symptoms. (3)

Prostate cancer can be further divided into hormone-sensitive or hormone-resistant. This classification discerns between the growth pattern of the tumour. Notably, hormone-sensitive prostate cancer grows when androgen hormones such as testosterone are present. The tumour stops growing with hormone suppressing therapy, which leads to testosterone depletion. Hormone-resistant prostate cancer on the other hand, continues to grow despite hormone suppressing therapy. (4) Hormone-resistance often develops over time. It is defined as a rise in serum prostate specific antigen (PSA) or clinical progression. Clinical progression takes a combination of imaging, expert opinion and worsening symptoms into account. In both cases, therapy failure with hormone suppressive drugs occurs. After, the cancer is considered hormone-resistant, also called castration-resistant, or hormone-refractory. (4) In this stage, patients have to decide whether they would like to continue treatment with conventional chemotherapy options, or receive palliative treatment to relieve existing symptoms. In other words, patient have to make the life-altering decision whether they would like to try life-extending treatments options which can be experienced as aggressive and invasive, or choose to focus on palliative and end-of-life care to relieve symptoms and come to terms with their expected survival time. Thus, hormone resistance not only limits the treatment options, it also forces patients to make painful decisions with regards to their life. In that sense, medically delaying hormone resistance could delay the decline in quality of life (QoL) for prostate cancer patients, as well as possibly extend their survival. The right anti-hormonal treatment, given at the right time and in the right combination with other anti-cancer therapies, could accomplish this.

A variety of anti-hormonal therapies is available on the market, all of which have an indication in locally advanced hormone-sensitive prostate cancer to suppress tumour growth which allows for surgical removal of the tumour or radiation, or in metastatic castration resistant prostate cancer to not induce further spread of the cancer due to androgenous hormones-induced growth. (5) A specific subgroup of prostate cancer patients is not well represented in these treatment options, namely patients with metastatic hormone sensitive prostate cancer (mHSPC). These patients are often diagnosed when the cancer has spread to distant parts of the body already. Late diagnosis can for example be due to a late onset of symptoms. mHSPC patients either have not been exposed to anti-hormonal therapy yet, or are responding to a first cycle of anti-hormonal therapy in an insufficient manner to suppress tumour growth. For this group of patients, timely treatment can delay the development of hormone-resistance

which can in turn extend survival time and time to worsening of the symptoms. As of yet, the only treatment option that has been studied in mHSPC patients specifically, is enzalutamide. (6)

Enzalutamide is an orally administered androgen receptor blocker that was designed to overcome acquired hormone-resistance after treatment with nonsteroidal anti-androgen (NSAA) drugs. (6) In the current UK guidelines, enzalutamide is recommended for metastatic hormone resistant prostate cancer, before or after a docetaxel regimen is administered, and in high-risk non-metastatic hormone resistant prostate cancer. Currently, two randomized clinical trials have investigated the effect of enzalutamide in mHSPC: the ACRHES trial and the ENZAMET trial. (6,7) The ARCHES trial investigated the effects of enzalutamide with continuous testosterone suppression (cTS) versus cTS alone in mHSPC patients on the radiographic progression free survival (PFS). The median follow-up time was 14.4 months, and the hazard-ratio (HR) was 0.39; 95%-confidence interval (CI), 0.30 to 0.50, $P < .001$. The ENZAMET trial investigated the effects of enzalutamide combined with cTS versus androgen deprivation therapy (ADT) combined with cTS through chemical or surgical castration on PFS and overall survival (OS) of mHSPC patients. The median follow-up time was 34 months, and the HR was 0.67; 95%-CI, 0.52 to 0.86; $P = 0.002$. (6)

In short, enzalutamide shows promising results in the treatment of mHSPC. Based on the current efficacy and safety profile, enzalutamide could be considered as a novel treatment for the underrepresented patient group of mHSPC patients. It could thus receive positive recommendation by the National Health Services (NHS) of the UK, and therefore be included in the NHS budget. However, not only the efficacy and safety are of importance in the recommendation of novel technologies. An equally important factor in the decision-making process of the inclusion of drugs in the NHS budget is the cost-effectiveness (CE). The CE assesses whether the benefits of the novel treatment outweigh the accompanying utilitarian and monetary risks. Additionally, it also assesses whether the novel treatment option is more acceptable in terms of medical benefits and monetary value than the existing treatment options. The latter is important to consider for uptake in the national healthcare budgets. After all, healthcare is a scarce good, with an endless demand side and a limited supply side. Additionally, healthcare expenditure is rising globally due to an aging population and continuous new medical advances. Therefore, uptake of medical treatments and procedures in national budgets needs to be rationalized. (8) In this case, the CE of enzalutamide, combined with cTS needs to be assessed for the UK population. As of yet, this CE-analysis has not been performed.

Therefore, the primary objective of this study is to provide the economic evaluation of the simultaneous use of enzalutamide with continuous testosterone suppression compared to first-generation AAs with continuous testosterone suppression in men with mHSPC in the UK. The CE is expressed as the incremental cost-effectiveness ratio (ICER) between the two treatments. Secondary objectives provide insight into alternative scenarios in which enzalutamide can be considered as cost-effective by means of scenario analyses and a probabilistic sensitivity analysis.

Chapter 2. Theoretical framework

In this chapter, the theoretical frame in which this CE-analysis will be performed is elaborated. First, the baseline information with regards to cancer diagnosis will be discussed to understand what treatment options are available at what stage. After, the mechanism of action for the available treatment options in general, as well as enzalutamide specifically, will be elucidated. Lastly, the design of the CE-analysis will be explained, as well as the target audience and the subsequent criteria for the analysis.

2.1 Male reproductive endocrinology

To understand the treatment options for prostate cancer, the male reproductive cycle needs to be explained. The crucial connection from the brain to the male reproductive organs is the hypothalamic-pituitary-gonadal (HPG)-axis, see figure 1. The HPG-axis has two primary functions: spermatogenesis (the maturing of sperm stem cells into sperm cells) and testosterone biosynthesis. The hypothalamus produces gonadotropin-releasing hormone (GnRH). This stimulates the anterior pituitary gland located at the base of the brain to release luteinizing hormone (LH) and follicle-stimulating hormone (FSH). LH and FSH regulate the further maturing of sperm cells and testosterone production. Androgens, as well as LH and growth hormones, are responsible for the physiological growth and functionality of the prostate. (9) One of the many theories with regards to the cause of prostate cancer, is an imbalance in the HPG-axis caused by external factors, leading to abnormal growth of the prostate. (10) Depending on the stage and hormone-responsiveness of the cancer, therapy targeted towards manipulation of the HPG-axis can be considered.

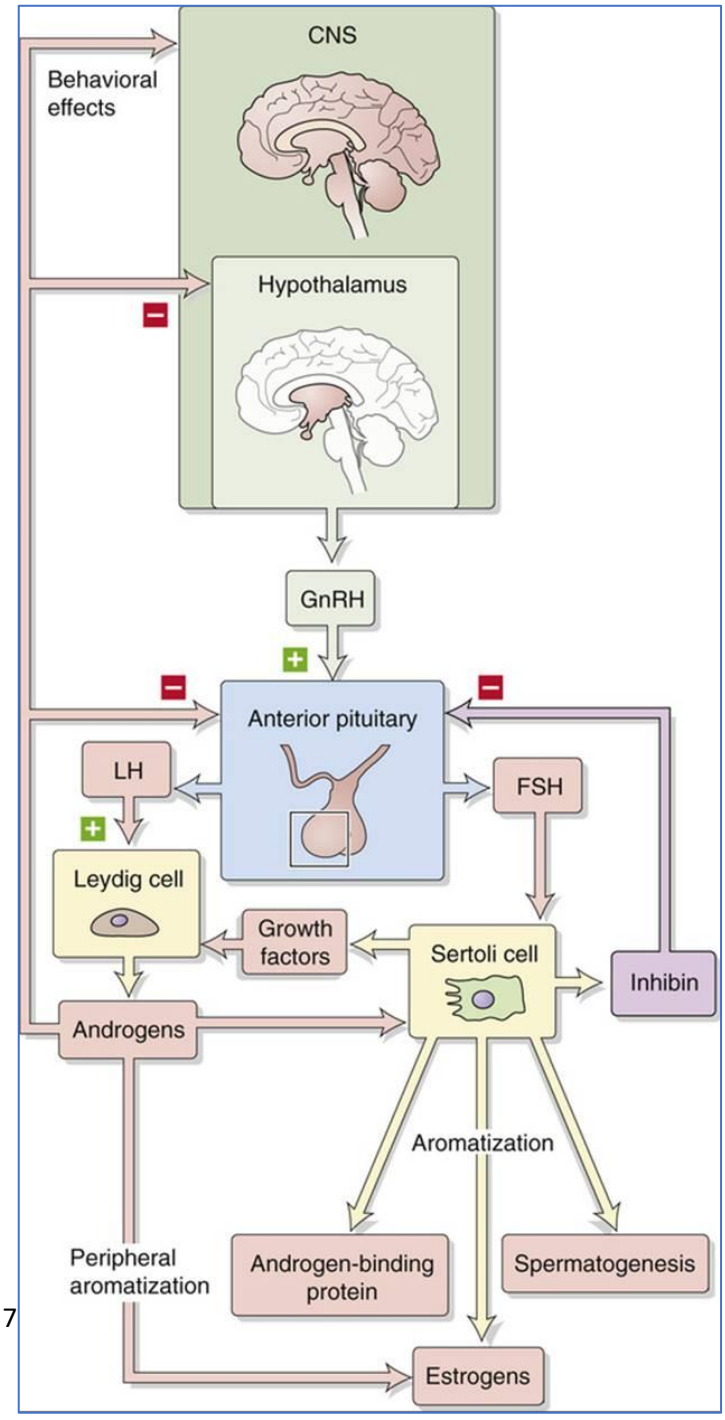


Fig. 1 HPG-axis. CNS = central nervous system; GnRH = gonadotropin-releasing hormone; LH = luteinizing hormone; FSH = follicle-stimulating hormone. (9)

2.2 Cancer staging and treatment options

As mentioned before, the available treatment options differ based on the staging and hormone-sensitivity of the cancer. Staging of cancers is based on the Tumour-Node-Metastasis (TNM)- system. (11) See figure 2 for an overview. The (T)umour letter says something about the original (primary) tumour. It describes the location, size, and spread of the primary tumour. There are different categories within T. TX means that the primary tumour cannot be measured, or no information is available for the primary tumour. T0 signifies that the primary tumour cannot be located. Tis stands for *in situ* primary tumour, which enunciates that the cancer cells are not growing into deeper cell layers, this is also called pre-cancer. Finally, T1-T4, indicate the size and growth of the tumour into nearby tissues. The higher the T number, the bigger the tumour is, or the more it has spread into nearby tissues. The (N)ode describes the number of nearby lymph nodes that contain cancer cells. The lymph nodes are part of the lymphatic system and usually serve as drains for immunological 'waste'. The lymphatic system is connected to the systemic blood circulation, in which toxins gathered through the lymph nodes are excreted through faeces, urine, and sweat. Cancer spreading occurs through transport via lymph nodes. Naturally, the lymph nodes near the primary tumour contain cancer cells if the tumour has spread. Nx describes the situation in which the nearby lymph nodes cannot be assessed, or there is no information available about these nodes. N0 signifies that no cancer cells are found in the nearby lymph nodes. N1-N3 describe the size, location, or the number of nearby lymph nodes that contain cancer cells. Finally, there is the (M)etastasis. A simple division is made into M0 (no distant metastases) and M1(distant metastases). For patients with mHSPC, the TNM staging is T1-4N1-N3M1. (11)

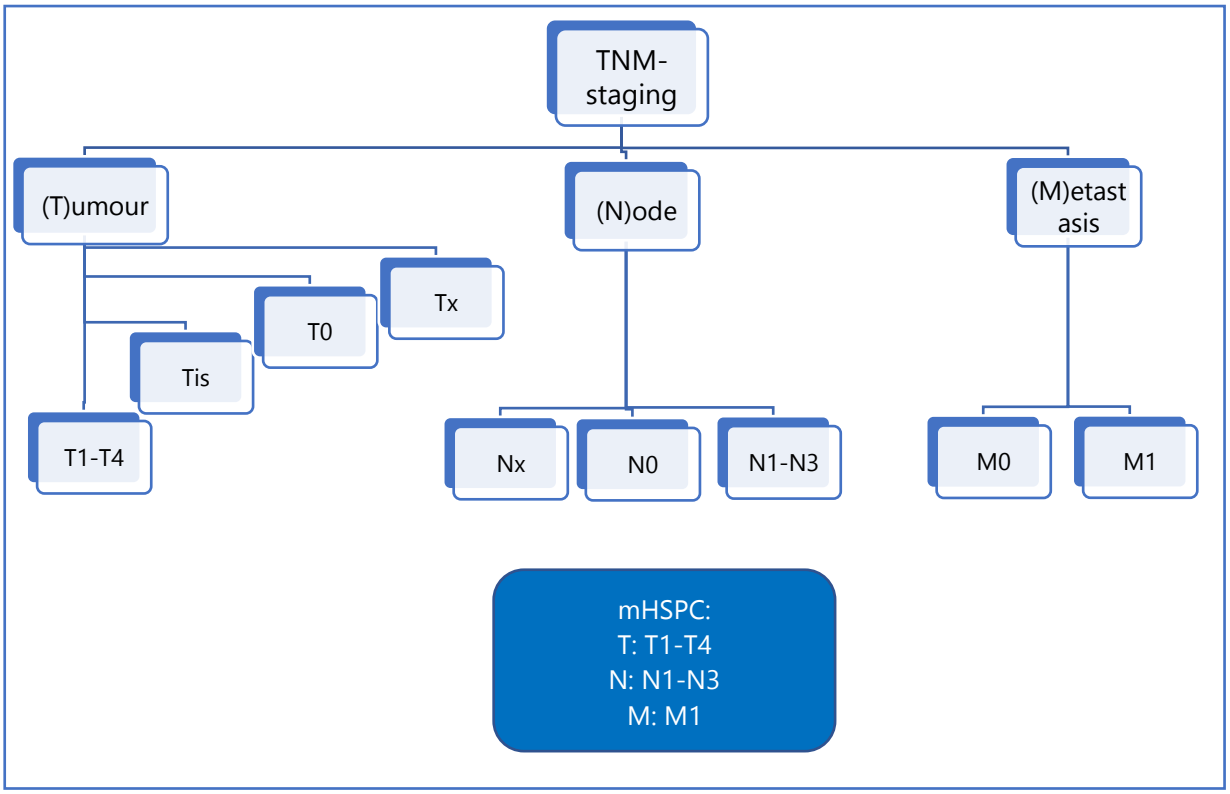


Fig. 2: TNM staging explained

In localized prostate cancer (T1-4,N0,M0), active surveillance is recommended. This entails regular check-ups for PSA-levels and PSA-kinetics. In the locally advanced stage, (T1-4,N1-3,M0) treatment is only recommended in high-risk patients. Prostate cancer is considered high-risk when it is likely to spread or recur. In this stage, radical therapies as well as chemotherapy is recommended. Radical treatment is further divided into cryotherapy, electroporation and ultrasound, prostatectomy and radiotherapy. Chemotherapy consists of docetaxel, which can be offered to patients that start long-term ADT to combine the tumour lysis effect of docetaxel and growth suppressing effect of ADT. If hormone-resistance develops in the localized state, darolutamide combined with ADT can be considered. Darolutamide is an androgen receptor blocker, similar to enzalutamide. (5)

In the metastatic state, the first-line treatment is docetaxel. Additionally, a bilateral orchidectomy can be offered to patients instead of chemical castration to enhance patient compliance and relieve the treatment burden. Furthermore, degarelix can be offered to patients with spinal metastases. (5) Degarelix is a GnrH- antagonist. By inhibiting the release of GnrH, both LH and FSH are quickly and strongly reduced, thus leading to testosterone levels far below castration levels. (12)

If hormone-resistance develops in the metastatic stage, patients can be offered corticosteroids as third-line hormonal therapy. Furthermore, enzalutamide and abiraterone have a marketing authorization for the treatment of metastatic castration-resistant prostate cancer as well. (5)

In short, the treatment guidelines followed in the UK do not provide adequate treatment options for mHSPC. Enzalutamide would thus be the first oncological drug to be granted market approval in the treatment of mHSPC. Although it is the first, it is likely that drugs of the same class of anti-androgens will be granted market approval for the same indication. To understand the benefit of enzalutamide, as well as anticipate what future developments will entail for mHSPC treatment, a closer look at the pharmacological class of anti-androgens is necessary.

2.3 Anti-androgens (AAs)

The class of anti-androgens all inhibit the physiological function of androgen, though through different mechanisms. Testosterone produced by the adrenal glands and the testes is metabolized by enzymes to dihydrotestosterone (DHT), which is an androgen. This androgen then binds to the androgen receptor (AR) located on the membrane of cell nuclei of prostate cells for example, leading to the internalization of the complex of androgen and its receptor into the nuclei. Through internalization, the complex can move from the membrane into the nuclei, which allows for activation of DNA transcription, thus leading to the development of new cells. In pathophysiological circumstances however, this process is uninhibited, thus leading to abnormal growth of prostate cells. The first-generation anti-androgens bicalutamide, nilutamide, and flutamide are steroid analogues for the AR, preventing androgen-AR binding, and thus preventing the activation of DNA transcription which in turn leads to the inhibition of androgen-dependent cell growth. Although the first generation anti-androgens are effective in inhibiting cell growth rapidly, the long-term efficacy is less positive. Notably, after extended use of first-generation anti-androgens, activation of the primary processes that lead to an increase of AR expression are observed, thus more ARs are available and thus more receptors can form a complex with autogenous androgens. Furthermore, the first generation anti-androgens are partial antagonists of the AR. This conveys that under the right circumstances, anti-androgens can also function as agonists. This has been observed when overexpression of ARs occurs. Anti-androgens then stimulate ARs, thus leading to worsening of prostate cancer (PC). (13)

The second generation of AAs was developed to address the major setback of the first generation AAs, namely hormone-resistance and a possible worsening of PC due to AA-therapy. Approved second generation AAs are abiraterone acetate, enzalutamide, apalutamide and darolutamide. Abiraterone

inhibits the enzymes responsible for the metabolization of testosterone into androgen, thus leading to less androgens being available to activate cell growth and division. Enzalutamide, apalutamide and darolutamide all inhibit androgen dependant cell growth through the same mechanism as the first generation AAs. (13) As of yet, only enzalutamide has been studied in the treatment of mHSPC.

To summarize the theory, little is known about the exact causes of prostate cancer, though one of the theories is based on an imbalance of the HPG-axis leading to abnormal (uninhibited) prostate cell growth and maturing. Anti-hormonal therapy has been used for decades in the treatment of prostate cancer, however the need for targeted therapy for the treatment of mHSPC specifically is still unanswered. Enzalutamide, a second generation AA, is the first to be granted approval for the treatment of mHSPC. As mentioned before, aside from the efficacy and safety, the cost-effectiveness also needs to be assessed for this treatment option to be included in the NHS budget. To understand the background of this CE-study, the basics of CE-evaluation will also be discussed.

2.4 Economic evaluation

There are different types of economic evaluations. The cost-benefit analysis (CBA) compares the resource costs per treatment group, and the benefits of both treatments in monetary terms. (14) This type of analysis is well-fitted to explore the most efficient resource allocation when the health benefits are equal between various treatment options for the same disease.

The cost-effectiveness analysis (CEA) compares the resource costs per treatment, and the respective health benefits expressed in a relevant clinical outcome measure. (14) CEAs are useful when little is known about the impact of the disease and its treatment on the quality of life.

Similar to a CEA, is the cost-utility analysis (CUA). This type of analysis compares the resource costs per treatment group, and the effects in a common unit of measure, such as the quality-adjusted life year (QALY). Using the QALY considers the possibility that a treatment affects both the quality of life and the length of life. (14) A CUA will be performed for this economic evaluation, as CUAs are most often used in health technology assessment.

As mentioned in the objectives, the outcome of this CE-study is the ICER. This ratio compares the incremental difference in costs and effects between the intervention (Enzalutamide + testosterone suppression) and the comparator (ADT + testosterone suppression). The effects of the novel treatment and the comparator on the quality (quality of life, QoL) and length of life (life years, LY) can be derived from clinical evidence. A clinical outcome that translates easily into life years, is the OS. The OS describes the length of time that a patient is still alive from the start of treatment. The quality of life is a subjective assessment of patient perception with regards to their health-related well-being. To formulate recommendations with regards to QoL gains and/or losses for novel treatments, the utility values are used. Utility values translate individual subjective patient perceived QoL-data into population based outcomes, which allows for comparison of benefits and risks across different treatment options, as well as different disease areas. This is expedient to stimulate rational use of the healthcare budget. Data about the survival time and the quality of life are thus needed to perform this CE-study.

It was briefly mentioned in the introduction that the ENZAMET trial and the ARCHES trial both assessed the use of enzalutamide in mHSPC. OS data will be extracted from the ENZAMET trial. This is an open-label phase III trial which assessed the efficacy and safety of enzalutamide with cTS compared to ADT with cTS (standard of care) in men with mHSPC. The primary endpoint of the study was OS, and secondary endpoints described progression-free survival (PFS), along with adverse events. A total of 1125 men were randomized, and the median follow-up was 34 months. The number of deaths in the enzalutamide group was significantly less than what was seen in the standard of care group (n=102 vs n=143, P=0.002). The OS estimates at 3 years were 80% for the enzalutamide group and 72% for the

control group based on the Kaplan-Meier survival curves. The incidence of adverse events was higher in the enzalutamide group. (6)

Data with regards to the QoL are extracted from the ARCHES trial. This was a multi-national, double blind phase III trial which assessed the efficacy and safety of enzalutamide combined with cTS vs cTS alone in men with mHSPC. A total of 1150 men were included, stratified by disease volume and prior docetaxel therapy. The primary endpoint was radiographic progression free survival (rPFS). Secondary outcomes assessed the time to PSA progression as well as undetectable PSA levels, time to initiation of new neoplastic therapy, objective response rate, time to deterioration in urinary symptoms, and OS. Furthermore, QoL was assessed, as well adverse events. At the cut-off date after 262 events occurred, a median follow-up of 14.4 months was reached. In the enzalutamide group, 91 (15.9%) events occurred, while 201 (34.9%) events occurred in the control group. Additionally, the enzalutamide group was significantly superior on the aforementioned secondary outcomes. (7) The QoL data have been reported separately in the paper by Stenzl et al. (15) The data about QoL from the ARCHES trial will be used alongside the survival data from the ENZAMET trial in decision analytic modelling to assess the incremental difference in QALYs between enzalutamide with cTS and SoC with cTS for the UK population of mHSPC patients.

The common characteristic of decision-analytic models is the fact that they all describe the movement of patients from one disease state to another. This is necessary, because the efficacy and safety data that result from phase III trials oftentimes covers part of the disease trajectory. Only using the available data from these trials to calculate the cost-effectiveness of a novel treatment would provide distorted CE-results, which lead to inaccurate predictions regarding healthcare expenditures, thus the inefficient allocation of the healthcare budget. When decision-analytic modelling is used, the trial data form the fundament of the model. Based on the best fitted model, data is extrapolated to allow for a better understanding and comparison of the long-term effects regarding both treatment groups. There are different decision-analytic models. Decision tree models and Markov models are the most commonly used in health economics.

Decision trees are well suited to describe 'one-off' decisions, i.e. acute care problems and once-only diseases. (16) This is not representative for the disease trajectory of mHSPC. Markov models describe diseases that develop or evolve over time. Patients are categorized in various disease states, which are all mutually exclusive and exhaustive. This is better suited to describe the disease trajectory in cohort studies. However, the individual tracking of patients is lost in the conventional Markov model, which leads to less accurate estimates of gained LYs per cycle. (16) The Markov trace model is an adjustment to the traditional Markov model. It describes the trajectory of each patient individually by computing the Monte Carlo simulation, which simulates the probabilities of a patient going through each health state in every cycle. (17) This model is best suited to describe the disease trajectory of patients with mHSPC and the treatment in question.

The total framework of costs and effects of the resources included in a CE-study differ based on the theoretical perspective in which it is framed. The theoretical perspective narrates the preferences of the audience with regards to the importance of different cost categories. The societal perspective for example is often used for an all-encompassing view, which includes direct and indirect medical costs, as well as non-medical costs. The healthcare perspective only accounts for the direct medical costs, since these costs are spent from the healthcare budget. The audience for this CE-study is NICE. The NICE provides evidence-based guidance and advice for (public) health practitioners, and social care workers in the UK. It is the main committee providing recommendations regarding (multi)national routine use of new and existing treatments, and the health technology appraisal of novel treatments is usually performed by the NICE. (18) This CE-study can be used as a stepping stone for the appraisal of

enzalutamide by the NICE. Therefore, the design of this CE-study will be based on the requirements set by the NICE. As such, the healthcare perspective will be used for the inclusion of cost categories.

To conclude the theoretical framework, the relevance of enzalutamide in mHSPC originates from the fact that this group of patients is underrepresented in the treatment guidelines in the UK. The ENZAMET and ARCHES trials showed promising results with regards to the efficacy, however, the CE also needs to be evaluated to rationalize the uptake of enzalutamide in the NHS budget. Therefore, a CUA is performed, with the requirements of the NICE guidance for single technology appraisal as the guiding document for narrating the outline of the economic evaluation.

Chapter 3. Research methods

3.1 Model structure

3.1.1 Disease states

The cost-effectiveness of enzalutamide will be assessed by means of a cost-utility analysis. The ICER is expressed as £/QALY. A three state Markov model is used, see figure 3. All patients will start in stable disease (SD), with the proportion of patients experiencing serious adverse events being considered a substate of the SD. This proportion is based on the ENZAMET trial. The cycle length is four weeks, which is in line with most of the monitoring visits as well as other CE-studies for orally administered chemotherapy. After the first cycle, patients can stay in SD, move to progression or to death. Patients can thus only re-enter their current health-state or a new health state, but cannot return to a previous health state.

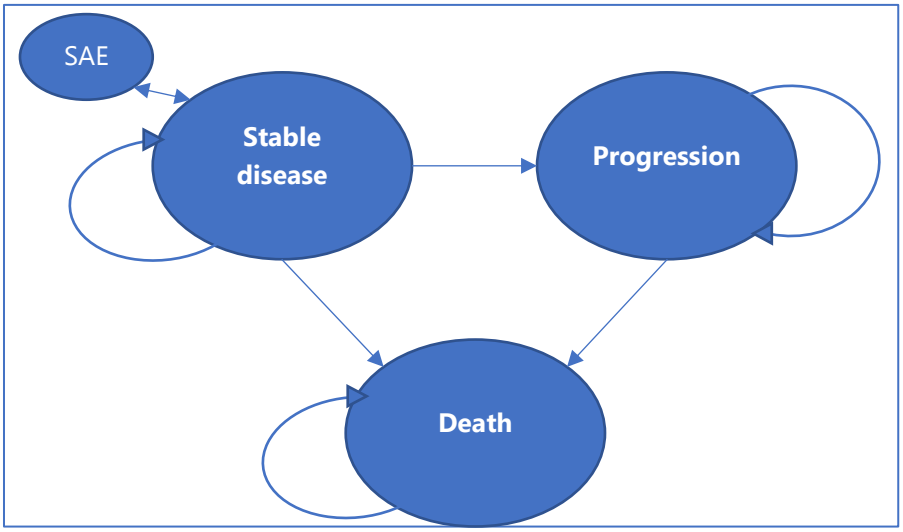


Fig. 3 Three state Markov model

3.1.2 Time horizon

As mentioned in the theoretical framework, the requirements for the model are based on the NICE guidance for single technology appraisal. According to the NICE guidelines, a lifetime horizon should be applied in the model, to account for the long-term effects and costs of the treatment under investigation. Prostate cancer in general has a survival rate of 97.7% at 10 years, however metastatic prostate cancer has a survival rate of 16.6% at 10 years. (19) It is therefore unlikely that the selected patient population survives beyond 15 years. Thus, the time-horizon of the model is 15 years. The follow-up in the ENZAMET trial was four years. Thus, extrapolation of the survival data is needed simulate the disease trajectory over 15 years.

3.2 Extrapolation

The survival curves from the ENZAMET trial published by Davis et al. are used to extrapolate the data. Ideally, estimates are obtained by parametric curve fitting based on individual patient level data. Since this data is not available, the Kaplan-Meier (KM) survival curves are used to apply the Hoyle and Henley method for improved curve fitting. The first step in this method is estimating the patient level data based on the number of patients at risk in both trial arms and the KM curves. The parametric curves are then fitted to these estimated patient level data, and the best fit is chosen based on the visual fit, the most

probable disease course, and the Akaike Information Criterion (AIC)-value. (20) The AIC value elucidates the estimated information loss when a prediction model is fitted over a reference case. A low AIC value indicates less loss in information, thus a higher model quality. There are four parametric model distributions which will be fitted over the reference case; Lognormal, loglogistic, Weibull, and exponential. These distributions use the KM survival data of the reference case to predict the further disease trajectory. The distribution used in this CE-study will be discussed in the results section.

3.3 Treatment

3.3.1 Stable disease treatment

Castration

Both treatment arms receive testosterone suppression. This is either done through surgical castration or medical castration. Surgical castration entails a bilateral orchidectomy. This method is often cheaper when compared to medical castration, simple, and effective in rapidly reducing testosterone levels. However, the psychological invasiveness of the intervention undermines the benefits for most patients and physicians, due to the altered physique of the genitals after castration. As the NICE guidance suggests, it should be offered as an alternative to medical castration, rather than serve as a first treatment option. Naturally, it is expected that the number of patients in the ENZAMET trial who opt for surgical castration is low. Unfortunately, the study flow of the ENZAMET trial is not available, and the proportion of patients that opted for surgical castration cannot be extracted from the trial data. Therefore, the utilization of surgical castration is based on the database study of Garje et al. They investigated the utilization and survival outcomes of surgical castration when compared to medical castration. The National Cancer Database of the US was used to identify patients diagnosed with metastatic prostate cancer between 2004 and 2014. A total of 33,585 patients were identified, of which 31,600 (94.1%) received medical castration, and 1985 (5.9%) underwent surgical castration. Based on these findings, the proportion of patients in this CE-study receiving surgical castration is set as 5.5%. (21)

Medical castration entails continuous testosterone suppression by influencing GnRH which eventually leads to testosterone decline. This can be achieved in two ways. Firstly, direct GnRH suppression is achieved with degarelix, which has been mentioned as a treatment option for castrate-resistant prostate cancer in the NICE treatment guidelines. Direct suppression of GnRH leads to inhibition of LH and FSH production, thus leading to suppression of testosterone production. The second option is the administration of GnRH agonists. This is a remarkable treatment option, since it requires the stimulation of GnRH which paradoxically contradicts the desired effect leading to testosterone suppression. However, the long-term continuous use of GnRH agonists result in exhaustion and insensitivity of the gonadotropic pituitary gland cells, which leads to a decline of LH-FSH production leading to the suppression of testosterone production. GnRH agonists registered in the UK are goserelin (Zoladex), leuprolerin, and triptorelin. All GnRH agonists are available as subcutaneous implants, which can be administered once monthly, once every 6 weeks or once every 12 weeks. Degarelix can only be administered as a once monthly implant. Additionally, the first month dose of degarelix is doubled to serve as a loading dose at first use. (22) This negatively affects patient compliance, and therefore the proportion of patients that receive degarelix in this CE-study is set at 19.9%. The proportion for the remaining treatment suppression is divided equally. See table 1 for an overview of the applied proportions for cTS.

Table 1. cTS treatment proportions

Treatment	Proportion
Bilateral orchidectomy	0.055
Degarelix	0.199
Goserelin	0.249
Leuprolerin	0.249
Triptorelin	0.249

Concomitant medication

Aside from castration, concomitant medication mentioned in the ENZAMET trial plan are calcium carbonate and vitamin D. They are considered standard of care for the prevention of osteoporosis during androgen deprivation therapy because of the higher incidence of osteoporosis observed with ADT. The combination is therefore included in this CE-study. A variety of preparations contain calcium carbonate and/or vitamin D. The most widely available option in the UK is Caltrate©, which is a combined preparation of 800 IE vitamin D and 500 mg calcium carbonate. The average price of a 60 pill bottle is included in this CE-study.

Investigated treatment

The intervention arm in SD receives 160 mg enzalutamide once daily, provided as four capsules of 40 mg administered orally. The ENZAMET control group in SD was randomized to different treatment options, which represented the standard of care (SoC). This treatment arm received first-generation AAs. The first-generation AAs registered in the UK are bicalutamide and flutamide. Bicalutamide is administered as once daily 50 mg capsules taken orally. Flutamide is administered once daily in a dose of 750 mg, taken as three oral capsules of 250 mg.

3.3.2 Progressed disease

For this specific patient population, disease progression automatically means that the description of the study population changes. Notably, disease progression signifies failure of anti-hormonal therapy. Thus, the cancer continues to grow and/or spread despite castration levels of testosterone. Therefore, the trial population of mHSPC patients after progression is best described as metastatic castration-resistant. The treatment options after progression are based on the NICE guidelines for the treatment of castration-resistant prostate cancer, and differs slightly based on the previous treatment arm in SD.

Enzalutamide arm

Patients that progressed after treatment with enzalutamide have three options for treatment. First, patients can choose to not receive a new line of chemotherapy and thus only receive best-supportive care (BSC) to relieve symptoms. Next, patients can receive an additional line of chemotherapy with abiraterone acetate (Zyntiga). As mentioned in the theoretical framework, abiraterone is also a second generation AA, however its mechanism of action is based on blockage of the enzymes that metabolize testosterone into androgens. Treatment with abiraterone is accompanied by the oral administration of prednisolone. Abiraterone is administered as oral therapy, taken once daily in the form of two tablets containing 500 mg abiraterone acetate. Prednisolone is also administered as oral therapy, taken as one tablet of 10 mg daily. Finally, patients could also receive docetaxel treatment, administered intravenously in a dose of 75 mg/m^2 for a maximum of six cycles of three weeks. Prednisolone is co-administered during docetaxel treatment in a dose of 10 mg, taken as oral tablets of 10 mg once daily. The proportion of patients that receive each treatment option are based on table S4 of the supplementary appendix of the ENZAMET trial, see table 2 for the relevant treatment options and proportions.

SoC arm

For the standard of care group after progression, the same treatment options as the enzalutamide group are available. Additionally, patients in the SoC arm can receive enzalutamide in progressed disease, seeing as this is one of the options for castrate-resistant prostate cancer. This option is exclusive for the SoC arm, because the investigators of the ENZAMET trial specified that treatment with enzalutamide stops after progression for the enzalutamide group. Enzalutamide in progressed disease is administered once daily as four capsules of 40 mg taken orally.

Table 2. Proportions post-progression treatment options

Treatment	**Proportion Enza arm**	**Proportion SoC arm**
Enzalutamide	-	0.38
Abiraterone acetate (Zyntiga) + prednisolone	0.315	0.30
Docetaxel + prednisolone	0.308	0.19
Best supportive care	0.377	0.13

3.4 Input parameters

3.4.1 Health-related quality of life (HRQoL)

According to the ENZAMET trial protocol, data regarding the HRQoL were collected in the trial. However, this data has only been reported at the European Society for Medical Oncology (ESMO) 2019 conference in the prostate cancer session, and no published article is available. (23)Therefore, the HRQoL data from the ENZAMET trial could not be used for the model. Instead, data from the ARCHES trial is used for this economic evaluation. Although similar to the ENZAMET trial with regards to the intervention, the outcomes and the patient population, the main difference between ENZAMET and ARCHES is the control group. In ENZAMET, the control group receives cTS plus first-generation AAs, whereas in ARCHED, the control group only receives cTS. The baseline utility for mHSPC patients starting enzalutamide, and the utility increment per cycle of enzalutamide can thus be readily used from the ARCHES trial. The utility increments per cycle for ADT plus NSAA will also be used, due to the fact that no alternative literature can be found regarding this treatment option in mHSPC. Utility increments will only be applied for 73 weeks since the follow-up for QoL-data in the ARCHES trial was 73 weeks. Thus, the utility increments for both treatment options in stable disease will be applied to cycle 1 – 18. From cycle nineteen onwards, the utility values for stable disease will stay the same as in cycle eighteen.

Patients in the ARCHES trial were only followed until disease progression. Thus, no utility values were gathered for patients that showed radiographic progression. For this CE-study, patients that progressed after treatment with enzalutamide or SoC, are considered to be castration-resistant. Therefore, the utility value of the PD state is based on the study of Lloyd et al. This study investigates the HRQoL and HR-utilities in metastatic castrate resistant prostate cancer patients in the UK. Patients were categorized in four disease states: 1. Asymptomatic/mildly symptomatic before chemotherapy; 2. Symptomatic before chemotherapy; 3. Currently receiving chemotherapy, and 4. Post-chemotherapy. For this CE-study, all patients in PD are considered to be symptomatic, and they could either choose to receive chemotherapy or best supportive care. Therefore, the weighted average utility of patients in state two and three of Lloyd et al. was used to represent all patients in the PD state of the model. (24) Table 3 provides an overview of the utility values that are used in this CE-study.

Table 3. Utility values used in the CE-study

Description	Value	Source
Baseline utility	0.74	Stenzl et al, results from the ARCHES trial
Utility increment Enzalutamide	0.028	Stenzl et al, results from the ARCHES trial
Utility increment SoC	0.019	Stenzl et al, results from the ARCHES trial
Utility PD	0.642	Lloyd et al, weighted average of category 2 and 3

3.4.2 Adverse events

The type and frequency of adverse events are extracted from the ENZAMET trial. Only serious adverse events graded based on the common terminology criteria for adverse events (CTCAE) score with a grade 3 or higher are included in the economic evaluation. Furthermore, only SAEs with a frequency of 5% or more in either of the treatment arms are taken into account. This is due to the fact that the adverse event management and the utility impact of these SAEs are expected to be considerable and thus will be able to impact the ICER substantially. The duration of the adverse events, as well as the utility decrements, are extracted from the single technology appraisal performed by the Aberdeen HTA group for Enzalutamide in the treatment of metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy. (25) Table 4 provides an overview of the included adverse events information.

Table 4. Adverse event information

Description	Incidence Enza	Incidence SoC	Disutility	Duration (days)
Neutropenia	0.0551	0.0287	0.09	10.50
Febrile neutropenia	0.0657	0.0573	0.12	10.50
Fatigue	0.0551	0.0072	0.13	84.00
Hypertension	0.0764	0.0448	0.15	10.50

3.4.3 Costs and resource use

All costs parameters which are considered direct medical costs, will be included in the model. For stable disease, this entails drug related costs (acquisition costs for all treatment options, concomitant medication, administration costs), healthcare resource use costs (monitoring visits, diagnostic tests), and adverse event management costs. For progressed disease, drug related costs, and healthcare resource use costs are included, as well as end of life costs. No adverse events are taken into account in PD, therefore no adverse event management costs are included for this part of the population.

The resource use differs per disease state. For stable disease, resource use is based on the ENZAMET trial assessment plan. All laboratory check-ups are performed once every three months with the exception of the liver function test, which is performed every month. See figure 4 for the excerpt from the trial assessment plan.

Where possible, the most recent cost values will be used. If these are not available, then the appropriate inflation rates will be applied based on the date of the cost value. Furthermore, to extrapolate the costs and effects into the future, a discount rate of 3.5% will be applied in accordance with the NICE guidelines for health technology appraisals. Finally, the number of patients per cycle will be half-cycle corrected to account for patients leaving at various times during a cycle.

ENZAMET

6 ASSESSMENT PLAN

6.1 *Schedule of assessments*

	Screening	Baseline[1]	On Study Treatment			After study treatment	
	Within 28 days prior to randomisation	Within 7 days prior to randomisation	Day 29[2] (±7 days)	Every 12 weeks (±1 week)[3] from randomisation until clinical progression[4]	At progression[5] (PSA and clinical) and end of treatment for reasons other than progression	30-42 days after the last dose of study treatment	Every 12 weeks (±2 weeks)
Informed consent	X						
Clinic assessment[6]	X	X	X	X	X	X	
Blood tests[7]:							
Haematology (CBE)	X	X	X				
Biochemistry (EUC, LFTs[8])	X	X	X	X	X		
PSA	X	X	X	X	X		
Bloods for translational research		X		X (wk 24 only)	X (first progression only)		
Imaging[9]:							
CT of abdomen and pelvis	X				X		
CXR or CT chest	X				X		
Whole body bone scan (WBBS)	X				X		
Compliance[10]			X	X (wk 12 only)			
Concomitant medications			Drugs used at the time of SAEs, and drugs known to interact with enzalutamide[11]				
Adverse Events[12]			X	X	X	X	
Quality of life assessments (EORTC QLQ C-30 PR-25, EQ-5D)		X	X	X	X	X	
Resource use form			X	X	X	X	
Patient status						X	X
Subsequent treatment for prostate cancer						X	X

Fig. 4 Assessment plan of the ENZAMET trial.

The resource use in progressed disease varies for patients that only receive BSC and patients that also receive second-line chemotherapy. This data was not available in the ENZAMET trial. Therefore, the resource use in progressed disease was extracted from the NICE technology appraisal 255, assessing cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. (26)

3.5 Probabilistic analyses

The input parameters for costs and utilities are sampled for the probabilistic sensitivity analysis (PSA). The PSA is a multivariate analysis in which the same calculations as in the deterministic model are repeated a number of times. This provides an indication of the spread in possible ICERs and the probability of these ICERs being accepted as cost-effective. Some parameters are not sampled for the PSA, because these are non-variable. Fixed parameters that are not sampled for the PSA, are the cycle length, the number of cycles, the number of patients per arm, the inflation rates for costs, and the list price of enzalutamide. For sampling the parameters, the beta distribution is used for all utility values. The gamma distribution is used for sampling costs, duration of adverse events and the resource use. Where provided, the standard error (SE) is used for completing the PSA. If the standard error is not provided, it is calculated as either 10% or 20% of the mean value. The distinction between 10% and 20% is made based on the likelihood of a parameter being widely variable. As such, the SE that equals 20% of the mean is used for all cost parameters and all durations in the model. The SE that equals 10% of the mean is solely used for utilities.

Additionally, at least two scenario analyses will be performed. These analyses provide deterministic results for a different scenario compared to the base case scenario. For example, the chosen parametric model distribution can be altered, and the impact of that difference can then be analysed by comparing the base case deterministic ICER to the deterministic ICER of the scenario analysis. The scenario analyses performed in this study will be based on the deterministic outcomes to assess the impact of the most remarkable features of the model.

Chapter 4. Results

4.1 Parametric curve fitting

The results of the different parametric models fitted over the survival data of the ENZAMET trial for both OS and PFS can be seen in figures 5 and 6. All AIC values can be found in table 5. The lowest AIC values for OS are achieved with the Weibull distribution. The best visual fit for OS is also achieved with the Weibull distribution, and based on the disease trajectory and expected survival of mHSPC patients, the Weibull distribution represents this population best. Thus, the Weibull distribution is used for extrapolation of the OS data. The lognormal distribution is used for the PFS data based on the AIC, visual fit and disease trajectory.

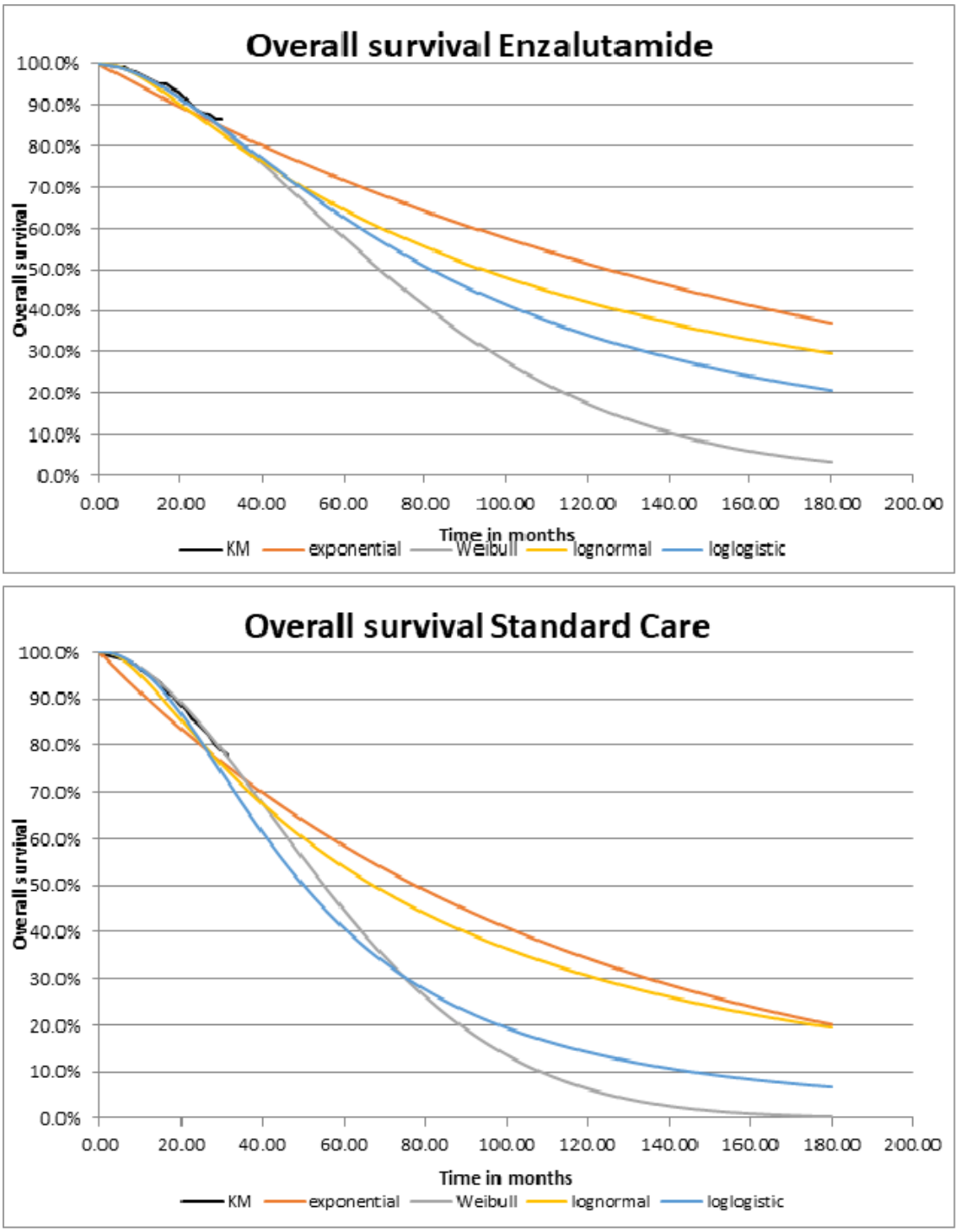
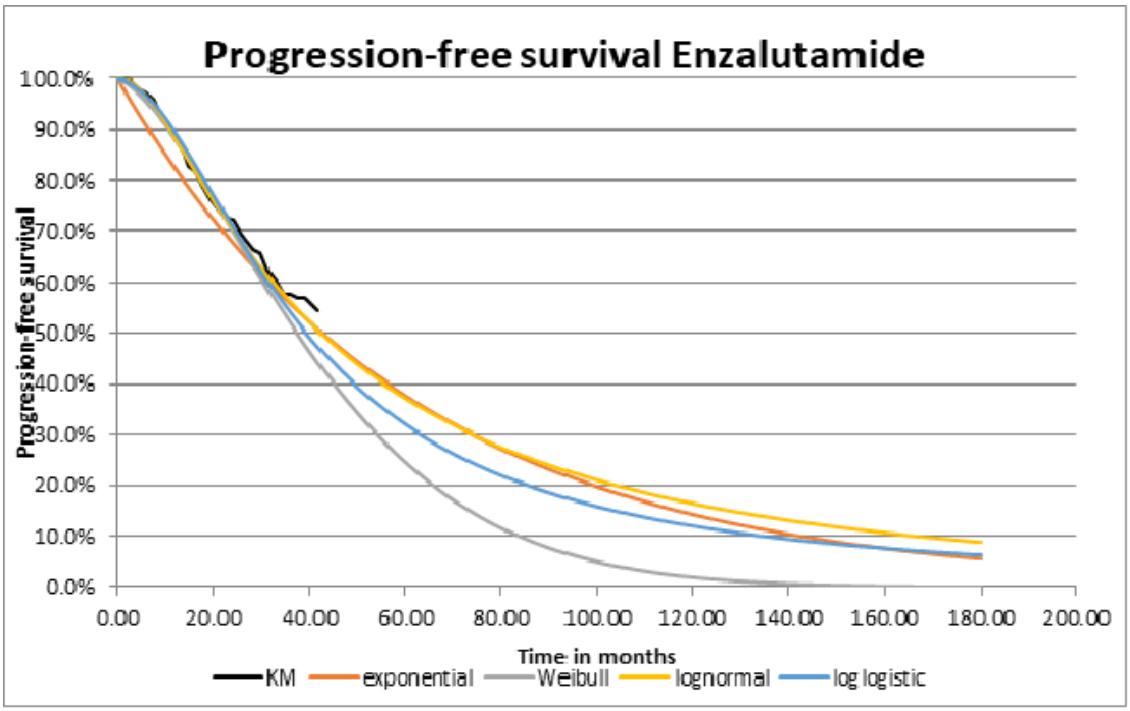


Fig. 5 OS parametric survival curves



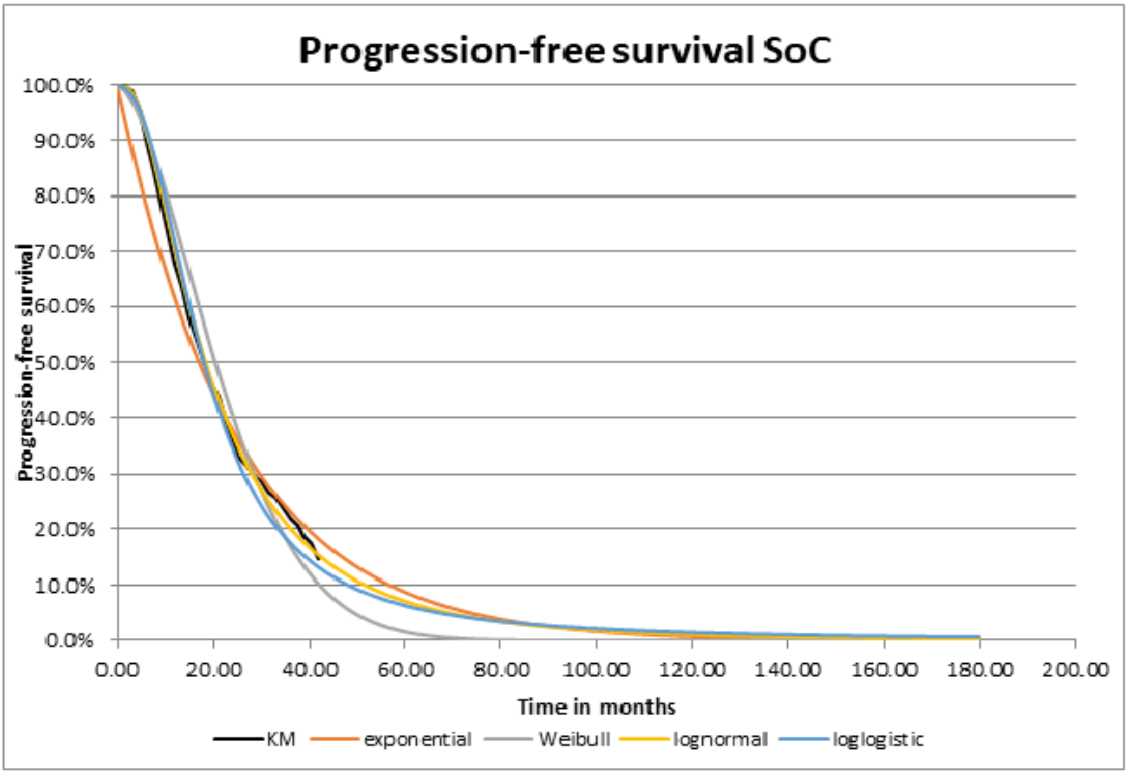


Fig. 6 PFS parametric survival curves

Table 5. AIC values for the parametric survival curves. Green boxes highlight the lowest AIC value.

Treatment	Outcome	Distribution	AIC
Enzalutamide	OS	Exponential	1739.944
		Weibull	1699.609
		Lognormal	1721.95
		Loglogistic	1704.135
	PFS	Exponential	1938.894
		Weibull	1932.223
		Lognormal	1918.189
		Loglogistic	1922.947
Treatment	**Outcome**	**Distribution**	**AIC**
Standard of Care	OS	Exponential	1868.931
		Weibull	1808.696
		Lognormal	1818.009
		Loglogistic	1809.662
	PFS	Exponential	1889.359
		Weibull	1864.02
		Lognormal	1795.16
		Loglogistic	1795.482

4.2 Base case scenario

The ICER in the base case scenario is £125,853 per QALY gained. The disaggregated results are presented in table 6. The incremental cost difference is negative, indicating that treatment with enzalutamide could possibly induce cost-savings. However, the incremental difference in QALYs is also negative, whereas the incremental difference in life years is positive, indicating that enzalutamide treatment leads to a lower quality of life, while increasing LYs. See table 7 for an overview of the summarized results. This is due to the higher incidence of adverse events in the enzalutamide group, leading to a bigger disutility caused by these adverse events. Based on these findings, two scenario analyses were performed. The first scenario describes the CE-results if the same adverse events are implemented in the PD state for patients that were previously treated with SoC. The adverse events are drug specific, thus it can be expected that the same adverse events would occur. The second scenario describes the CE-results if the frequency of adverse events in the enzalutamide group are 20% higher when compared to SoC. The SoC entails anti-androgen therapy, similar to enzalutamide, thus the safety profile should in theory be comparable. Finally, the multivariate probabilistic sensitivity analysis was performed to assess the range of ICERs that the included input parameters could result in.

Table 6. Average patients outcomes over 15 years:

	Enzalutamide	Standard of care	Increment
Treatment related costs	£164,448	£13,352	**£152,975**
Resource use	£3,888	£2,108	
Adverse events	£423	£324	
Total costs in stable disease	**£168,759**	**£15,784**	
Post-progression treatment costs	£145,473	£347,144	**-£204,345**
Post-progression resource use	£17,161	£19,265	
End of life costs	£1,866	£2,436	
Total costs in progression	**£164,501**	**£368,845**	
Accrued lifeyears in stable disease	4.08	2.15	**1.58**
Accrued lifeyears in progression	3.53	3.89	
Total lifeyears	**7.62**	**6.04**	
QALYs accrued in stable disease	3.13	1.62	**-0.40**
QALYs accrued in progression	2.27	2.50	
QALYs lost due to adverse events	2.37	0.69	
Total QALYs	**3.03**	**3.43**	

Table 7. Summarized results base case scenario

Description	Incremental outcome	ICER
LYs	1.58	-£32,488
QALYs	-0.41	£125,853
Costs	-£51,370	

4.3 Scenario 1: Addition of enzalutamide adverse events in the PD state.

In scenario 1, the incremental difference in QALYs describes a QALY gain in favour of enzalutamide after inclusion of the adverse events for enzalutamide in the PD state, see table 8. This is expected since the number of patients of the SoC group that end up in the PD state is higher than the number of patients treated with enzalutamide in the SD state. The deterministic ICER in scenario 1 changed from £125,853 to -£223,176 per QALY, which implies cost-savings and effect gains when treating patients with enzalutamide in mHSPC.

Table 8. Summarized results scenario 1

Description	Incremental outcome	ICER
LYs	1.58	-£32,488
QALYs	0.23	-£223,176
Costs	-£51,370	

4.4 Scenario 2: Adverse events frequency in enzalutamide group 20% of SoC group.

Table 9 provides an overview of the summarized results for scenario 2. Similar to scenario 1, the ICER in this scenario is also negative, namely -£45,118 per QALY, which indicates a cost-saving effect and a gain QALYs. This scenario does show a bigger incremental QALY gain compared to the previous scenario.

Table 9. Summarized results scenario 2

Description	**Incremental outcome**	**ICER**
LYs	1.58	-£32,502
QALYs	1.14	-£45,118
Costs	-£51,391	

4.5 Probabilistic sensitivity analysis (PSA)

The results of the PSA are presented in table 10. The ICER ranges from -£90,421.82 to -£1,731.04 which implies that all possible ICERs in the base case scenario lead to cost saving per QALY gained, though this is not necessarily the case. This finding will be further explained in the discussion.

Table 10. PSA results

Incremental difference outcome	**Average**	**Minimum**	**Maximum**
LYs	1.57	- 0.13	2.93
QALYs	- 0.42	- 2.51	0.98
Costs	- £40,032.58	- £88,613.38	£4,344.91
ICER	£ 95,315.67	- £ 90,421.82	- £ 1,731.04

Chapter 5. Discussion

5.1 Results discussion

The base case scenario showed that the ICER of enzalutamide in the treatment of mHSPC in the UK cannot be considered cost-effective when tested against the NICE thresholds of £20,000 to £30,000 per QALY gained. The PSA showed that the average ICER is £ 95,315.67, ranging from - £ 90,421.82 to £ 1,731.04 per QALY. However, the ICER range does not represent all the possible ICERs accurately, due to the fact that both the costs as well as the effects can range from positive to negative values. To further explain this, the minimum and maximum ICER both represent a combination of the most extreme outcomes. In this study, the most extreme outcomes are negative, thus leading to a negative ICER range. However, some combinations of costs and effects could entail both positive outcomes, positive and negative outcomes simultaneously, or both negative outcomes. As a result, the possible ICERs can range from negative values to positive values. Thus, the minimum and maximum ICERs do not represent this range, rather they only represent what the ICER would be, should minimal costs and maximal effects be present, or maximal costs and minimal effects. Therefore, the CE plane is more valuable in providing recommendations with regards to the CE of enzalutamide. See figure 7.

As can be seen in figure 7, about 70% of all possible ICERs are a consequence of a loss in both QALYS and costs. This indicates that the treatment with enzalutamide could induce cost-savings in most cases, but is more often than not associated with loss of QALYs. This loss can be explained through the higher incidence of adverse events in the enzalutamide group. In particular, fatigue has almost a ten-fold higher incidence in the enzalutamide group. This is noteworthy, seeing as the comparator and intervention both belong to the anti-androgens. Drugs from the same pharmacological class often have similar adverse events profile. Nevertheless, in the base case scenario, the treatment effects of enzalutamide are positive when it comes to the extension of LYs, but negative when it comes to QALYs. This finding echoes the results of Stenzl et al. with regards to the treatment benefits of enzalutamide. (15) They found that the time to worsening of QoL was extended in the enzalutamide group, as well as PFS, but no significant differences where observed in the QoL for patients treated with enzalutamide when compared to ADT.

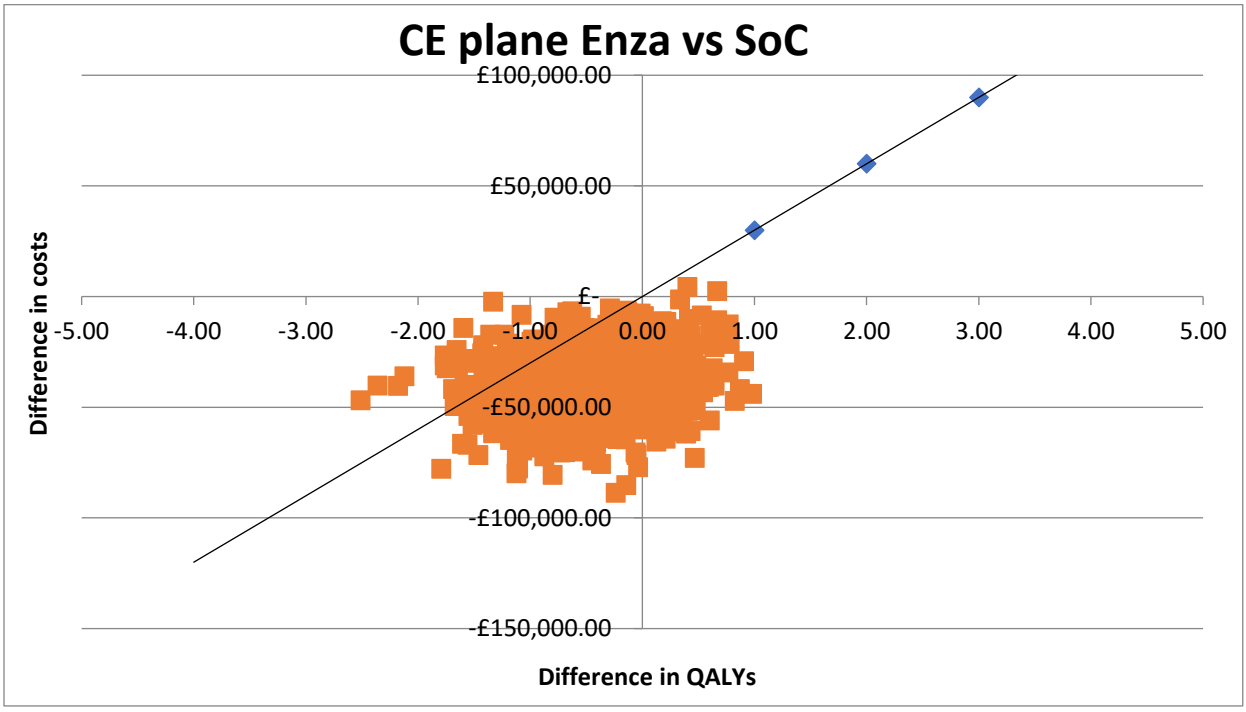


Fig. 7. CE-plane for enzalutamide compared to SoC. The linear line demonstrates the threshold value of £ 30,000 per QALY gained.

The scenario analyses considered alterations to the inclusion of adverse events in the model. In the first scenario, the same adverse event incidences, disutilities and costs were applied to all newly progressed patients in the SoC arm. This is because enzalutamide is also recommended as an option in metastatic castration resistant prostate cancer after failure of hormone therapy before chemotherapy is indicated. Since adverse events are mainly drug specific instead of disease specific, it can be expected that the same adverse events as observed in the ENZAMET trial occurred. The costs and disutilities are only applied to the proportion of newly progressed patients that were given enzalutamide after SoC. In this scenario, the deterministic ICER was -£223,176, due to an incremental positive difference in QALYs (+0.23) and negative difference in costs (-£51,370). Thus, in scenario 1, treatment of mHSPC patients with enzalutamide induces cost-savings while increasing QALYs. This is considered highly cost-effective. Although promising, it should be mentioned that inclusion of adverse events only for the enzalutamide group of patients in progressed disease is not accurate. Ideally, the incidences of adverse events, as well as their disutilities and treatment costs, are included for all post-progression treatments in both the intervention group and the control group. This is mostly relevant for the adverse events of the docetaxel treatment since the proportion of patients receiving this treatment after progression is vastly different (Enzalutamide group = 0.308 ; SoC = 0.19). The adverse event incidence for docetaxel is then by default higher in the enzalutamide group, thus leading to a bigger loss of QoL and more costs relatively. This could lead to a smaller negative difference in incremental costs, or possibly a positive difference in costs, as well as a greater loss of QALYs in the enzalutamide group, thus leading to the CE-plane shifting further left. The possibility of enzalutamide being CE is then smaller.

In the second scenario, the frequency of adverse events in the enzalutamide group is based on the incidence of adverse events in the SoC group. As mentioned before, the SoC and enzalutamide are all considered in the same pharmacological class of drugs. Although differences between these drugs are existent in both effects and side effects, the consensus is that drugs in the same pharmacological group are comparable. Therefore, the safety profile of enzalutamide should in theory be comparable to the SoC. Scenario 2 is thus simulating a comparable safety profile through increasing the incidence of the included SAEs as observed in the SoC group by 20% for the enzalutamide group. The deterministic ICER is then -£45,118, with the incremental difference in QALYS being 1.14, thus indicating that enzalutamide results in QALY gains as well as cost-savings.

In short, the results showed that enzalutamide cannot be considered cost-effective in the base case scenario, despite the possible cost-savings. This is due to the high incidence of adverse events in the enzalutamide group, which leads to a bigger loss of QALYs. However, the loss of QALYs due to adverse events can be compensated if the safety profile of enzalutamide is targeted. As mentioned before, enzalutamide has proven to increase the OS in mHSPC patients, and the time to worsening of QoL was extended as well. Early treatment of mHSPC patients with enzalutamide is thus still relevant. As such, the loss of QALYs due to adverse events needs to be compensated for enzalutamide to be acknowledged as a treatment option in mHSPC. Influencing the burden of the adverse events can for example be achieved by providing pre-medication for SAEs that would otherwise result in substantial disutility. Costs for premedication could add to the monetary burden of enzalutamide. However, the costs for treatment of SAEs are less in this hypothetical arrangement, therefore the overall costs of treatment would stay the same, whereas less QALY loss is induced.

The cost-effectiveness of enzalutamide in mHSPC is not only up for assessment by NICE. Zhang et al. performed a CE analysis as well for the USA and China scenario. (27) Similar to this study, the treatment outcomes were extracted from the ENZAMET trial, a Markov model was created, and the Weibull distribution was chosen to perform the CE-analysis. The utility values for stable disease and progressed disease differ, since this study focused on the UK patient population whereas Zhang et al. assessed a different target population. The most noteworthy difference is the fact that utility values were invariable

in their model, regardless of the influence of adverse events. The authors concluded that the ICERs were $430,933.95/QALY and $225,444.74/QALY for the USA and China population, respectively. Enzalutamide was not considered cost-effective when tested against the threshold values of $100,000.00/QALY in the US and $28,988.40/QALY in China. (27)

Similar to these results is the most recent paper by Sung et al. In this study, five treatment options (ADT alone, ADT+Docetaxel, ADT+Abiraterone, ADT+ Apalutamide, ADT + Enzalutamide) which could all be considered for mHSPC patients were compared with regards to their treatment effects and cost-effectiveness for the US population. The authors found that abiraterone + ADT represented high-value healthcare the most with a deterministic ICER of $38,897 per QALY. The deterministic ICER for Enzalutamide + ADT was $509,813 per QALY, which is not considered cost-effective when tested against the US ICER threshold. (28)

To conclude the discussion of the results, enzalutamide has proven its effect on OS and PFS, and the costs for treatment vary widely in different CE-models due to the variety in input parameters. The main contributor to the loss of QALYs in this model can be attributed to the higher incidence of adverse events in the enzalutamide group, and a targeted approach to prevent these adverse events could lessen the burden of treatment. Aside from the results, a few other points should be discussed. First, a few underlying assumptions and decisions with regards to the model need to be addressed.

5.2 Model structure

As mentioned in the results, the chosen distribution for OS was Weibull, and the distribution for PFS was lognormal. This was based on the AIC value, the visual fit, and the expected disease trajectory. Whereas the substantiation of the chosen distribution is a strength of this study, the mathematical risk to choosing the lognormal distribution can be a threat to the accuracy of the extrapolation. Notably, the lognormal distribution is characterised by a rapid decline followed by a long tail at the end that continues long past the rational point of the disease trajectory. This is especially relevant for extrapolated models in which the KM data is less than half of the total time horizon, which is the case for this CE study. The PFS in both groups is then overestimated, which distorts the LYs accrued in stable disease and progressed disease. However, since the effect of this distortion would be applicable for both treatment arms, it is expected that the ICER will not be affected.

Furthermore, the ENZAMET investigators defined two types of PFS, namely PFS based on PSA-levels, and clinical PFS based on radiographic imaging and (worsening) symptoms. The KM-curves for both types of survival differ, see figure 7. The main difference is the rate of decline. Notably, the decline in PSA-based PFS starts earlier when compared to clinical PFS, even though the cut-off values are roughly the same. The paper mentions that both treatment options are continued until clinical disease progression. This is why the KM-curves for clinical PFS have been used in this CE-study. Even though this is legitimate based on the design of the ENZAMET trial, it does create an opportunity for careful discussion whether the current method of prostate cancer progression diagnosis should still be the golden standard. Earlier diagnosis of disease progression could possibly influence the eventual treatment outcomes should patients decide to start second-line chemotherapy. Evaluation of the literature with regards to treatment outcomes and the specification of disease progression is needed to assess whether there is an added benefit of earlier detection of disease progression.

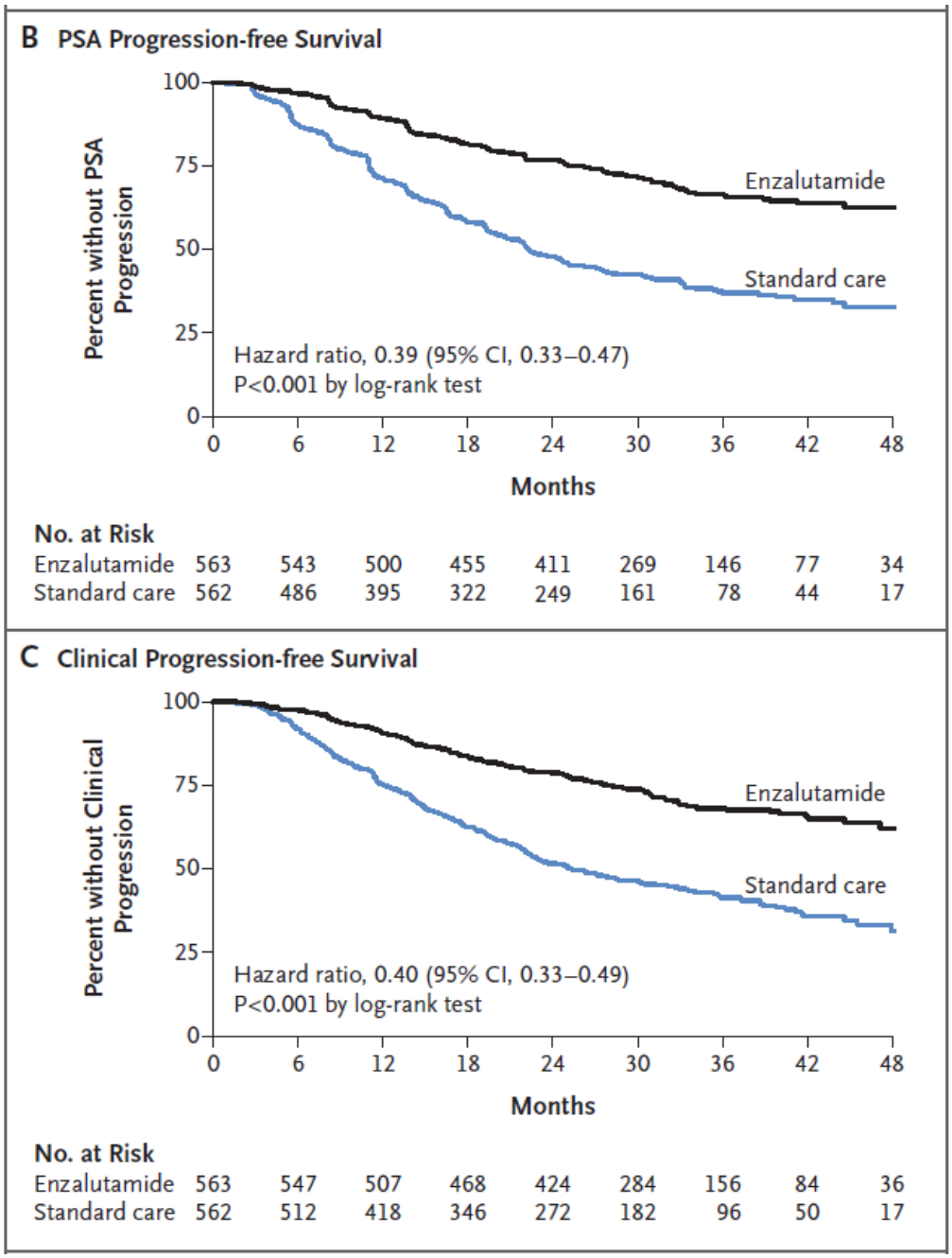


Fig. 7 PFS KM curves ENZAMET trial.

A final point that should be addressed with regards to the model structure is the post-progression treatment. The proportions of patients receiving each option were based on the ENZAMET trial. However, table S4 from the trial shows more treatment options aside from the ones included in this CE-study. This is because the included treatment options are also mentioned in the NICE guidelines for the treatment of castration-resistant prostate cancer. Additionally, the included treatment options are also the three most commonly administered post-progression treatments in the trial population. Therefore, the limited inclusion of the treatment options mentioned in the trial is valid.

5.3 Input parameters

There are some strengths and limitations to the included input parameters. Firstly, the survival data as well as the QoL data are accurate depictions of the disease trajectory and the influence of therapy on this trajectory. This improves the quality of the results presented in this CE-study. Furthermore, the resources are based on the trial assessment plan of the ENZAMET trial. The investigators of the trial clarified that the monitoring visits and the laboratory diagnostics have been set up according to the real-world requirements for healthcare resources in prostate cancer patients. Therefore, the included resources pose as an advantage to the external validity of this CE-study. However, the values of the included resources were more difficult to extract. Different studies were used for a variety of input parameters. This makes the values by default less robust due to the fact that different studies have different trial populations, trial endpoints, and comparative treatments. In other words, the sources which were used to extract the values for the input parameters from, are heterogenous, and therefore less reliable. Ideally, a tornado diagram could elucidate the most influential input parameters, and justification of those resources could then be further assessed for possible ameliorations. Especially for this study, it would have been of great benefit to assess what input parameters should be further researched. However, a tornado diagram has not been incorporated in the analysis due to the appointed timeframe. Inclusion of a tornado diagram in CE- analysis should be incorporated in future CE-studies.

A different aspect with regards to the input parameters which needs mentioning, is the exclusion of premedication. In ENZAMET, no premedication was administered, and therefore, this was excluded from the CE-analysis. However, the results showed that the loss of QALYs in the enzalutamide group is mainly due to the higher incidence of adverse events. Premedication is usually administered to prevent adverse events that substantially impact the quality of life perception of the patients getting treated. It would have been interesting to see what the impact would be of administering premedication prior to enzalutamide treatment in mHSPC patients. This has not been incorporated in the base case scenario or the scenario analyses performed in this CE-study, due to the fact that no information is available with regards to the difference in incidence and disutility of enzalutamide adverse events when premedication is administered. While this is a shortcoming of this CE-study and it could provide to be the tipping point for enzalutamide to be considered cost-effective, it also provides an opportunity for future research to address this knowledge gap.

Chapter 6. Conclusion and policy implications

This study assessed the cost-effectiveness of the simultaneous use of enzalutamide and continuous testosterone suppression compared to the combination of first-line anti-androgens and continuous testosterone suppression in mHSPC patients in the UK. The cost-utility analysis showed that the base case ICER is £125,853 per QALY gained. When tested against the NICE threshold for life-extending technology appraisals of £30,000, the use of enzalutamide cannot be considered cost-effective in the base case scenario. The CE-plane showed that most ICERs induce cost-savings as well as QALY losses, while the survival time has been proven to be extended. The QALY losses are due to the higher incidence of adverse events in the ENZAMET trial when compared to the control group. Though unconventional based on the base case scenario, enzalutamide can still be considered cost-effective provided that the adverse events incidence and disutility are addressed. This could be done through the administration of premedication for example. More research is however needed to determine how exactly these adverse events can be addressed. Most importantly, the current guidelines do not provide targeted treatment for mHSPC patients, and enzalutamide is the first to address this lack of therapies. Therefore, policy makers should consider whether enzalutamide, despite the loss of QALYs, could prove to be of added value for these patients. Furthermore, enzalutamide is not the only existing anti-androgen, and thus it can be expected that future trials will assess the efficacy of authorized second-generation anti-androgens such as abiraterone and darolutamide in mHSPC patients. The consideration for policy

makers then lies in whether timely patient access by recommending enzalutamide is more important, or improved patient outcomes but delayed patient access when recommending other second-generation anti-androgens is preferred. In any case, this CE-study is pioneering a new class of treatment options in mHSPC patients, and it provides stepping stones for future research in the field of health technology assessments of anti-androgens specifically.

References

1. UCLA Health. *What is Prostate Cancer. https://www.uclahealth.org/urology/prostate-cancer/what-is-prostate-cancer (accessed 23 June 2021).*
2. Cancer Research UK. *Prostate cancer statistics. https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/prostate-cancer#heading-Zero (accessed 19 January 2021).*
3. NHS UK. *Prostate Cancer. https://www.nhs.uk/conditions/prostate-cancer/ (accessed 26 January 2021)*
4. National Cancer Institute. *Castrate-resistant prostate cancer. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/castrate-resistant-prostate-cancer (accessed 16 February 2021).*
5. National Institute for Health and Care Excellence. *Prostate cancer: diagnosis and management NICE guideline [NG131]. https://www.nice.org.uk/guidance/ng131/chapter/Recommendations#ftn.footnote_1 (accessed 23 June 2021).*
6. Davis ID, Martin AJ, Stockler MR, Begbie S, Chi KN, Chowdhury S, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. *New England Journal of Medicine* 2019; 381(2): . https://www-nejm-org.proxy.library.uu.nl/doi/full/10.1056/nejmoa1903835 (accessed 23 June 2021).
7. Armstrong AJ, Szmulewitz RZ, Petrylak DP, Holzbeierlein J, Villers A, Azad A et al.. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. *J Clin Oncol* 2019; 37(32): . 10.1200/JCO.19.00799 (accessed 23 June 2021).
8. Scheunemann LP, White DB. The Ethics and Reality of Rationing in Medicine. *CHEST* 2011; 140 (6): . 10.1378/chest.11-0622 (accessed 23 June 2021).
9. Boron WF, Boulpaep EL. *Medical physiology*, 3rd ed. China: Elsevier ; 2017.
10. Reiter E, Hennuy B, Bruyninx M, Cronet A, Klug M, McNamara M et al.. Effects of Pituitary Hormones on the Prostate. *The Prostate* 1999; 38(2): . https://doi-org.proxy.library.uu.nl/10.1002/(SICI)1097-0045(19990201)38:2<159::AID-PROS10>3.0.CO;2-5 (accessed 23 June 2021).
11. The American Cancer Society. *Cancer Staging. https://www.cancer.org/treatment/understanding-your-diagnosis/staging.html (accessed 23 June 2021).*
12. Farmacotherapeutisch Kompas. *Degarelix. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/d/degarelix (accessed 23 June 2021).*
13. Rice MA, Malhotra SV, Stoyanova T.. Second-Generation Antiandrogens: From Discovery to Standard of Care in Castration Resistant Prostate Cancer. . *Front Oncol* 2019; 9(801): . 10.3389/fonc.2019.00801 (accessed 23 June 2021).
14. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. Methods for the Economic Evaluation of Health Care Programmes. 198 Madison Avenue, New York, NY 10016, United States of America: Oxford University Press; 2015. https://ebookcentral.proquest.com/lib/uunl/reader.action?docID=4605509 (accessed 21 February 2021).
15. Stenzl A, Dunshee C, De Giorgi U, Alekseev B, Iguchi T, Szmulewitz R, et al. . Effect of Enzalutamide plus Androgen Deprivation Therapy on Health-related Quality of Life in Patients with Metastatic Hormone-sensitive Prostate Cancer: An Analysis of the ARCHES Randomised,

Placebo-controlled, Phase 3 Study. *Eururo* 2020; 78(4): Supplementary Material - 8. https://doi.org/10.1016/j.eururo.2020.03.019 (accessed 29 May 2021).
16. Joore M. Introduction to decision analytic modelling. https://www.mumc.nl/sites/default/files/masterclass_model-based_economic_evaluation_part_1.pdf (accessed 17 February 2021).
17. Al M. Introduction advanced modelling. https://canvas.eur.nl/courses/29343/pages/introduction-to-the-course?module_item_id=389003 (accessed 17 February 2021).
18. National Institute for health and Care Excellence. About us. https://www.nice.org.uk/about (accessed 16 February 2021).
19. National Cancer Institute. Prostate Cancer SEER Survival Rates by Time Since Diagnosis, 2000-2016. https://seer.cancer.gov/explorer/application.html?site=66&data_type=4&graph_type=6&compareBy=race&chk_race_1=1&chk_race_5=5&chk_race_4=4&chk_race_3=3&chk_race_6=6&chk_race_8=8&chk_race_2=2&hdn_sex=2&age_range=1&stage=106&advopt_precision=1&advopt_display=2 (accessed 18 February 2021).
20. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies.. *BMC Med Res Methodol* 2011; 11(138): . https://doi.org/10.1186/1471-2288-11-139 (accessed 23 June 2021).
21. Garje R, Chennamadhavuni A, Mott SL, Chambers IM, Gellhaus P, Zakharia Y et al.. Utilization and Outcomes of Surgical Castration in Comparison to Medical Castration in Metastatic Prostate Cancer. *Clin Genitourin Cancer* 2020; 18(2): . 10.1016/j.clgc.2019.09.020 (accessed 23 June 2021).
22. Farmacotherapeutisch Kompas. *Gonadoreline-agonisten. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/g/gosereline (accessed 23 June 2021).*
23. Uro Today. *ESMO 2019: Health-Related Quality of Life in a Randomized Phase 3 Trial of Enzalutamide with Standard First Line Therapy for Metastatic Hormone-Sensitive Prostate Cancer: ENZAMET, ANZUP-led, International, Co-Operative Group Trial. https://www.urotoday.com/conference-highlights/esmo-2019/esmo-2019-prostate-cancer/115343-esmo-2019-health-related-quality-of-life-in-a-randomized-phase-3-trial-of-enzalutamide-with-standard-first-line-therapy-for-mhspc-enzamet-an-anzup-led-international-co-operative-group-trial.html (accessed 23 June 2021).*
24. Lloyd AJ, Kerr C, Penton J, Knerer G. Health-related quality of life and health utilities in metastatic castrate-resistant prostate cancer: A survey capturing experiences from a diverse sample of UK patients. *Value in Health.* 2015;18(8):1152–1157. doi: 10.1016/j.jval.2015.08.012 (Accessed 30 May 2021)
25. Robertson C, Cummins E, Fielding S, Lam T, Fraser C, Ramsay CR. Enzalutamide for treating metastatic hormone-relapsed prostate cancer not previously treated with chemotherapy: a single technology appraisal. *Aberdeen HTA Group*, 2014.
26. NICE. *Cabazitaxel for hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen Technology appraisal guidance [TA255]. https://www.nice.org.uk/guidance/ta255 (accessed 23 June 2021).*
27. Zhang PF, Dan X, Qiu L. Adding Enzalutamide to First-Line Treatment for Metastatic Hormone-Sensitive Prostate Cancer: A Cost-Effectiveness Analysis . *Front. Public Health* 2021; 9(): . 10.3389/fpubh.2021.608375 (accessed 23 June 2021).
28. Sung WWY, Choi HCW, Luk PHY, Him So Tsz. A Cost-Effectiveness Analysis of Systemic Therapy for Metastatic Hormone-Sensitive Prostate Cancer. *Front. Oncol.* 2021; 11(): . https://doi.org/10.3389/fonc.2021.627083 (accessed 23 June 2021).