Horizon Scanning in Oncology

Enzalutamide (Xtandi®) in addition to standard first-line therapy in men with metastatic hormone-sensitive prostate cancer (mHSPC)

Ludwig Boltzmann Institut
Health Technology Assessment

DSD: Horizon Scanning in Oncology No. 90
ISSN online 2076-5940

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Ludwig Boltzmann Institut
Health Technology Assessment

Vienna, September 2019

Institute for Health Technology Assessment
Ludwig Boltzmann Gesellschaft

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Publisher:

Ludwig Boltzmann Gesellschaft GmbH
Nußdorferstr. 64, 6 Stock, A-1090 Vienna
http://www.lbg.ac.at/de/lbg/impressum

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ISSN-online: 2076-5940

http://eprints.hta.lbg.ac.at/view/types/

Abstract

Introduction

Patients with metastatic hormone-sensitive prostate cancer (mHSPC) have never received androgen deprivation therapy (ADT) before, meaning that they are sensitive to ADT. Enzalutamide (Xtandi®) is an androgen receptor inhibitor, which is neither approved by the European Medicines Agency (EMA) nor by the US Food and Drug Administration (FDA) as an addition to first-line treatment of patients with mHSPC.

Methodology

Published and grey literature were identified by searching the Cochrane Library, Embase, Ovid Medline, PubMed, Internet sites and contacting the manufacturer, resulting in 137 references overall. A quality assessment was conducted to assess the risk of bias at the study level based on the EUnetHTA internal validity for randomised controlled trials. To evaluate the magnitude of "meaningful clinical benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used.

Results from the ENZAMET trial

The aim of the ENZAMET trial was to compare the efficacy and safety of adding enzalutamide to testosterone suppression. Since the trial is currently ongoing, the presented data is the first interim analysis. Overall survival (OS) was statistically significantly prolonged with enzalutamide: the hazard ratio (HR) was 0.67; however, the median OS time was not estimable in either treatment group. The benefit in favour of enzalutamide has also been observed for the following secondary endpoints: prostate-specific antigen progression-free survival (PSA PFS, HR 0.39) and clinical PFS (HR 0.40). For two of the pre-specified endpoints, health-related quality of life (HRQoL) and health outcomes relative to costs, no results are available yet. According to the authors, these results will be reported separately. Among patients of the enzalutamide group who have received early docetaxel, PFS was prolonged whilst OS was not. The incidence of serious adverse events (AEs) was higher among patients of the enzalutamide group (42%) than in patients receiving standard care (34%). In patients of the enzalutamide group who received additional early docetaxel treatment, toxic effects occurred more often than in patients of the control group. Seizures occurred in seven patients receiving enzalutamide and in none of standard-care group patients.

Conclusion

Recently published results from the ENZAMET trial indicate that patients with mHSPC benefit from the addition of enzalutamide to standard first-line treatment in terms of OS and PSA PFS. However, the administration of enzalutamide was associated with a higher rate of serious AEs as compared to standard care. Due to the ongoing status of the trial, mature final and long-term data are lacking. However, due to the nature of the open-label study design, a high risk of bias is existent and will remain even with mature data. Since final OS data and HRQoL data are not available yet, the clinical benefit for affected patients cannot be assessed. More mature data, acquired over a longer treatment duration, are required to prove the present results.

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1 Research questions

The HTA Core Model® for Rapid Relative Effectiveness Assessment of Pharmaceuticals was used for structuring this report [1]. The Model organises HTA information according to pre-defined generic research questions. Based on these generic questions, the following research questions were answered in the assessment.

EUnetHTA HTA Core Model®

Element ID	Research question
Description of the technology	
B0001	What is enzalutamide and the comparator(s)?
A0022	Who manufactures enzalutamide?
A0007	What is the target population in this assessment?
A0020	For which indications has enzalutamide received marketing authorisation?
Health problem and current use	
A0002	What is prostate cancer?
A0004	What is the natural course of prostate cancer?
A0006	What are the consequences of prostate cancer?
A0023	How many people belong to the target population?
A0005	What are the symptoms and the burden of prostate cancer?
A0003	What are the known risk factors for prostate cancer?
A0024	How is prostate cancer currently diagnosed according to published guidelines and in practice?
A0025	How is prostate cancer currently managed according to published guidelines and in practice?
Clinical effectiveness	
D0001	What is the expected beneficial effect of enzalutamide on mortality?
D0006	How does enzalutamide affect progression (or recurrence) of prostate cancer?
D0005	How does enzalutamide affect symptoms and findings (severity, frequency) of prostate cancer?
D0011	What is the effect of enzalutamide on patients' body functions?
D0012	What is the effect of enzalutamide on generic health-related quality of life?
D0013	What is the effect of enzalutamide on disease-specific quality of life?
Safety	
C0008	How safe is enzalutamide in relation to the comparator(s)?
C0002	Are the harms related to dosage or frequency of applying enzalutamide?
C0005	What are the susceptible patient groups that are more likely to be harmed through the use of enzalutamide?
A0021	What is the reimbursement status of enzalutamide?

2 Drug description

Generic/Brand name/ATC code:

Enzalutamide/Xtandi®/L02BB04

B0001: What is enzalutamide and the comparator(s)?

androgen receptor inhibitor

Enzalutamide (Xtandi®) is an androgen receptor inhibitor that blocks several steps in the androgen receptor signalling pathway. It blocks androgen binding to the respective receptors, thereby inhibiting nuclear translocation of activated receptors and the association of the activated androgen receptor with deoxyribonucleic acid (DNA). Thus, enzalutamide decreases the growth of prostate cancer cells and can induce the death of cancer cells and tumour regression. These mechanisms of action also work in the setting of androgen receptor overexpression and in prostate cancer cells that are resistant to anti-androgens [2, 3].

CRPC: 160 mg enzalutamide orally once daily

concomitant use of LHRH analogue

For the treatment of patients with non-metastatic or metastatic castration-resistant prostate cancer (CRPC), the recommended dose of enzalutamide is 160 mg (4x40 mg soft capsules), administered as a single oral daily dose. The soft capsules can be taken with or without food and should be swallowed whole; they should not be chewed, dissolved or opened. During enzalutamide treatment, the administration of a luteinising hormone-releasing hormone (LHRH) analogue should be continued if patients are not surgically castrated. In the case of grade ≥3 toxicities or intolerable adverse reactions, the dosing of enzalutamide should be withheld for one week or until the symptoms improve to grade ≥2. If warranted, the administration of enzalutamide – at the same or a reduced dose (120 mg or 80 mg) – can be continued. The concomitant use of strong CYP2C8 inhibitors should be avoided. Special warnings and precautions for use are listed below (see C0005) [2, 3].

comparator: standard NSAA

Participants of the ENZAMET trial who were assigned to the control group received a conventional non-steroidal anti-androgen (NSAA), including bicalutamide, nilutamide or flutamide [4].

A0022: Who manufactures enzalutamide?

Astellas Pharma Europe B.V.

3 Indication

A0007: What is the target population in this assessment?

added to standard first-line treatment in men with mHSPC

Enzalutamide (Xtandi®) is indicated in addition to standard first-line therapy in patients with metastatic hormone-sensitive prostate cancer (mHSPC).

4 Current regulatory status

A0020: For which indications has enzalutamide received marketing authorisation?

To date, enzalutamide (Xtandi®) is neither approved by the European Medicines Agency (EMA) nor by the U.S. Food and Drug Administration (FDA) for the administration with standard first-line therapy in men with mHSPC.

FDA and EMA: currently not licensed for the assessed indication

In Europe, the EMA granted marketing authorisation for enzalutamide for the following indications [3]:

EMA-approved indications

- The treatment of adult men with high-risk non-metastatic CRPC;
- The treatment of adult men with metastatic CRPC who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated;
- The treatment of adult men with metastatic CRPC whose disease has progressed on or after docetaxel therapy.

The FDA approved enzalutamide for the treatment of patients with CRPC [2].

approved by FDA for CRPC treatment

5 Burden of disease

A0002: What is prostate cancer?

Prostate cancer develops in the tissue of the prostate gland. Patients with mHSPC have metastatic prostate cancer and have never received ADT before, meaning that these patients are sensitive to ADT [5].

mHSPC patients are sensitive to ADT

A0004: What is the natural course of prostate cancer?

Three stages of prostate cancer can be distinguished: localised, locally-advanced and advanced prostatic cancer [6]. According to data from the US population, 77% of prostate cancer cases are diagnosed at a local stage (confined to the primary site), 13% are diagnosed at a regional stage (spread to regional lymph nodes) and 6% of cases are diagnosed at a distant stage, when the disease has already metastasised. 4% of prostate cancer cases remain unstaged [7].

77% of prostate cancer cases are diagnosed at the local stage

In Austria, the relative survival rate following diagnosis in patients with prostate cancer (2009–2013) is 95.6% at one year, 93.1% at three years and 91.5% at five years. In 2016, the age-standardised mortality rate of the European Standard Population (2013) was 38.7 per 100,000 men per year; 1,225 men died from prostate cancer. At the end of the year 2016, 63,415 men diagnosed with prostate cancer were alive; more than 40% of the affected patients (25,572 men) were diagnosed at least ten years ago [8].

Austria: 5-year relative survival rate of 91.5%

A0006: What are the consequences of prostate cancer for the society?

A0023: How many people belong to the target population?

Austria: incidence rate of 138.3/100,000 men/year

In Austria, 5,245 men were newly diagnosed with prostate cancer in 2016; the age-standardised incidence rate of the European Standard Population (2013) is 138.3 per 100,000 men per year (2016).

mHSPC constitutes approx. 5% of prostate cancer cases

According to data from the US[1], from 2004–2012 mHSPC is estimated to constitute approximately 5% of prostate cancer cases [5]. Prostate cancer is most frequently diagnosed among men between the ages of 65 and 74 years; the median age at diagnosis is 66 years [7]. A study of current and forecast incidence trends of metastatic prostate cancer in 25,033 men aged 45 to 94 years who were diagnosed with metastatic prostate cancer from 2004 to 2014, showed a median age at diagnosis of 71 years [9].

median age at diagnosis of metastatic prostate cancer: 71 years

A0005: What are the symptoms and the burden of prostate cancer?

mostly diagnosed at asymptomatic, local stage

Most cases of prostate cancer are diagnosed at the local stage when patients are asymptomatic. Patients rarely present with non-specific urinary symptoms, including haematuria or haematospermia, that are usually associated with non-malignant conditions [10].

symptoms of metastatic disease

Patients with metastatic disease at the time of diagnosis may present with bone pain; other symptoms are weight loss, weakness or pain caused by spinal cord compression or due to pathologic fractures, fatigue due to anaemia, renal or urinary symptoms (haematuria, inability to void, incontinence), as well as symptoms that are associated with chronic renal failure. A clinical sign that can be associated with prostate cancer is an elevation of PSA on laboratory testing. However, PSA is not specific for malignancy, since an elevation may also be caused by a number of benign conditions. Although PSA is not specific for prostate cancer, the measurement of the PSA level is the most commonly used and most valuable test to detect prostate cancer at an early stage. Further clinical signs that may indicate the presence of prostate cancer are abnormal findings on the digital rectal examination (DRE). A DRE may enable the detection of prostate nodules, indurations or asymmetries potentially associated with prostate cancer. However, only tumours that are localised in the posterior and lateral aspects of the prostate gland can be detected by a DRE; tumours in other parts of the gland are not reachable or not palpable [11].

A0003: What are the known risk factors for prostate cancer?

The risk for the development of clinically significant prostate cancer is related to the following factors [11-15]:

increasing age

- Age: Increasing age is the most important risk factor for the development of prostate cancer. The disease is rare in men younger than 40 years, but its incidence increases progressively thereafter.

African Americans: higher risk

- Ethnicity: African Americans have a higher risk of developing prostate cancer and the disease occurs at an earlier stage. Furthermore, prostate cancer is associated with a more aggressive clinical course in African Americans than in other ethnic groups.

[1] There is no data available regarding incidence rates of mHSPC in Europe.

- Family history: There is a strong inherited component regarding the development of prostate cancer; a family history of prostate cancer and other cancers can increase the risk. There are genetic factors (especially germline mutations in DNA repair genes, e.g., BRCA2) which seem to play an important role in the development of certain types of prostate cancer and may be associated with a more aggressive course of the disease. Genetic risk assessment should be conducted, including a detailed personal and family cancer history in first- and second-degree relatives (type of cancer, age at diagnosis and ancestry). If a suggestive family history is established, patients should be referred for genetic counselling, and genetic testing should be conducted.

strong inherited component

- PSA level: The likelihood of the presence of prostate cancer increases with a more elevated PSA value. Although PSA is consistently expressed in almost all prostate cancers, high-grade prostate cancer can occur in men with a "normal" PSA level.

elevated PSA level

- Free/total PSA ratio (f/t PSA): The percentage of f/t PSA may be used for a higher sensitivity of cancer detection in patients with a total PSA within the normal range (<4 ng/ml) and to increase the specificity to detect prostate cancer when total PSA is in the "grey zone" (4.1 to 10 ng/ml).

f/t PSA ratio

- Findings on DRE, including prostate nodules, indurations or asymmetries.

suspicious findings on DRE

- Whether a prior vasectomy increases risk for prostate cancer is controversial.

controversial role of prior vasectomy

- Other factors, including diet, hormone levels and obesity, may have some effect on the incidence of prostate cancer; however, the role of these factors appears to be limited.

other factors: limited role

A0024: How is prostate cancer currently diagnosed according to published guidelines and in practice?

An elevation in PSA levels or an abnormality on DRE can be a signs of prostate cancer that warrant additional evaluation. There is no consistent PSA threshold for defining an abnormal PSA value [11].

no consistent PSA threshold

The final diagnosis of prostate cancer is based on the histology of tissue which is obtained by conducting a core needle biopsy of the prostate. If the results indicate the presence of prostate cancer, a Gleason grade (which correlates closely with clinical behaviour) is generated by using architectural features of the obtained cells. The Gleason grade for the two most prevalent differentiation patterns is used to create the Gleason score and is now used in the new grading (grade group) system; the latter provides a more accurate risk stratification. Due to the fact that sampling techniques which have a substantial potential for missing malignant tissue are used for prostate biopsies, the possibility of the presence of prostate cancer cannot be ruled out by conducting a biopsy. In case the PSA level increases further, or findings on DRE or prostate imaging indicate prostate cancer, a repetition of the biopsy is warranted [11, 16].

final diagnosis is based on histological examination

grading system

EAU-ESTRO-ESUR-SIOG recommendations

According to the EAU-ESTRO-ESUR-SIOG[2] Guidelines on Prostate Cancer [17], frequent post-treatment PSA surveillance leads to earlier detection of disease progression in non-metastatic CRPC. Approximately one-third of patients with a rising PSA develop bone metastases within two years. However, there is no evidence available demonstrating a benefit for immediate treatment. A consensus statement by the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group suggested the conduction of a bone scan and a CT when the PSA level has reached 2 ng/ml. If the results are negative, the imaging procedures should be repeated when the PSA has reached 5 ng/ml and then again after every doubling of the PSA level based on PSA measurement every three months for asymptomatic patients. If patients are symptomatic, they should undergo relevant examination. Bone scanning should be performed in symptomatic patients independent of the PSA level, Gleason score or clinical stage. The most widely used method for evaluating bone metastases in patients with prostate cancer is the ^{99}mTc-bone scan [17].

differential diagnosis

Differential diagnosis should be considered for prostate cancer. Lower urinary tract symptoms, including frequency, urgency, nocturia, and hesitancy, occur commonly among men and are usually related to benign conditions rather than to prostate cancer. An elevation of the PSA level can be caused by transient conditions, such as prostatitis or perineal trauma, and by persistent causes such as benign prostate hyperplasia (BPH) [11].

6 Current treatment

A0025: How is prostate cancer currently managed according to published guidelines and in practice?

EAU recommendations

According to the European Association of Urology (EAU) – Updated Guidelines for mHSPC [18], it is strongly recommended to offer the following treatment options:

- Surgical or medical castration (LHRH agonist or antagonist) as ADT;
- Castration combined with chemotherapy (docetaxel) to all patients whose first presentation is M1 disease and who are fit enough for chemotherapy;
- Castration combined with abiraterone acetate + prednisone to all patients whose first presentation is M1 disease and who are fit enough for the regimen;
- Castration, with or without an anti-androgen, to patients unfit for a combination with docetaxel or abiraterone acetate + prednisone, or who are unwilling to consider it.

NCCN guidelines

According to the National Comprehensive Cancer Network (NCCN) guideline [19], options for the systemic therapy for castration-naïve disease (M1) include:

[2] EAU = European Association of Urology, ESTRO = European Society for Radiotherapy & Oncology, ESUR = European Society of Urogenital Radiology, SIOG = International Society of Geriatric Oncology.

- ADT and docetaxel 75 mg/m² for six cycles (category 1 recommendation, based upon high-level evidence), or
- ADT and abiraterone with prednisone (category 1 recommendation, based upon high-level evidence), or
- ADT and external beam radiotherapy (EBRT) to the primary tumour for low-volume M1, or
- ADT, or
- ADT and abiraterone with methylprednisolone.

7 Evidence

systematic literature search in 3 databases: 107 hits

manual search: 30 additional references

A literature search was conducted on 15 July 2019 in four databases: the Cochrane Library, Embase, Ovid Medline and PubMed. Search terms were "enzalutamide", "xtandi", "L02BB04", "prostate cancer", "prostate neoplasms", "metastatic", "first-line" and "initial". The manufacturer was also contacted and submitted five references (one of them had already been identified by systematic literature search). A manual search identified 30 additional references (web documents and journal articles, including all references used in this report).

overall: 137 references included: 2 studies

Overall, 137 references were identified. Included in this reported are:

- ENZAMET [4, 20, 21], a multinational, open-label, randomised phase III study evaluating the efficacy and safety of adding enzalutamide to standard first-line therapy in men with mHSPC
- ARCHES [22], a multinational, double-blind, randomised, placebo-controlled phase III trial, aiming to assess the efficacy and safety of enzalutamide plus ADT in men with mHSPC.

study level risk of bias assessed based on EUnetHTA internal validity for RCTs

To assess the risk of bias at the study level, the assessment of the methodological quality of the evidence was conducted based on the EUnetHTA internal validity for randomised controlled trials (RCTs) [23]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 6 of the Appendix.

applicability of study results

The external validity of the ENZAMET trial was assessed using the EUnetHTA guideline on the applicability of evidence in the context of a relative effectiveness assessment of pharmaceuticals, considering the following elements: population, intervention, comparator, outcomes and setting (see Table 5) [24].

magnitude of meaningful clinical benefit assessed based on ESMO-MCBS

To evaluate the magnitude of "meaningful clinical benefit" that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [25]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [26]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.

7.1 Quality assurance

internal and external review

This report has been reviewed by an internal reviewer and an external reviewer. The latter was asked for the assessment of the following quality criteria:

- How do you rate the overall quality of the report?
- Are the therapy options in the current treatment section used in clinical practice and are the presented standard therapies correct?
- Is the data regarding prevalence, incidence and the amount of eligible patients correct?
- Are the investigated studies correctly analysed and presented (data extraction was double-checked by a second scientist)?
- Was the existing evidence from the present studies correctly interpreted?
- Does the current evidence support the final conclusion?
- Were all important points mentioned in the report?

quality assurance method

The LBI-HTA considers the external assessment by scientific experts from different disciplines to be a quality assurance method of scientific work. The final version and the policy recommendations are under full responsibility of the LBI-HTA.

7.2 Clinical efficacy and safety – phase III studies

ENZAMET: open-label, randomised phase III trial

The ENZAMET trial [4, 20, 21] is a multinational, multicentre (83 sites), open-label, randomised phase III trial aiming to determine the effects of adding enzalutamide to first-line treatment in men with mHSPC. Between March 2014 and March 2017, a total of 1,125 men who underwent randomisation were assigned in a 1:1 ratio to receive testosterone suppression plus either enzalutamide (n = 563) or standard care (n = 562). Randomisation was stratified according to the volume of disease (high/low), the planned use of early docetaxel (yes/no), the planned use of bone resorptive therapy (yes/no) and the score on the Adult Comorbidity Evaluation 27 (ACE-27, 0/1 or 2/3) and trial site. Patients were eligible to participate in the ENZAMET trial if they had prostatic adenocarcinoma with metastases on computed tomography (CT), ^{99}mTc-bone scan, or both, an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less, and adequate bone marrow, liver and renal function. Detailed inclusion and exclusion criteria can be found in Table 5.

median age of 69 years

Patients of both groups had a median age of 69 years, more than half of them were Australians; further patients were enrolled throughout Canada, Ireland, New Zealand, the United Kingdom and the United States. There is no information available regarding the percentage of participants who were of African American descent. The percentage of patients who showed a high-volume disease was similar in both groups: 52% (enzalutamide group) and 53% (standard-care group). Visceral metastases were diagnosed in 11% of enzalutamide group patients and 12% of standard-care group patients; the median time since the diagnosis of metastasis was 1.9 months in patients of either group. More than half of the patients (60% in the enzalutamide group and 57% in the standard-care group) had a Gleason score of 8 to 10. 51% of enzalutamide group patients and 56% of standard-care group patients received an anti-androgen therapy prior to the study treatment; 73% (enzalutamide group) and 74% (standard-care group) were treated with a LHRH agonist or antagonist (LHRHa). Previous docetaxel was administered in 17% of enzalutamide group patients and 15% of standard-care group patients. In the enzalutamide group, 10% of patients had prior adjuvant ADT as compared to 7% of patients in the standard-care group; 1% of patients in either group underwent bilateral orchiectomy. With 45% (enzalutamide group) and 44% (standard-care group), the planned use of docetaxel was balanced between the treatment groups. Detailed patient characteristics can be found in Table 5.

more than 50% in either group had high-volume disease, Gleason score 8-10 and prior anti-androgen therapy

45% (enzalutamide group) and 44% (standard-care group) planned docetaxel use

enzalutamide group: 160 mg/day of enzalutamide

standard-care group: standard NSAA

Patients assigned to the enzalutamide group received enzalutamide at a total daily dose of 160 mg daily, provided as four orally administered 40 mg soft gelatine capsules. Patients of the standard-care group received a conventional NSAA, i.e., bicalutamide 50 mg daily, nilutamide 150 mg daily, or flutamide 250 mg three times a day (cyproterone was not permitted). The type of NSAA was chosen at the discretion of the treating physician and drug administration was performed according to the respective product information guide.

background therapy: testosterone suppression

Patients of both groups received a standard background therapy with an LHRHa or surgical castration; the choice between these two options was at the discretion of the treating clinician. LHRHa should be administered according to the product information guide; options included, but were not restricted to goserelin, leuprorelin, triptorelin, and degarelix. In case of surgical castration with bilateral orchiectomy (instead of LHRHa treatment), it had to be done less than twelve weeks before randomisation or within seven days after randomisation. Patients of both groups had the possibility to initiate early treatment with docetaxel. If docetaxel was administered, the patients received 75 mg/m^2 of body-surface area every three weeks for a maximum of six cycles (without prednisone or prednisolone). 65% of patients in the enzalutamide group and 76% of standard-care group patients received the full planned course of six cycles of docetaxel. Before randomisation, up to two cycles of docetaxel were permitted. Trial patients received the study treatment until the occurrence of clinical disease progression or prohibitive toxic effects.

early docetaxel treatment possible

OS: primary endpoint

Overall survival (OS) was the primary endpoint of the ENZAMET trial, defined as the interval from randomisation to death from any cause or to the date at which the patient was last known to be alive. PSA progression-free survival (PFS) was a secondary endpoint, measured as the interval from randomisation to the earliest event of PSA progression according to the criteria of the Prostate Cancer Working Group 2 (a confirmed relative increase in the PSA level from the nadir value by ≥25% and by ≥2 ng/ml), clinical progression, death from any cause, or the last known date of follow-up without PSA progression. Clinical progression, another secondary endpoint, was defined as the earliest sign of radiographic progression according to the criteria of the Prostate Cancer Working Group 2 for bone lesions and the Response Evaluation Criteria in Solid Tumours (RECIST version 1.1) for soft-tissue lesions, the development of symptoms attributable to cancer progression or the initiation of another anti-cancer treatment for prostate cancer. Clinical efficacy data are presented in Table 1. Data with regard to adverse events (AEs) were collected during the treatment period and a final safety assessment was conducted 30 to 42 days after the termination of study treatment. AE data are presented in Table 2. The authors announced that trial results regarding health-related quality of life (HRQoL), resource use and incremental cost-effectiveness are to be reported separately.

secondary endpoints: PFS, clinical progression and AEs

HRQoL data is not yet available

interim analysis data presented

The first interim analysis of OS was performed on 28 February 2019, after the occurrence of 235 deaths; the median follow-up time was 34 months. At three years, 62% of enzalutamide group patients and 34% of standard-care group patients were still receiving study treatment. 66% of patients treated with enzalutamide and 71% of patients who received standard care discontinued the trial regimen due to disease progression or death.

median follow-up time: 34 months

ENZAMET is ongoing until 12/2020

The ENZAMET trial is ongoing until December 2020 (estimated study completion date) [27]; the presented data is interim analysis data.

7.2.1 Clinical efficacy

D0001: What is the expected beneficial effect of enzalutamide on mortality?

interim analysis: OS was statistically significantly longer with enzalutamide

On 28 February 2019, after the occurrence of 235 deaths, the first planned interim analysis of OS was performed. In patients of the enzalutamide group, 102 deaths were reported, as compared to 143 deaths in patients of the standard-care group (hazard ratio [HR] for death was 0.67, 95% confidence interval [CI] 0.52–0.86, p = 0.002). The reported results include ten additional deaths (resulting in a total of 245 deaths) after a review to ascertain the survival status of all patients after a median follow-up time of 34 months (as of 28 February 2019). In both treatment groups, the median survival time was not yet estimable. The Kaplan-Meier estimates of OS at three years were 80% in patients of the enzalutamide group (based on 94 events) and 72% in patients of the standard-care group (based on 130 events). The effect of enzalutamide on OS was smaller in the following stratified subgroups: bone anti-resorptive therapy, planned early docetaxel treatment and high-volume disease [4].

median overall survival time not yet estimable

D0006: How does enzalutamide affect progression (or recurrence) of prostate cancer?

In patients who received enzalutamide, PSA progression was statistically significantly prolonged as compared to patients of the standard-care group. 174 events (enzalutamide group) and 333 events (standard-care group) were reported; the rate of event-free survival at three years was 67% and 37%, respectively (HR 0.39, 95% CI 0.33–0.47, $p < 0.001$). After termination of the trial regimen, 113 patients of the enzalutamide group and 275 patients of the standard-care group received anti-cancer therapies [4].

PSA progression statistically significantly prolonged with enzalutamide

D0005: How does enzalutamide affect symptoms and findings (severity, frequency) of prostate cancer?

With regard to clinical PFS, 167 events were reported from the enzalutamide group compared to 320 events in the standard-care group. Analysis showed rates of event-free survival at three years of 68% in patients who received enzalutamide versus 41% in patients who received standard care (HR 0.40, 95% CI 0.33–0.49, $p < 0.001$). Among the patients who had clinical progression, 67% (enzalutamide group) and 85% (standard-care group) of patients received one or more subsequent life-prolonging therapies [4].

clinical PFS prolonged in patients of the enzalutamide group

D0011: What is the effect of enzalutamide on patients'body functions?

In patients of the enzalutamide group, the occurrence of hypertension of grades 3 to 5 was more frequent (8%) than in patients of the standard-care group (4%). In each treatment group, one patient died from myocardial infarction and cardiac arrest, respectively. 4% of patients receiving enzalutamide were affected by syncope, as compared to 1% of patients in the standard-care group. Fatigue was more common in patients of the enzalutamide group (6%) than in patients receiving standard care (1%) [4].

hypertension, syncope and fatigue: more frequent with enzalutamide

D0012: What is the effect of enzalutamide on generic health-related quality of life?

D0013: What is the effect of enzalutamide on disease-specific quality of life?

No data regarding generic HRQoL or disease-specific quality of life (QoL) is available yet. The authors announced the separate reporting of HRQoL-, resource use- and incremental cost-effectiveness-data [4].

HRQoL data currently not available

Table 1: Efficacy results of ENZAMET trial [4]

Descriptive statistics and estimate variability	Treatment group	Enzalutamide	Standard care
	Number of patients	563	562
	Number of deaths at the time of the 1st interim analysis	102	143
	OS, median	NE	NE
	Kaplan-Meier estimates of OS at 3 years, %	80	72
	PSA PFS, number of events	174	333
	Rate of event-free survival at 3 years (PSA PFS), %	67	37
	Clinical PFS, number of events	167	320
	Rate of event-free survival at 3 years (clinical PFS), %	68	41
	HRQoL	NR	NR
	Health outcomes relative to costs	NR	NR
Effect estimate per comparison	*Comparison groups*		Enzalutamide vs. Standard care
	Number of deaths at the time of the 1st interim analysis	HR for death	0.67
		95% CI	0.52–0.86
		p-value	0.002
	Rate of event-free survival at 3 years (PSA PFS)	HR	0.39
		95% CI	0.33–0.47
		p-value	<0.001
	Rate of event-free survival at 3 years (clinical PFS), %	HR	0.40
		95% CI	0.33–0.49
		p-value	<0.001

Abbreviations: CI = confidence interval, HR = hazard ratio, HRQoL = health-related quality of life, OS = overall survival, PFS = progression-free survival, PSA = prostate-specific antigen, NE = not estimable, NR = not reported

7.2.2 Safety

C0008: How safe is enzalutamide in relation to the comparator(s)?

higher rate of grade 3 AEs in patients of enzalutamide group

6 deaths in the enzalutamide group, 7 deaths in the standard-care group

AEs of grade 1 and 2 occurred in 43% of enzalutamide group patients and 55% of standard-care group patients. The rate of AEs of grade 3 was higher in patients of the enzalutamide group (49%) than in patients of the standard-care group (35%). In either treatment group, 7% of patients were affected by AEs of grade 4. Among patients of the enzalutamide group, six patients (1%) had a grade 5 AE; of these, two patients died from an unknown cause and one patient each was affected by stroke, myocardial infarction, aspiration pneumonia and acidosis. In patients of the standard-care group, seven patients (1%) had an AE of grade 5; sepsis occurred in two patients, and one patient each was affected by cardiac arrest, sudden death from an unknown cause, gastric haemorrhage, urinary tract infection and symptomatic progression of prostate cancer. Toxic effects (especially peripheral neuropathy) were more frequently reported from patients of the enzalutamide group who received early docetaxel [4].

Serious AEs were reported in 42% of enzalutamide group patients and in 34% of standard-care group patients. Among the grade 3 to 5 AEs that occurred in at least 2% of the patients in either group (or were selected as being events of special interest), hypertension (8%), febrile neutropenia (7%), neutrophil count decrease (6%) and fatigue (6%) were most frequently reported in patients of the enzalutamide group as compared to febrile neutropenia (6%), hypertension (4%) and neutrophil count decrease (3%) in the standard-care group patients. Seizures occurred in seven patients (1%) of the enzalutamide group and in none of the standard-care group patients; six patients (1%) discontinued enzalutamide treatment due to the occurrence of seizure, one patient (<1%) discontinued enzalutamide due to clinical progression prior to the seizure event [4].

higher incidence of serious AEs with enzalutamide

1% of patients discontinued enzalutamide due to seizures

C0002: Are the harms related to dosage or frequency of applying enzalutamide?

In patients of the ENZAMET trial, the mode of enzalutamide administration conforms to the recommended dosing regimen for the treatment of patients with CRPC (160 mg administered orally once daily). In case of the occurrence of grade ≥3 toxicities or intolerable side effects, dose interruption and/or dose reduction are recommended. [2].

ENZAMET: dosing regimen according to approved regimen for CRPC

According to the authors, the larger number of serious AEs among patients of the enzalutamide group was proportional with the longer duration of trial treatment: At three years, the percentage of patients who were still receiving a study treatment was 62% in the enzalutamide group and 34% in the standard-care group. The frequency of serious AEs per person-year of exposure to a trial regimen was similar in both treatment groups: 0.34 in patients of the enzalutamide group vs. 0.33 in patients of the standard-care group [4].

rate of serious AEs per person-year of exposure similar in both groups

C0005: What are the susceptible patient groups that are more likely to be harmed through the use of enzalutamide?

There are several warnings and precautions listed with regard to the administration of enzalutamide [2, 3]:

warning and precautions for enzalutamide use

- The use of enzalutamide has been associated with seizure. Whilst the EMA suggests taking the decision to continue treatment in patients who develop seizure case by case, the FDA recommends permanently discontinuing enzalutamide when seizure occurs.
- The occurrence of posterior reversible encephalopathy syndrome (PRES), a rare neurological disorder with rapidly evolving symptoms (including seizure, headache, lethargy, confusion, blindness and other visual and neurological disturbances, with or without associated hypertension), has been reported in patients who have received enzalutamide. In patients who develop PRES, enzalutamide treatment should be discontinued.
- In patients receiving enzalutamide, hypersensitivity reactions, including oedema of the face, tongue or lip and pharyngeal oedema, have been observed. Hence, patients should be on notice of possible adverse reactions; if serious hypersensitivity reactions occur, enzalutamide should be discontinued permanently.

- Patients who receive enzalutamide need to be monitored for signs and symptoms of ischaemic heart disease; enzalutamide needs to be discontinued in case of grade 3–4 ischaemic heart disease. If enzalutamide is prescribed to patients with a recent cardiovascular disease, it should be taken into account that patients with certain cardiovascular diseases were excluded from several phase III studies. Furthermore, ADT may prolong the QT interval.
- The occurrence of falls and fractures were reported from patients who received enzalutamide. Patients at risk for fractures have to be monitored and managed according to established treatment guidelines. Furthermore, the use of bone-targeted agents has to be considered.
- The co-administration of enzalutamide with warfarin and coumarin-like anticoagulants should be avoided. If enzalutamide is co-administered with an anticoagulant metabolised by CYP2C9, additional International Normalized Ratio (INR) monitoring should be conducted.
- Caution is required for patients with severe renal impairment, since there is no data for enzalutamide treatment in this patient population.
- The safety and efficacy of the concomitant use of enzalutamide with cytotoxic, chemotherapeutical agents has not been established. Although the co-administration of enzalutamide is deemed to have no clinically relevant effect on the pharmacokinetics of intravenous docetaxel, an increase in the occurrence of docetaxel-induced neutropenia cannot be excluded.
- In patients with rare hereditary problems of fructose intolerance, enzalutamide should not be administered.

effective contraception required

Since enzalutamide is not for use for women of childbearing potential, its safety and efficacy has not been established in females. However, studies in animals have shown reproductive toxicity. There is no evidence whether enzalutamide or its metabolites are present in the semen; hence, effective contraception is required during enzalutamide treatment and for three months after the last dose [2, 3].

Table 2: Most frequent adverse events [4]

Adverse Event (according to NCI CTCAE version 4.02)	**Enzalutamide** (n = 563)	**Standard care** (n = 558)
Any AE – number of patients (%)		
Grade 1	40 (7)	77 (14)
Grade 2	202 (36)	230 (41)
Grade 3	277 (49)	194 (35)
Grade 4	38 (7)	40 (7)
Grade 5	6 (1)	7 (1)
Serious AE		
Number of patients (%)	235 (42)	189 (34)
Number of events	385	297
Rate during treatment exposure (95% CI) – number/year	0.34 (0.29–0.40)	0.33 (0.28–0.39)
AE leading to treatment discontinuation at any time – number of patients	33	14
Grade 3 to 5 AE – number of patients (%)*		
Febrile neutropenia	37 (7)	32 (6)
Hypertension	43 (8)	25 (4)
Neutrophil count decreased	31 (6)	16 (3)
Fatigue	31 (6)	4 (1)
Syncope	20 (4)	6 (1)
Surgical or medical procedure	13 (2)	10 (2)
Anaemia	4 (1)	5 (1)
Fall	6 (1)	2 (<1)
Thromboembolic event	4 (1)	4 (1)
Acute coronary syndrome	3 (1)	4 (1)
Myocardial infarction	5 (1)	2 (<1)
Chest pain from cardiac cause	3 (1)	2 (<1)
Stroke	1 (<1)	2 (<1)
Seizure	2 (<1)	0 (0)
Delirium	0 (0)	1 (<1)

Abbreviations: AE = adverse event, CI = confidence interval, CTCAE = Common Terminology Criteria for Adverse Events, n = number, NCI = National Cancer Institute

** These AEs occurred in at least 2% of the patients in either group or were selected as being events of special interest.*

7.3 Clinical effectiveness and safety – further studies

ARCHES: phase III trial comparing enzalutamide + ADT vs. placebo + ADT

ARCHES [22] is a multinational, double-blind, randomised, placebo-controlled, phase III trial, conducted to assess the efficacy and safety of enzalutamide plus ADT in men with mHSPC, regardless of prior docetaxel or disease volume. To this end, a total of 1,150 patients were randomly assigned to receive either enzalutamide at a dose of 160 mg/day plus ADT (n = 574) or placebo plus ADT (n = 576). Prior ADT and prior docetaxel (up to six cycles) were permitted. ARCHES trial participants had a median age of 70 years, more than 75% of patients had an ECOG performance status of 0. The majority of patients were Whites; 1.4% of patients in either group were of African American descent. Approximately two-thirds of the trial patients had high-volume disease; more than 80% of patients in either group did not receive prior docetaxel chemotherapy. The median treatment duration was 12.8 months among patients of the enzalutamide plus ADT group and 11.6 months in patients of the placebo plus ADT group. The ARCHES trial is currently ongoing; the estimated study completion date is December 2023 [27].

ongoing until 12/2023

statistically significant improvement of rPFS, time to PSA progression, time to antineoplastic therapy, undetectable PSA rate, ORR, time to castration resistance

The primary endpoint of the ARCHES trial was radiographic progression-free survival (rPFS). Analyses showed that the risk of radiographic progression or death was statistically significantly reduced with enzalutamide plus ADT as compared to placebo plus ADT (HR 0.39, 95% CI 0.30–0.50, $p < 0.001$). This benefit of adding enzalutamide to ADT has been observed across all pre-specified subgroups. Median rPFS was not reached (enzalutamide plus ADT group) versus 19.0 months (placebo plus ADT group). Statistically significant improvements with enzalutamide were reported for the following secondary endpoints: the median time to PSA progression, the median time to initiation of a new antineoplastic therapy, undetectable PSA rate (<0.2 ng/ml), the objective response rate (ORR) and the median time to castration resistance. At baseline, the mean Functional Assessment of Cancer Therapy-Prostate (FACT-P) total score was high for both treatment groups and was maintained over time.

FACT-P scores consistent in both groups over time

In terms of safety, there was a high rate of AEs of all grades of approximately 85% in both groups; most frequently reported were hot flash, fatigue and arthralgia in patients receiving enzalutamide plus ADT and hot flash, fatigue and back pain in patients treated with placebo plus ADT. The rates of AEs of grade ≥3 were similar in either group: 24.3% in the enzalutamide plus ADT group and 25.6% in the placebo plus ADT group. Drug-related serious AEs were reported in 3.8% of patients (enzalutamide plus ADT group) and in 2.8% of patients (placebo plus ADT group). The rate of AEs leading to death was higher in patients of the enzalutamide plus ADT group (2.4%) than in patients receiving placebo plus ADT (1.7%).

higher rate of AEs leading to death with enzalutamide + ADT

8 Estimated costs

A0021: What is the reimbursement status of enzalutamide?

28 days of enzalutamide treatment = € 2,895.35

In Austria, 112 (4x28) enzalutamide (Xtandi®) 40 mg soft capsules are available at € 2,895.35 (ex-factory price) [28]. Patients of the ENZAMET trial received four 40 mg capsules of enzalutamide once daily, resulting in a total daily dose of 160 mg [4]. Based on this treatment regimen, 28 days of enzalutamide treatment would cost € 2,895.35.

median follow-up time: 34 months
€ 98,441.90

There was no median treatment duration reported from patients participating in the ENZAMET trial. The median follow-up time was 34 months; at three years, 62% of patients in the enzalutamide group were still receiving a trial regimen [4]. Considering this, 34 months of enzalutamide treatment would cost € 98,441.90.

additional costs for testosterone suppression and optional docetaxel therapy

In addition to enzalutamide treatment, costs for testosterone suppression as combination therapy as primary therapy incur. If docetaxel was administered (a decision that was left up to the individual patients and their physicians), patients received docetaxel at a dose of 75 mg/m² of body-surface area (BSA) without prednisone or prednisolone given every three weeks for a maximum of six cycles [4]. Assuming an average BSA of 1.73 m², 129.75 mg of docetaxel would be needed for one dose. Docetaxel (Taxotere®) 160 mg concentrate for solution for infusion is available at an ex-factory price of € 1,308.12 [28], resulting in costs of € 7,848.72 for six cycles of treatment.

standard-care group costs

Patients of the standard-care group received conventional NSAA therapy as chosen at the discretion of the treating clinician. Bicalutamide 50 mg daily, nilutamide 150 mg daily, or flutamide 250 mg three times a day were permitted [20]. As an example, bicalutamide 50 mg, which is approved by the FDA (trade name: Casodex®) for use in combination with a LHRH analogue for the treatment of stage D2 metastatic carcinoma of the prostate [29] and which is authorised in Austria [30], is available at an ex-factory price of € 48.27 (30 tablets á 50 mg) [28]. Here, too, costs for testosterone suppression and – possibly – for docetaxel treatment incur.

9 Ongoing research

ENZAMET + ARCHES: ongoing phase III trials for the assessed indication

In July 2019, a search in the databases www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu was conducted. Currently, both phase III trials included in this report are ongoing:

- ENZAMET (NCT02446405, EudraCT number: 2014-003190-42) is ongoing until December 2020 (estimated study completion date)
- ARCHES (NCT02677896, EudraCT number: 2015-003869-28) is ongoing until December 2023 (estimated study completion date).

one phase II trial

NCT03246347 is a phase II trial that compares the efficacy and safety of ADT, docetaxel and enzalutamide compared to ADT and docetaxel. The estimated study completion date is March 2027.

numerous trials of enzalutamide in mCRPC

Several other phase III trials, evaluating the use of enzalutamide in metastatic castration-resistant prostate cancer (mCRPC) could be identified.

10 Discussion

currently not approved for the assessed indication

To date, the androgen-receptor inhibitor enzalutamide (Xtandi®) is neither approved by the EMA nor by the FDA for the addition to first-line treatment of patients with mHSPC.

interim analysis data

OS statistically significantly prolonged with enzalutamide, but median not estimable

HRQoL outcomes not available

higher incidence of serious AEs with enzalutamide

more toxic effects with enzalutamide + docetaxel than in control group

The aim of ENZAMET [4, 20, 21], a multinational, open-label, randomised phase III trial was to compare the efficacy and safety of adding enzalutamide to testosterone suppression. Since the trial is currently ongoing, the presented data is the first interim analysis. OS was the primary endpoint of the ENZAMET trial and was statistically significantly prolonged with enzalutamide (HR 0.67); however, the median OS time was not estimable in either treatment group. The benefit in favour of enzalutamide has also been observed for the following secondary endpoints: PSA PFS (HR 0.39) and clinical PFS (HR 0.40). For two of the pre-specified endpoints, HRQoL and health outcomes relative to costs, no results are available yet. According to the authors, these results will be reported separately. Among patients of the enzalutamide group who have received early docetaxel, PFS was prolonged whilst OS was not. The incidence of serious AEs was higher among patients of the enzalutamide group (42%) than in patients receiving standard care (34%); febrile neutropenia, hypertension and fatigue were more common in patients of the enzalutamide group. In patients of the enzalutamide group who received additional early docetaxel treatment, toxic effects occurred more often than in patients of the control group.

seizures only in enzalutamide group patients

Seizures occurred in seven patients receiving enzalutamide and in none of the standard-care group patients. Of note, patients with a history of seizure or any condition that may predispose to seizure were excluded from the ENZAMET trial. A direct comparison of enzalutamide to darolutamide would be of high interest, since darolutamide (an androgen receptor antagonist) is deemed to have a lower risk of inducing Central Nervous System (CNS)-related AEs than enzalutamide [31].

The efficacy and safety results of the ENZAMET study are supported by recently published results of the ARCHES trial [22], assessing enzalutamide plus ADT compared to placebo plus ADT in men with mHSPC. Analyses showed that the risk of radiographic progression or death was statistically significantly reduced with enzalutamide plus ADT as compared to placebo plus ADT (HR 0.39); this benefit of adding enzalutamide to ADT has been observed across all pre-specified subgroups. Median rPFS was not reached (enzalutamide plus ADT group) versus 19.0 months (placebo plus ADT group). Statistically significant improvements with enzalutamide were reported for the median time to PSA progression, the median time to initiation of a new antineoplastic therapy, undetectable PSA rate, ORR and the median time to castration resistance. The FACT-P total score was high for both treatment groups at baseline and was maintained over time. There was a high rate of AEs of all grades of approx. 85% in both groups; the rates of AEs of grade ≥3 were similar in either group. Drug-related serious AEs were reported from 3.8% of patients (enzalutamide plus ADT group) and 2.8% of patients (placebo plus ADT group); the rate of AEs leading to death was higher in patients of the enzalutamide plus ADT group (2.4%) than in patients receiving placebo plus ADT (1.7%). However, like the ENZAMET study, the ARCHES trial is currently ongoing and final results are not available. With regard to the applicability of ARCHES trial results, it is noteworthy that persons of African American descent were underrepresented.

ARCHES trial: risk of radiographic progression or death statistically significantly reduced with enzalutamide + ADT

rate of AEs leading to death higher with enzalutamide + ADT

ARCHES is ongoing, final results are lacking

Since both trials investigating enzalutamide in men with mHSPC are currently ongoing and interim analysis data were presented, final results are urgently required. The median follow-up time in the ENZAMET trial was 34 months; hence, long-term results are needed to assess the efficacy and safety of enzalutamide for this indication. Furthermore, HRQoL results are required to determine the clinical benefit of enzalutamide treatment.

ENZAMET and ARCHES: final analysis data + long-term results required

An important issue to discuss is the choice of the appropriate treatment for the individual patient. Considering the range of available treatment options for men with mHSPC, including docetaxel, abiraterone acetate, apalutamide and enzalutamide (of note, the last two have not been approved yet for the treatment of mHSPC), it might be challenging to determine the appropriate therapy. In this regard, the identification of novel biomarkers that may guide precision medicine in the near future [32] may play an important role. Furthermore, randomised, comparative studies with consistent inclusion criteria are required to assess which patients benefit the most from the respective therapy. The final decision on the applied therapy is likely to depend on the individual safety profile of docetaxel, abiraterone and enzalutamide, respectively.

how to determine the optimal treatment for the individual patient?

The ENZAMET trial was conducted as an open-label study. Thus, patients and clinicians knew about the intervention; however, there is no information available whether the assessors were blinded or not. In the course of the ENZAMET trial, 1,125 patients were treated in 83 centres. This fact suggests that only a small number of patients were treated in each centre, leading to a high susceptibility for bias. The generation of randomisation sequence as well as allocation concealment was adequate. Reasons for discontinuations were reported. Since the trial is currently ongoing, only data from the first interim analysis is available; final analysis data is lacking. For two of the prespecified endpoints – HRQoL and health outcomes relative to costs – results are not available yet and will be presented separately as announced by the authors. An aspect that increases the risk of bias was the funding of ENZAMET by the manufacturer. Overall, a high risk of bias – mainly due to the

high risk of bias

limited applicability

lack of blinding – was detected. Patients with a significant cardiovascular disease within the last three months, including myocardial infarction, unstable angina, congestive heart failure, ongoing arrhythmias of Grade > 2 or thromboembolic events, were excluded from the ENZAMET trial. Although the median age at diagnosis of metastatic prostate cancer is 71 years, the applicability of results might be limited. There is a higher incidence of prostate cancer in African Americans; since no information on the ethnic groups of ENZAMET trial participants is available, the applicability of study results is unclear in this regard.

ESMO-MCBS evaluations were not applicable due to lack of median OS and PFS data

Given the non-curative setting of enzalutamide and the statistically significant primary endpoint OS, we applied form 2a of the ESMO-MCBS in order to assess whether enzalutamide satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5) [19]. However, since neither median OS nor PFS were estimable for the enzalutamide group, no score calculations could be applied.

28 days of enzalutamide treatment = € 2,895.35

additional costs for testosterone suppression and optional docetaxel therapy

Based on the treatment regimen of the ENZAMET trial, costs for 28 days of enzalutamide treatment are € 2,895.35 [28]. The median follow-up time was 34 months; at three years, 62% of patients in the enzalutamide group were still receiving a trial regimen [4]. 34 months of enzalutamide treatment would cost € 98,441.90. In addition to enzalutamide treatment, costs for testosterone suppression as background therapy incur and – if requested – also for docetaxel (€ 7,848.72 for six cycles of treatment). For comparison, conventional NSAA therapy with bicalutamide (50 mg daily) would result in monthly costs of € 48.27 (30 tablets á 50 mg) [28]. Here, too, costs for testosterone suppression and for optional docetaxel treatment incur.

benefit with enzalutamide, but higher rate of serious AEs

mature data required to determine the clinical benefit

Recently published results from the ENZAMET trial indicate that patients with mHSPC benefit from the addition of enzalutamide to standard first-line treatment in terms of OS and PSA PFS. However, the administration of enzalutamide was associated with a higher rate of serious AEs as compared to standard care. Due to the ongoing status of the trial, mature final and long-term data are lacking. However, due to the nature of the open-label study design, a high risk of bias is existent and will remain even with mature data. Since final OS data and HRQoL data are not available yet, the clinical benefit for affected patients cannot be assessed. More mature data, acquired over longer treatment duration, are required to prove the present results.

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [25, 26]

ESMO-MCBS	Active substance	Indication	Intention	PE	Form	MG standard treatment	Efficacy				Safety		AJ	FM
							MG months	*HR (95% CI)*	*Score calculation*	*PM*	*Toxicity*	*QoL*		
Adapted ESMO-MCBS	Enzalutamide	mHSPC	NC	OS	2a	-	-	-	-	-	-	-	-	**NA**[3]
Original ESMO-MCBS	Enzalutamide	mHSPC	NC	OS	2a	-	-	-	-	-	-	-	-	**NA**[3]

Abbreviations: AJ = Adjustments, CI = confidence interval, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, mHSPC = metastatic hormone-sensitive prostate cancer, NA = not applicable, OS = overall survival, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life

DISCLAIMER

The scores achieved with the ESMO Magnitude of Clinical Benefit Scale are influenced by several factors: by the specific evaluation form used, by the confidence interval (CI) of the endpoint of interest, and by score adjustments due to safety issues. Ad form: Every individual form measures a different outcome. The meaning of a score generated by form 2a is not comparable to the exact same score resulting from the use of form 2c. To ensure comparability, we report the form that was used for the assessment. Ad CI: The use of the lower limit of the CI systematically favours drugs with a higher degree of uncertainty (broad CI). Hence, we decided to avoid this systematic bias and use the mean estimate of effect. Ad score adjustments: Cut-off values and outcomes that lead to an up- or downgrading seem to be arbitrary. In addition, they are independent of the primary outcome and, therefore, a reason for confounding. Hence, we report the adjustments separately.

[3] An ESMO-MCBS score cannot be assessed, since none of the available study endpoints were applicable for an evaluation.

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12 Appendix

Table 4: Administration and dosing of enzalutamide (Xtandi®) [3, 20]

	Technology	Comparator
Administration mode	Enzalutamide (Xtandi®) is provided as 40 mg soft gelatine capsules administered as 160 mg (4 capsules) orally once daily. The tablets should not be cut, crushed or chewed, but should be swallowed whole with water, and can be taken with or without food.	Patients of the control group receive a conventional NSAA, i.e., bicalutamide 50 mg daily, nilutamide 150 mg daily, or flutamide 250 mg three times a day. The choice of NSAA is at the discretion of the treating clinician. Drug administration should be according to the product information guide. Cyproterone is not permitted.
Description of packaging	Soft capsule. White to off-white oblong soft capsules (approximately 20 mm x 9 mm) imprinted with "ENZ" in black ink on one side. Each soft capsule contains 40 mg of enzalutamide.	-
Total volume contained in packaging for sale	40 mg film-coated tablets: Cardboard wallet incorporating a PVC/PCTFE/aluminium blister of 28 film-coated tablets. Each carton contains 112 film-coated tablets (4 wallets).	-
Dosing	The recommended dose for adult men with metastatic/non-metastatic CRPC is 160 mg enzalutamide (four 40 mg soft capsules) as a single oral daily dose.	Dosing according to the respective product information guide.
Median treatment duration	Not reported.	Not reported.
Contraindications	Hypersensitivity to the active substance(s) or to any of the excipients: ✪ Capsule contents: caprylocaproyl macrogol-8 glycerides, butylhydroxyanisole (E320) , butylhydroxytoluene (E321) ✪ Capsule shell: gelatin, sorbitol sorbitan solution, glycerol, titanium dioxide (E171), purified water ✪ Printing ink: iron oxide black (E172), Polyvinyl acetate phthalate	According to the respective product information guide.
Drug interactions	<u>Potential for other medicinal products to affect enzalutamide exposures</u>: CYP2C8 inhibitors, CYP3A4 inhibitors, CYP2C8 and CYP3A4 inducers. <u>Potential for enzalutamide to affect exposures to other medicinal products:</u> enzyme induction, CYP1A2 and CYP2C8 substrates, P-gp substrates, BCRP, MRP2, OAT3 and OCT1 substrates, medicinal products which prolong the QT interval. <u>Effect of food on enzalutamide exposures:</u> no clinically significant effect on the extent of exposure to enzalutamide.	According to the respective product information guide.

Abbreviations: CRPC = castration-resistant prostate cancer, NSAA = non-steroidal anti-androgen

Table 5: Characteristics of ENZAMET trial

Title: Enzalutamide with standard first-line therapy in metastatic prostate cancer [4, 20, 21]			
Study identifier	NCT02446405, EudraCT number: 2014-003190-42, ANZCTR number: ACTRN12614000110684		
Design	Multinational, open-label, randomised, phase 3 trial		
	Duration of main phase:		Assignment to treatment groups: from March 2014 through March 2017 Date of the first interim analysis of the primary endpoint: 28 February 2019 Median follow-up: 34 months
Hypothesis	Superiority		
Funding	Funded by Astellas Scientific and Medical Affairs and others.		
Treatment groups	Intervention (n = 563)		Patients received enzalutamide provided as 40 mg soft gelatine capsules administered as 160 mg (4 capsules) orally once daily until clinical disease progression or prohibitive toxicity.
	Control (n = 562)		Patients of the control group will receive a conventional NSAA, i.e., bicalutamide 50 mg daily, nilutamide 150 mg daily, or flutamide 250 mg three times a day. The choice of NSAA is at the discretion of the treating clinician. Drug administration should be according to the product information guide.
Endpoints and definitions	Overall survival (primary endpoint)	OS	Defined as the interval from the date of randomisation to date of death from any cause, or the date of last known follow-up alive.
	PSA progression-free survival (secondary endpoint)	PSA PFS	PSA PFS is defined as the interval from the date of randomisation to the date of first evidence of PSA progression, clinical progression, or death from any cause, whichever occurs first, or the date of last known follow-up without PSA progression. PSA progression is defined as: a rise in PSA by more than 25% and more than 2ng/mL above the nadir (lowest PSA point). This needs to be confirmed by a repeat PSA performed at least 3 weeks later.
	Clinical progression-free survival (secondary endpoint)	Clinical PFS	Clinical PFS is defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression. Clinical progression is defined by progression on imaging, development of symptoms attributable to cancer progression, or initiation of other anti-cancer treatment for prostate cancer.
	Health-related quality of life (secondary endpoint)	HRQoL	-
	Health outcomes relative to costs (secondary endpoint)	-	Information on the following areas of health-care resource usage will be collected: hospitalisations, visits to health professionals, and medications. Australian unit costs will be applied to the resource usage data to estimate the incremental cost of the addition of enzalutamide to standard treatment.
Database lock	NR		

Title: Enzalutamide with standard first-line therapy in metastatic prostate cancer [4, 20, 21]		
Study identifier	NCT02446405, EudraCT number: 2014-003190-42, ANZCTR number: ACTRN12614000110684	
Results and analysis		
Analysis description	**Primary Analysis** It was determined that the enrolment of 1,100 patients (with 470 deaths) would provide a power of at least 80% to detect a 25% lower hazard of death in the enzalutamide group than in the standard-care group (HR 0.75), with a two-sided type I error rate of 0.05. In these calculations, a 3-year survival rate of 65% in the standard-care group on the basis of two previous studies of enzalutamide in men with metastatic CRPC was assumed. Protocol versions 1 and 2 called for an interim analysis of OS after the occurrence of 67% of the pre-specified 470 deaths with the use of the Lan–DeMets alpha-spending function. Protocol version 3, which was written after external evidence, became available for improved OS with early abiraterone treatment, added interim analyses of OS after the occurrence of 50% and 80% of the pre-specified 470 deaths. The trial executive committee made these decisions without any knowledge of outcomes in each treatment group. Efficacy analyses were based on the ITT principle and included all the patients who had undergone randomisation. The relevant follow-up times of patients who did not have an event were included in time-to-event analysis as censored observations. These analyses included patients who were lost to follow-up or who withdrew consent for continued follow-up after the date of consent withdrawal. Patients who had undergone randomisation and received a dose of any trial drug were included in analyses of drug exposure and safety. The Kaplan–Meier method was used to summarise time-to-event endpoints and to calculate event probabilities at 3 years. An unadjusted log-rank test was used for the primary comparison of randomly assigned trial groups. Cox proportional-hazards regression was used to estimate HRs, their 95% CIs, and interactions between group assignment and pre-specified baseline characteristics. The proportional-hazards assumption was tested. All P values and CIs are two-sided. It was pre-specified that consistency of the treatment effect would be evaluated across the following subgroups: Gleason score (≤ 7 vs. 8 to 10); age at trial entry (< 70 years or ≥ 70 years); ECOG performance status score (0 vs. 1 or 2); the presence or absence of visceral metastases in the lung, liver, or other organs; volume of disease (high or low); planned use or non-use of early docetaxel treatment; planned use or non-use of bone anti-resorptive therapy; the ACE-27 comorbidity score (0 or 1 vs. 2 or 3); prior local treatment (radiation, surgery, or neither); and geographic region (Australia or New Zealand vs. North America vs. Ireland or United Kingdom). It was pre-specified that the effects of enzalutamide according to the volume of disease and the use of early docetaxel treatment were of particular interest. The Benjamini–Hochberg method was used to account for multiple comparisons associated with subgroup analyses.	
Analysis population	Inclusion	✪ Male aged 18 or older with metastatic adenocarcinoma of the prostate defined by - documented histopathology or cytopathology of prostate adenocarcinoma from a biopsy of a metastatic site or - documented histopathology of prostate adenocarcinoma from a TRUS biopsy, radical prostatectomy, or TURP and metastatic disease consistent with prostate cancer or - metastatic disease typical of prostate cancer (i.e., involving bone or pelvic lymph nodes or para-aortic lymph nodes) and a serum concentration of PSA that is rising and > 20ng/mL. ✪ Target or non-target lesions according to RECIST 1.1 ✪ Adequate bone marrow function: Hb ≥ 100g/L and WCC ≥ 4.0 x 109/L and platelets ≥ 100 x 109/L. ✪ Adequate liver function: ALT <2 x ULN and bilirubin < 1.5 x ULN, (or if bilirubin is between 1.5-2x ULN, they must have a normal conjugated bilirubin). If liver metastases are present ALT must be <5xULN. ✪ Adequate renal function: calculated creatinine clearance > 30 ml/min (Cockcroft-Gault) ✪ ECOG performance status of 0-2. Patients with performance status 2 are only eligible if the decline in performance status is due to metastatic prostate cancer. ✪ Study treatment both planned and able to start within 7 days after randomisation ✪ Willing and able to comply with all study requirements, including treatment and required assessments ✪ Completed baseline HRQoL questionnaires unless unable to complete because of limited literacy or vision ✪ Signed, written, informed consent.

Title: Enzalutamide with standard first-line therapy in metastatic prostate cancer [4, 20, 21]

Study identifier	NCT02446405, EudraCT number: 2014-003190-42, ANZCTR number: ACTRN12614000110684	
	Exclusion	✪ Prostate cancer with significant sarcomatoid or spindle cell or neuroendocrine small cell components ✪ History of: - seizure or any condition that may predispose to seizure (e.g., prior cortical stroke or significant brain trauma) - loss of consciousness or transient ischemic attack within 12 months of randomisation - significant cardiovascular disease within the last 3 months including: myocardial infarction, unstable angina, congestive heart failure (NYHA functional capacity class II or greater, ongoing arrhythmias of grade > 2 (NCI CTCAE, version 4.03), thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism). Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed. ✪ Life expectancy of less than 12 months ✪ History of another malignancy within 5 years prior to randomisation, except for either non-melanomatous carcinoma of the skin or, adequately treated, non-muscle-invasive urothelial carcinoma of the bladder (Tis, Ta and low grade T1 tumours) ✪ Concurrent illness, including severe infection that might jeopardise the ability of the patient to undergo the procedures outlined in this protocol with reasonable safety (HIV-infection is not an exclusion criterion if it is controlled with anti-retroviral drugs that are unaffected by concomitant enzalutamide) ✪ Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse ✪ Patients who are sexually active and not willing/able to use medically acceptable forms of barrier contraception ✪ Prior ADT for prostate cancer (including bilateral orchidectomy), except in the following settings: - Started less than 12 weeks prior to randomisation and PSA is stable or falling. The 12 weeks starts from whichever of the following occurs earliest: first dose of oral anti-androgen, LHRHa, or surgical castration. - In the adjuvant setting, where the completion of adjuvant hormonal therapy was more than 12 months prior to randomisation and the total duration of hormonal treatment did not exceed 24 months. For depot preparations, hormonal therapy is deemed to have started with the first dose and to have been completed when the next dose would otherwise have been due, e.g., 12 weeks after the last dose of depot goserelin 10.8 mg ✪ Participation in other clinical trials of investigational agents for the treatment of prostate cancer or other diseases.

Characteristics	Intervention n = 563	Control n = 562
Mean age, years Median age (IQR), years	68.9 ± 8.1 69.2 (63.2–74.5)	68.8 ± 8.3 69.0 (63.6–74.5)
Region, n (%) Australia Canada Ireland New Zealand United Kingdom United States	 324 (58) 97 (17) 39 (7) 20 (4) 63 (11) 20 (4)	 321 (57) 107 (19) 43 (8) 19 (3) 50 (9) 22 (4)
Planned use of early docetaxel, n (%)	254 (45)	249 (44)
Volume of disease, n (%) High Low	 291 (52) 272 (48)	 297 (53) 265 (47)
Visceral metastases, n (%)	62 (11)	67 (12)
Number of months since diagnosis of metastasis Mean Median (IQR)	 2.9 ± 6.9 1.9 (0.9–2.8)	 3.1 ± 7.2 1.9 (1.0–2.8)

Title: Enzalutamide with standard first-line therapy in metastatic prostate cancer [4, 20, 21]			
Study identifier	NCT02446405, EudraCT number: 2014-003190-42, ANZCTR number: ACTRN12614000110684		
	Gleason score, n (%) ≤7 8-10 Missing data	 152 (27) 335 (60) 76 (13)	 163 (29) 321 (57) 78 (14)
	Previous therapy, n (%) Adjuvant ADT Anti-androgen therapy LHRHa Bilateral orchiectomy Docetaxel	 58 (10) 285 (51) 411 (73) 5 (1) 95 (17)	 40 (7) 316 (56) 418 (74) 8 (1) 83 (15)
Applicability of evidence			
Population	There is no information on the ethnic groups of the ENZAMET trial participants. Since there is a higher incidence of prostate cancer in African Americans than in other ethnic groups, the applicability of results in this regard is unclear. Patients with a significant cardiovascular disease within the last 3 months including myocardial infarction, unstable angina, congestive heart failure, ongoing arrhythmias of grade > 2 and thromboembolic events were excluded from the ENZAMET trial. Since the trial was conducted in elderly patients (median age of participant was 69 years), the applicability of results might be limited.		
Intervention	To date, enzalutamide is not approved for the assessed indication. However, the dosing regimen of enzalutamide in ENZAMET trial patients was consistent with the administration in patients with CRPC, an indication that is already licensed. No issue regarding intervention applicability was identified.		
Comparators	In the ENZAMET trial, conventional NSAAs (including bicalutamide, flutamide and nilutamide) were chosen as comparators. Since this intervention is no longer the standard of care, the chosen comparator is considered to be inappropriate.		
Outcomes	There is evidence that the addition of enzalutamide to standard first-line therapy in patients with mHSPC is associated with an improvement in PFS and OS. Since the ENZAMET trial is ongoing and first interim data was presented, final results for all endpoints are lacking. Hence, the applicability of outcomes cannot be assessed yet.		
Setting	ENZAMET is an international trial, conducted in 83 centres across Australia, New Zealand, Canada, the United Kingdom and Ireland. There was no information found regarding the ethnicity of the participants. No issue regarding setting applicability was found.		

Abbreviations: ADT = androgen deprivation therapy, ALT = alanine aminotransferase, ANZCTR = Australian New Zealand Clinical Trials Registry, CI = confidence interval, CRPC = castration-resistant prostate cancer, CTCAE = Common Terminology Criteria for Adverse Events, ECOG = Eastern Cooperative Oncology Group, Hb = haemoglobin, HIV = human immunodeficiency virus, HR = hazard ratio, HRQoL = health-related quality of life, ITT = intention-to-treat, IQR = interquartile range, LHRHa = luteinizing hormone releasing hormone analogue, n = number, NCI = National Cancer Institute, NR = not reported, NSAA = non-steroidal anti-androgen, NYHA = New York Heart Association, OS = overall survival, PFS = progression-free survival, PSA = prostate-specific antigen, RECIST = Response Evaluation Criteria In Solid Tumors, TRUS = transrectal ultrasound guided, TURP = transurethral resection of the prostate, ULN = upper limit normal, WCC = white cell count

Table 6: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [4, 20, 23]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: Central randomisation system		yes
Adequate allocation concealment: Following randomisation, participants will be allocated to receive either enzalutamide or NSAA in addition to their LHRHa (or surgical castration) via a central randomisation system that stratifies for volume of disease, site, co-morbidities and use of anti-resorptive therapy – denosumab, zoledronic acid or neither at time of starting ADT.		yes
Blinding: open-label	**Patient:** Unblinded	no
	Treating physician: Unblinded	no
Selective outcome reporting unlikely: The ENZAMET trial is currently ongoing; hence, only data from the first interim analysis is available. Final analysis data is lacking. There is no data available for two pre-specified endpoints (HRQoL and health outcomes relative to costs); according to the authors, these results will be reported separately. Reasons for discontinuations have been reported.		unclear
No other aspects which increase the risk of bias: The trial was funded by Astellas Scientific and Medical Affairs and others. Astellas Pharma provided enzalutamide and financial support for trial conduct; representatives of the manufacturer reviewed drafts of the protocol and trial report, but were not otherwise involved in any aspects of the trial design, data accrual, data analysis, or manuscript preparation.		no
Risk of bias – study level		high

Abbreviations: ADT = androgen deprivation therapy, HRQoL = health-related quality of life, LHRH = luteinizing hormone releasing hormone analogue, NSAA = non-steroidal anti-androgen