Horizon Scanning in Oncology

Enzalutamide (Xtandi®) in patients with nonmetastatic, castration-resistant prostate cancer (CRPC)

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Abstract

Introduction

Castration-resistant prostate cancer (CRPC) is prostate cancer that keeps growing even when the testosterone level is reduced to very low levels. Enzalutamide (Xtandi®) is an orally bioavailable, organic, non-steroidal small-molecule androgen receptor (AR) signalling inhibitor. The US Food and Drug Administration (FDA) approved enzalutamide for nonmetastatic and metastatic CRPC in July 2018. To date, enzalutamide is not yet approved by the European Medicines Agency (EMA) for the assessed indication.

Methodology

Published and grey literature were identified by searching the Cochrane Library, CRD Database, Embase, Ovid Medline PubMed, Internet sites and contacting the manufacturer, resulting in 94 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 "clinically meaningful 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 PROSPER trial

The PROSPER trial assessed the efficacy and safety of enzalutamide versus placebo in patients with nonmetastatic CRPC and a rapidly rising prostate-specific antigen (PSA) level. Analyses showed that patients of the enzalutamide group had a statistically significant benefit in median metastasis-free survival (MFS) (HR 0.29, 95% CI, 0.24–0.35, $p < 0.001$); hence, patients who received enzalutamide had a 71% lower risk of metastasis or death than patients who received the placebo. Patients of the enzalutamide group also had a statistically significant delay regarding the median time to PSA progression (HR 0.07, 95% CI, 0.05–0.08, $p < 0.001$) and the median time to first use of subsequent antineoplastic therapy (HR 0.21, 95% CI, 0.17–0.26, $p < 0.001$). For overall survival (OS), only data from the first interim analysis is available; at that point of time, 11% of the patients of the enzalutamide group and 13% of placebo-group patients had died. The median OS was not reached in either treatment group. One third of enzalutamide-group patients had an adverse event (AE) of grade 3 or higher. Serious AEs were more frequent among patients of the enzalutamide group than in placebo-group patients (24% vs. 18%); 3% of enzalutamide patients had an AE that led to death, compared to 1% in the placebo group.

Conclusion

The administration of enzalutamide in patients with nonmetastatic CRPC and a rapidly rising PSA prolonged MFS and delayed PSA progression and the use of subsequent antineoplastic therapy. However, the clinical benefit of enzalutamide reflected in OS prolongation and an improvement of the patients' quality of life (QoL) has not been established yet. Final analyses of the PROSPER trial and further ongoing studies may provide information about whether prolonged MFS also implies prolongation of OS. At any rate, the benefits of enzalutamide treatment need to be weighed against the risks, always considering the patients' QoL. Additionally, a direct comparison of enzalutamide and apalutamide is needed to verify the optimal treatment for this patient population.

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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 predefined 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?
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	
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A0004	What is the natural course of prostate cancer?
A0006	What are the consequences of prostate cancer for the society?
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A0003	What are the known risk factors for prostate cancer?
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A0025	How is nonmetastatic CRPC currently managed according to published guidelines and in practice?
Clinical effectiveness	
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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?
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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?

enzalutamide binds directly to the AR

inhibition of androgen binding, AR nuclear translocation and AR-mediated DNA binding

Enzalutamide (Xtandi®) is an orally bioavailable, organic, non-steroidal small-molecule androgen receptor (AR) signalling inhibitor [2]. Enzalutamide blocks several steps in the AR signalling pathway including the binding of androgens to the AR (competitively), the nuclear translocation of the activated receptor and the association of the activated AR with deoxyribonucleic acid (DNA) (even in the setting of AR overexpression and in prostate cancer cells that are resistant to anti-androgens). Enzalutamide thus decreases the growth of prostate cancer cells and is able to induce cancer cell death and tumour regression [3]. By inhibiting the activity of prostate cancer cell ARs, enzalutamide may lead to a reduction in prostate cancer cell proliferation and to a reduction in the serum prostate-specific antigen (PSA) [2].

160 mg enzalutamide orally once daily

concurrent GnRH analogue or previous bilateral orchiectomy

For the treatment of patients with (metastatic) castration-resistant prostate cancer (CRPC), the recommended dose is 160 mg enzalutamide (four 40-mg soft capsules) administered orally once daily. The soft capsules should be swallowed whole with water, should not be chewed, dissolved or opened. Enzalutamide can be taken with or without food. In case a patient experiences grade 3 (or higher) toxicity or an intolerable adverse reaction, the dosing of enzalutamide should be withheld for one week or until the symptoms improve to grade 2 (or lower). Then, if warranted, enzalutamide can be resumed at the same or a reduced dose (120 mg or 80 mg) [3, 4]. In patients who receive enzalutamide, a gonadotropin-releasing hormone (GnRH) analogue should be administered concurrently or patients should have had bilateral orchiectomy [3].

A0022: Who manufactures enzalutamide?

Astellas Pharma Europe B.V.

3 Indication

A0007: What is the target population in this assessment?

men with nonmetastatic CRPC and PSADT ≤ 10 months

Enzalutamide (Xtandi®) is indicated in patients with nonmetastatic CRPC and a PSA doubling time (PSADT) of ten months or less.

4 Current regulatory status

A0020: For which indications has enzalutamide received marketing authorisation?

not approved by the EMA for the assessed indication

To date, enzalutamide has not been approved by the European Medicines Agency (EMA) for the assessed indication. The EMA granted marketing authorisation for enzalutamide (Xtandi®) for the treatment of the following two other indications [5]:

- Metastatic CRPC in adult men whose disease has progressed on or after docetaxel therapy (indication approved in 2013)
- CRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (extension of indication in 2014).

FDA-approved for nonmetastatic and metastatic CRPC since 07/2018

In the US, enzalutamide (Xtandi®) was initially approved in 2012 for the treatment of patients with metastatic CRPC who had previously received docetaxel. In 2014, the approved indication was changed to: enzalutamide for the treatment of patients with metastatic CRPC [6]. In July 2018, the approved indication was extended to include patients with both nonmetastatic and metastatic CRPC [4, 7].

5 Burden of disease

A0002: What is prostate cancer?

CRPC grows despite low testosterone levels

Prostate cancer develops in the tissue of the prostate gland. CRPC is prostate cancer that keeps growing even when the testosterone level is reduced to very low levels. Whilst many early-stage prostate cancers need normal testosterone levels to grow, CRPCs do not [8]. CRPC is defined as a castrate serum testosterone level < 50 ng/dl or 1.7 nmol/l and has either one of the following progression characteristics:

- Biochemical progression: three consecutive rises in PSA one week apart (resulting in two 50% increases over the nadir) and PSA > 2 ng/ml or
- Radiological progression: the appearance of two or more new bone lesions on bone scan or a soft tissue lesion using the Response Evaluation Criteria in Solid Tumours (RECIST) [9].

nonmetastatic CRPC: no radiological findings

Patients who are affected by nonmetastatic CRPC show rising PSA and castrate testosterone levels, with no radiological findings indicating metastatic disease on computed tomography (CT) and bone scans [10].

A0004: What is the natural course of prostate cancer?

78.2% of prostate cancers diagnosed at local stage

Three stages of prostate cancer can be distinguished: localised, locally-advanced and advanced prostate cancer [11]. According to data from the US population, 78.2% of prostate cancers are diagnosed at the local stage; 12% of prostate cancer cases are diagnosed at a locally-advanced stage and 5% are diagnosed when the cancer has already spread and metastasised [12].

Austria: 5-year survival rate is 91.8%

In Austria, the relative survival rate following diagnosis in patients with prostate cancer (2008–2012) is 95.7% at one year, 93.1% at three years and 91.8% at five years. In 2015, the age-standardised mortality rate for the European Standard Population (2013) was 37.0 per 100,000 men per year. In 2015, 1,128 men died from prostate cancer. At the end of the year 2015, 61,348 men diagnosed with prostate cancer were alive; more than one third of the affected patients were diagnosed with prostate cancer ten years (or longer) earlier [13].

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

A0023: How many people belong to the target population?

incidence rate in Austria: 130.6/100,000 men/year

In Austria, 4,854 men per year (2015) are newly diagnosed with prostate cancer. The age-standardised incidence rate for the European Standard Population (2013) is 130.6 per 100,000 men per year [13].

median age at diagnosis: 66 years

In the United States, prostate cancer is most frequently diagnosed among men aged 65 to 74 years; the median age at diagnosis is 66 years [12].

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

often asymptomatic at the time of diagnosis

Due to the fact that most patients are diagnosed with prostate cancer when the disease is at a localised stage, there are often no clinical manifestations at the time of diagnosis. Patients rarely present with symptoms that are attributable to prostate cancer. Uncommon symptoms may be non-specific urinary symptoms, haematuria or haematospermia, which are usually caused by non-malignant conditions. Since the bones are the predominant site of prostate cancer dissemination, patients whose disease is metastatic at the time of diagnosis may present with bone pain. Symptoms that may be related to metastatic disease include weight loss, weakness or pain due to spinal cord compression or due to pathologic fractures, fatigue caused by anaemia, or renal/urinary symptoms (e.g. haematuria, inability to void, incontinence, or symptoms associated with chronic renal failure) [14].

clinical signs potentially associated with prostate cancer:

Clinical signs that can be associated with prostate cancer include [14]:

elevated PSA

- Elevated PSA: In men affected by prostate cancer, laboratory-tested PSA is often elevated. PSA is not specific for malignancy, elevated PSA may also be caused by a number of benign conditions. On the contrary, a PSA value in the normal range does not prove the absence of prostate cancer. Although there is a lack of specificity for prostate cancer, PSA measurement is the most commonly used and most valuable test to detect prostate cancer at an early stage.

abnormal findings on DRE

- Abnormal findings on digital rectal examination (DRE), such as prostate nodules, indurations or asymmetry. How-

ever, only tumours in the posterior and lateral aspects of the prostate gland can be detected by DRE.

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

risk factors:

The risk for the development of clinically significant prostate cancer is related to the following factors [14-18]:

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

  increasing age

- Ethnicity: African Americans have a higher risk to develop 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.

  African Americans: higher risk

- 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 digital rectal examination (DRE) including prostate nodules, indurations or asymmetries.

  suspicious findings on DRE

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 signs of prostate cancer that warrant additional evaluation. There is no consistent PSA threshold for defining an abnormal PSA value [14].

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.

final diagnosis is based on histological examination

grading systems

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 more accurate risk stratification. Due to the fact that the sampling techniques are used for prostate biopsies which have a substantial potential for missing malignant tissue, 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 [14, 19].

≥ 95% are adenocarcinomas

The most commonly diagnosed malignancies are adenocarcinomas (more than 95%); other histological types are urothelial carcinoma, basal cell carcinoma, small cell carcinoma, lymphoma and sarcoma [19].

differential diagnosis

Regarding prostate-cancer differential diagnosis, lower-urinary-tract symptoms (e.g. urgency, nocturia and hesitancy) are common but usually caused by benign conditions. Elevated PSA can be caused by transient conditions, such as prostatitis or perineal trauma or by persistent causes such as benign prostate hyperplasia (BPH) [14].

6 Current treatment

A0025: **How is nonmetastatic CRPC currently managed according to published guidelines and in practice?**

nonmetastatic CRPC requires varying treatment approaches

According to the European Association of Urology (EAU) nonmetastatic CRPC is a heterogeneous disease that requires varying treatment approaches. For some patients, observation may be an option; for patients with a PSADT of ten months (or lower), enzalutamide and apalutamide may be the appropriate treatment. It is likely that, in the near future, more accurate imaging modalities and circulating tumour biomarker assays are going to redefine the assessment of nonmetastatic CRPC [10].

NCCN recommendation

According to the National Comprehensive Cancer Network (NCCN), for patients with CRPC and no signs of distant metastasis, observation can be considered. This applies especially to patients with a PSADT longer than ten months, since these patients' disease is considered relatively indolent. For patients with a shorter PSADT, secondary hormone therapy (specifically with apalutamide, but also other secondary hormone therapies) is an option [20].

7 Evidence

systematic literature search in 5 databases: 59 hits
manual search: 35 additional references

A literature search was conducted on 11 October 2018 in five databases: the Cochrane Library, CRD Database, Embase, Ovid Medline and PubMed. Search terms were "enzalutamide", "Xtandi", "prostate cancer", "prostatic neoplasms", "nonmetastatic" and "castration-resistant prostate cancer"; 59 references were identified The manufacturer was also contacted, who submitted 12 references (six of them had already been identified by systematic literature search). A manual search identified 35 additional references (web documents and journal articles).

overall: 94 references

Overall, 94 references were identified. Included in this report are:

included: 2 studies

- Interim analysis data from PROSPER, an international, double-blind, randomised, placebo-controlled phase III trial evaluating the efficacy and safety of enzalutamide in patients with nonmetastatic CRPC [21-23] and
- STRIVE, a multicentre, randomised, double-blind phase II trial assessing enzalutamide treatment versus bicalutamide treatment in patients with nonmetastatic or metastatic CRPC [24].

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) [25]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patients and treating physicians, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table (see Appendix).

applicability of study results

The external validity of the included phase III trial was assessed using the EUnetHTA guideline on 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) [26].

magnitude of clinically meaningful benefit assessed based on ESMO-MCBS

To evaluate the magnitude of "clinically meaningful 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 [27]. Additionally, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [28]. 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 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 a method of quality assurance 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 study

PROSPER trial: double-blind, placebo-controlled phase III trial

The PROSPER trial [21-23] is an international (300 sites in 32 countries), double-blind, randomised, placebo-controlled phase III trial that is conducted to evaluate the efficacy and safety of enzalutamide in patients with non-metastatic CRPC. Between November 2013 and June 2017, a total of 1,401 patients were enrolled and were randomised in a 2:1 ratio to the enzalutamide group (n = 933) and to the placebo group (n = 468). Since the PROSPER trial is currently ongoing, interim analysis data was presented; final analysis of overall survival (OS) has not yet been performed. Patients who were eligible had to have pathologically confirmed prostate adenocarcinoma without neuroendocrine differentiation, signet-cell features or small-cell features; patients had to have a rising PSA level despite castration-associated testosterone levels (serum testosterone level 1.73 nmol/l, 0.50 ng/ml). Included patients had to have been receiving androgen deprivation therapy (with a GnRH agonist or antagonist) or to have undergone bilateral orchiectomy. As assessed by CT or magnetic resonance imaging (MRI) for soft tissue disease and by whole-body radionuclide bone scanning, eligible patients had no previous or current evidence of metastatic disease. Patients with suspected brain metastases, active leptomeningeal disease or those with a history of seizure (or with a condition that may confer a predisposition to seizure) were excluded. Stratification of patients was applied according to PSADT (< 6 months versus ≥ 6 months) and previous or current use of a bone-targeting agent at baseline.

patient characteristics

The patients had a median age of 74 years (ranging from 50 to 95 years in the enzalutamide group) and 73 years (ranging from 53 to 92 years in the placebo group). The majority of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (80% of patients in the enzalutamide group and 82% in the placebo group). The median serum PSA value of patients in the enzalutamide group was 11.1 ng/ml and 10.2 ng/ml in patients of the placebo group; the median PSADT was 3.8 months among enzalutamide-group patients and 3.6 months in placebo-group patients. In both groups, 77% of patients had a PSADT < 6 months. 89% of enzalutamide-group patients and 90% of placebo-group patients did not use a bone

targeting agent. Detailed patient characteristics including inclusion and exclusion criteria can be found in Table 5.

Patients of the enzalutamide group received enzalutamide at a dose of 160 mg per day, administered orally as four 40-mg soft capsules once daily. Patients of the placebo group received placebo capsules (identical in appearance to enzalutamide capsules), administered in the same manner as enzalutamide. Study drug administration was continued until radiographic progression, as evaluated by central independent blinded radiographic review.

enzalutamide: 160 mg/day, administered orally

The primary endpoint of the PROSPER trial was metastasis-free survival (MFS) which was defined as the time from randomisation to radiographic progression or as the time to death from any cause during the period from randomisation to 112 days after discontinuation of the trial regimen (without evidence of radiographic progression), whichever occurred first. Secondary endpoints were time to PSA progression, PSA response rate (based on a decrease from baseline of ≥ 50%), time to first use of subsequent antineoplastic therapy, assessment of the quality of life (QoL), overall survival (OS) and safety.

primary endpoint: MFS

The median duration of study treatment was 18.4 months in patients of the enzalutamide group and 11.1 months in patients of the placebo group. At the data cut-off date on 28 June 2017, 634 patients of the enzalutamide group and 176 patients in the placebo group were receiving the trial regimen. Clinical efficacy data of the PROSPER trial is presented in Table 1 and AEs are listed in Table 2.

median duration of treatment: 18.4 months (enzalutamide group) vs. 11.1 months (placebo group)

The PROSPER trial is currently ongoing; the estimated study completion date is 31 May 2020 [29].

PROSPER trial is ongoing until 2020

7.2.1 Clinical efficacy

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

OS was a secondary efficacy endpoint of the PROSPER trial, defined as the time from randomisation to death from any cause. At the first interim analysis, median OS was not reached in either group; hazard ratio (HR) was 0.80 (95% confidence interval, CI, 0.58–1.09, p = 0.15). In the enzalutamide group, 11% of patients had died compared to 13% of patients in the placebo group. The analysis of OS (using a stratified log-rank test to compare the treatment groups) will not be performed until at least 480 deaths have been observed. OS is one of the key study endpoints of the PROSPER trial, hence, all patients must be followed for survival status until death [22].

1st interim analysis: median OS not reached in either group; 11% of enzalutamide group and 13% of placebo group had died

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

enzalutamide-group patients had a 71% lower risk of radiographic progression/death than placebo-group patients

MFS was the primary endpoint of the PROSPER trial; at the cut-off date in June 2017, 23% of patients in the enzalutamide group and 49% of placebo-group patients had a primary endpoint event. The primary analysis (including all deaths without evidence of radiographic progression from randomisation within 112 days after treatment discontinuation) showed a median MFS of 36.6 months in the enzalutamide group compared to 14.7 months in the placebo group. With a HR of 0.29 (95% CI, 0.24–0.35, $p < 0.001$), patients who received enzalutamide had a 71% lower risk of radiographic progression or death than patients who received the placebo. These results were consistent with the results of a pre-specified sensitivity analysis (including all deaths without evidence of radiographic progression, regardless of timing): HR for radiographic progression or death was 0.30 (95% CI, 0.25–0.36). Median follow-up was 18.5 months in the enzalutamide group and 15.1 months in the placebo group. Of the 23% of enzalutamide-group patients who had a primary endpoint event, 85% had radiographic progression and 15% died without radiographic progression (of these, two deaths were considered by the investigator to be study-drug related). In the placebo group, 49% of patients had a primary endpoint event, 98% of them had radiographic progression and 2% died without radiographic progression. Patients who died without radiographic progression had a median age of 80 years (enzalutamide group) and 81 years (placebo group). In patients of the enzalutamide group, 58% of cases of radiographic progression were found in soft tissue, compared to 59% in placebo-group patients. The superiority of enzalutamide treatment regarding MFS was consistent across all pre-specified subgroups [21].

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

median time to PSA progression: 37.2 months (enzalutamide group) vs. 3.9 months (placebo group)

In patients who received enzalutamide, the median time to PSA progression was 37.2 months versus 3.9 months in placebo-group patients (HR 0.07, 95% CI, 0.05–0.08, $p < 0.001$). The number of patients with PSA progression was 208 (22%) in the enzalutamide group and 324 (69%) in the placebo group.

higher confirmed PSA response rate in enzalutamide group

In the enzalutamide group, the confirmed PSA response rate of 50% or more was higher than in the placebo group, applying to 76% versus 2% of patients.

median time to first subsequent antineoplastic therapy: twice as long in enzalutamide group

15% of enzalutamide-group patients discontinued the trial regimen and received subsequent antineoplastic therapy, as did 48% of patients in the placebo group; the most commonly administered antineoplastic therapy (in both groups) was abiraterone acetate. The median time to first use of subsequent antineoplastic therapy was 39.6 months among enzalutamide-group patients and 17.7 months among placebo-group patients (HR 0.21, 95% CI, 0.17–0.26, $p < 0.001$). The median time interval between discontinuation of the study treatment and subsequent antineoplastic therapy was 25 days in patients who received enzalutamide and 18 days in patients who received the placebo.

Further chemotherapy-related endpoints including chemotherapy-free disease-specific survival (CFDS) and chemotherapy-free survival (CFS) were improved statistically significantly by the administration of enzalutamide when compared to placebo: median CFSD was 39.6 months in the enzalutamide group) versus 38.9 months in the placebo group (HR 0.40, 95% CI, 0.31–0.52, $p < 0.001$); median CFS was 38.1 months in the enzalutamide group versus 34.0 months in the placebo group (HR 0.50, 95% CI, 0.40–0.64, $p < 0.001$) [30].

statistically significant improvement of chemotherapy-related endpoints

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

PROSPER trial analyses showed that enzalutamide treatment prolonged urinary and bowel symptom control (results available in the form of an abstract) [31].

prolongation of urinary and bowel symptom control

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?

The generic health related (HRQoL) and the disease-specific quality of life (QoL) were evaluated by the use of the European Quality of Life-5 Dimensions-5 Levels (EQ-5D-5L) health questionnaire, the Brief Pain Inventory-Short Form (BPI-SF), the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and the Quality of Life Questionnaire-Prostate 25 (QLQ-PR25) module (this information is based on an abstract [32]).

QoL evaluated by using EQ-5D-5L, BPI-SF, FACT-P and QLQ-PR25

The results of EQ-5D-5L and QLQ-PR25 were published online and listed in tabular form for each item individually [29]. Analyses of BPI-SF, including the items "worst pain in the last 24 hours", "mean pain severity" and "mean pain interference" favoured enzalutamide over placebo treatment. Overall, no statistically significant or clinically meaningful difference regarding HRQoL or pain could be established between enzalutamide-group patients and placebo-group patients over 96 weeks [32].

no difference in HRQoL or pain between treatment groups over 96 weeks

Analyses of FACT-P showed that the median time to FACT-P score degradation was equal in both groups: 11.1 months (HR 0.92, 95% CI, 0.79–1.08). In total, 54% of patients in the enzalutamide group and 51% of patients in the placebo group had score degradation [23]. Analyses showed a trend favouring enzalutamide for all domains of FACT-P except physical well-being. For the FACT-P item "social well-being", a statistically significant difference in favour of enzalutamide treatment was observed. Overall, comparing enzalutamide versus placebo treatment over 96 weeks, the patients' HRQoL could be maintained with minimal decline (due to the fact that there were no physical disease-related effects at baseline) [32].

median time to FACT-P score degradation equal in both groups

HRQoL maintained with enzalutamide and placebo over 96 weeks

Table 1: Efficacy results of the PROSPER trial [23]

Descriptive statistics and estimate variability	Treatment group	Enzalutamide	Placebo
	Number of patients	933	468
	Median MFS, months	36.6	14.7
	Metastasis or death, n (%) Radiographic progression, n/total, n (%) New bone metastases New soft-tissue metastases Metastases to lymph node Visceral metastases Concurrent new bone and soft-tissue metastases Metastases to lymph node Visceral metastases Death, n/total, n (%)	219 (23) 187/219 (85) 71/219 (32) 109/219 (50) 79/219 (36) 34/219 (16) 7/219 (3) 7/219 (3) 3/219 (1) 32/219 (15)	228 (49) 224/228 (98) 79/228 (35) 132/228 (58) 116/228 (51) 27/228 (12) 13/228 (5) 12/228 (5) 1/228 (<1) 4/228 (2)
	PSA progression Median time to progression, months Patients with progression, n (%)	 37.2 208 (22)	 3.9 324 (69)
	Use of subsequent antineoplastic therapy Median time to first use, months Patients with use, n (%)	 39.6 142 (15)	 17.7 226 (48)
	OS Median survival, months Patients who died, n (%)	 NR 103 (11)	 NR 62 (13)
	Confirmed PSA response ≥ 50%, n (%)	712 (76)	11 (2)
	FACT-P score degradation Median time to score degradation, months Patients with score degradation, n (%)	 11.1 506 (54)	 11.1 239 (51)
Effect estimate per comparison	Comparison groups		Enzalutamide vs. placebo
	Median MFS	HR	0.29
		95% CI	0.24—0.35
		p value	< 0.001
	Median time to PSA progression	HR	0.07
		95% CI	0.05—0.08
		p value	< 0.001
	Median time to first use of subsequent antineoplastic therapy	HR	0.21
		95% CI	0.17—0.26
		p value	< 0.001
	Median OS	HR	0.80
		95% CI	0.58—1.09
		p value	0.15
	Median time to FACT-P score degradation	HR	0.92
		95% CI	0.79—1.08
		p value	-

Abbreviations: CI = confidence interval, FACT-P = Functional Assessment of Cancer Therapy-Prostate, HR = hazard ratio, MFS = metastasis-free survival, n = number, NR = not reached, OS = overall survival, PSA = prostate-specific antigen

7.2.2 Safety

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

AEs of any grade occurred in 87% of patients in the enzalutamide group and in 77% of patients in the placebo group; the median reporting period for AEs was 18.0 months in the enzalutamide group compared to 11.1 months in the placebo group. AEs of grade 3 or higher were more frequent among patients of the enzalutamide group (31%) than in patients of the placebo group (23%). Serious AEs (according to the protocol defined as events that resulted in death, were life-threatening, resulted in prolonged hospitalisation, inability to conduct normal life functions, or events that led to a congenital anomaly or birth defect) occurred in 24% of enzalutamide-group patients and in 18% of placebo-group patients. In 9% (enzalutamide group) compared to 6% of patients (placebo group), the occurrence of one or more AEs led to a discontinuation of the trial regimen.

AEs grade ≥ 3: 31% in enzalutamide group vs. 23% in placebo group

9% (enzalutamide group) and 6% (placebo) group discontinued treatment due to an AE

The most frequent AEs occurring in ≥ 5% of patients receiving enzalutamide were fatigue, hot flush, hypertension, nausea and fall. Among patients of the placebo group, the most common AEs occurring in ≥ 5% of patients were hypertension, fatigue and haematuria. The most common AEs of special interest were hypertension, major adverse cardiovascular events and mental disorders[1], occurring in 12%, 5% and 5% of enzalutamide-group patients respectively, and hypertension, major cardiovascular events, hepatic impairment and neutropenia in 5%, 4%, 1% and 1% of placebo-group patients respectively. During the trial, no events of posterior reversible encephalopathy syndrome (PRES) were reported. Five patients who received enzalutamide had a "non-infectious encephalopathy or delirium"; three patients had convulsions (serious and drug-related), which occurred within 180 days after initiation of enzalutamide. One patient who received enzalutamide and was affected by convulsions discontinued the trial regimen. Another enzalutamide-group patient had convulsions and a complication leading to death.

no PRES occurred during the trial; neurological AEs within 180 days after enzalutamide initiation

In 3% of enzalutamide-group patients and 1% of placebo-group patients, AEs led to death; most frequently caused by cardiac events (1% of enzalutamide-group patients and < 1% in placebo-group patients). In both groups, patients with a history of cardiovascular disease, hypertension, diabetes mellitus or hyperlipidaemia at baseline age ≥ 75 years showed a higher incidence of major adverse cardiac events.

AEs leading to death in 3% (enzalutamide group) and 1% (placebo group) of patients

The most common reason for discontinuation of the study treatment among patients of both groups was disease progression, which applied to 14.8% of patients in the enzalutamide group and 44.2% in placebo-group patients. The second most common reason to stop the study treatment was the occurrence of adverse events (AEs). This concerned 9.8% of enzalutamide-group patients and 6.2% of placebo-group patients.

study treatment discontinuation due to disease progression in 14.8% of enzalutamide-group patients

[1] including memory impairment, disturbance in attention, cognitive disorders, amnesia, Alzheimer's disease, senile dementia, mental impairment and vascular dementia

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

The mode of administration and dosing of enzalutamide used in PROSPER trial partcipants is consistent with the FDA-approved license [4].

dose reduction in case of toxicity

If a patient experiences grade ≥ 3 toxicity or an intolerable adverse reaction, the dosing of enzalutamide should be withheld for one week or until the symptoms improve to grade ≤ 2. If warranted, enzalutamide can be resumed at the same or a reduced dose (120 mg or 80 mg) afterwards [3, 4].

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

special warnings and precautions for use

According to the Summary of Product Characteristics, the following special warnings and precautions for use are listed [3]:

- In patients with a history of seizures or predisposing factors (e.g. underlying brain injury, stroke, primary brain tumours, brain metastases, alcoholism), enzalutamide should be administered with caution. The risk of seizure may also be increased due to concomitant medicinal products that lower the seizure threshold. In patients who develop seizure, the decision whether to continue enzalutamide treatment or stop the administration should be taken individually.
- The (rare) occurrence of PRES, a reversible, neurological disorder, was reported from patients who received enzalutamide. In patients who develop PRES, a discontinuation of enzalutamide is recommended.
- In patients who receive medicinal products that are sensitive substrates of many metabolising enzymes or transporters, the concomitant use of enzalutamide should be avoided.
- Enzalutamide should be administered with caution in patients with severe renal impairment (enzalutamide has not been studied in this patient population) and in patients with severe hepatic impairment (an increased half-life of enzalutamide has been observed among these patients).
- 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 the phase III studies. Furthermore, androgen deprivation therapy may prolong the QT interval.
- Since the safety and efficacy of enzalutamide administration with cytotoxic chemotherapy has not been established, the concomitant use is listed among the precautions of use/special warnings.
- Enzalutamide soft capsules contain sorbitol (E420) and should not be administered to patients with hereditary problems of fructose intolerance.
- Hypersensitivity reactions, e.g. tongue, lip and pharyngeal oedema have been observed in patients who received enzalutamide.

reproductive toxicity in animal studies: contraception required

Since there is no evidence whether enzalutamide or its metabolites are present in the semen, contraception is required during and for three months after treatment with enzalutamide. Reproductive toxicity has been demonstrated in animal studies [3].

Table 2: PROSPER trial adverse events [23]

Adverse event (according to NCI CTCAE version 4)	**Intervention** (n = 930)		**Control** (n = 465)	
	Any grade n (%)	Grade ≥ 3 n (%)	Any grade n (%)	Grade ≥ 3 n (%)
Any AE	808 (87)	292 (31)	360 (77)	109 (23)
Any serious AE	226 (24)	-	85 (18)	-
AE leading to discontinuation of trial regimen	87 (9)	-	28 (6)	-
AE leading to death	32 (3)	-	3 (1)	-
Most common AEs, occurring in ≥ 5% of patients				
Fatigue	303 (33)	27 (3)	64 (14)	3 (1)
Hot flush	121 (13)	1 (< 1)	36 (8)	0 (0)
Nausea	106 (11)	3 (< 1)	40 (9)	0 (0)
Diarrhoea	91 (10)	3 (< 1)	45 (10)	2 (< 1)
Hypertension	111 (12)	43 (5)	24 (5)	10 (2)
Fall	106 (11)	12 (1)	19 (4)	3 (1)
Constipation	85 (9)	2 (< 1)	32 (7)	2 (< 1)
Dizziness	91 (10)	4 (< 1)	20 (4)	0 (0)
Arthralgia	78 (8)	1 (< 1)	32 (7)	1 (< 1)
Asthenia	82 (9)	11 (1)	28 (6)	1 (< 1)
Decreased appetite	89 (10)	2 (< 1)	18 (4)	1 (< 1)
Back pain	73 (8)	2 (< 1)	33 (7)	1 (< 1)
Headache	85 (9)	2 (< 1)	21 (5)	0 (0)
Haematuria	62 (7)	16 (2)	36 (8)	13 (3)
Urinary tract infection	38 (4)	7 (1)	30 (6)	3 (1)
Weight loss	55 (6)	2 (< 1)	7 (2)	0 (0)
Urinary retention	20 (2)	4 (< 1)	28 (6)	5 (1)
AEs of special interest				
Hypertension	114 (2)	43 (5)	25 (5)	11 (2)
Major adverse cardiovascular event	48 (5)	34 (4)	13 (3)	8 (2)
Mental impairment disorders	48 (5)	1 (< 1)	9 (2)	0 (0)
Hepatic impairment	11 (1)	5 (1)	9 (2)	2 (< 1)
Neutropenia	9 (1)	5 (1)	1 (< 1)	1 (< 1)
Convulsion	3 (< 1)	2 (< 1)	0 (0)	0 (0)
Posterior reversible encephalopathy syndrome	0 (0)	0 (0)	0 (0)	0 (0)

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

7.3 Clinical effectiveness and safety – further studies

STRIVE: randomised, double-blind, phase II trial

enzalutamide (160 mg/day) versus bicalutamide (50 mg/day)

Penson et al. [24] conducted STRIVE, a multicentre (62 sites in the US), randomised, double-blind phase II trial, aiming to evaluate the efficacy and safety of enzalutamide versus bicalutamide in men with nonmetastatic or metastatic CRPC. A total of 396 patients were randomly assigned to receive enzalutamide (n = 198) at a dose of 160 mg per day (four 40-mg capsules plus one placebo capsule) or bicalutamide (n = 198) at a dose of 50 mg per day (one capsule plus four placebo capsules). Enrolled patients had histologically or cytologically confirmed adenocarcinoma of the prostate, a serum testosterone level ≤ 50 ng/dl (1.73 nmol/l) and progressive disease despite androgen deprivation therapy. Patients had a median age of 72 years (enzalutamide group) and 74 years (bicalutamide group) respectively, and were predominantly white (both groups). At baseline, 74.7% of enzalutamide-group patients and 73.2% of bicalutamide-group patients had an ECOG performance status of 0. The median baseline serum PSA was 11.0 µg/l (enzalutamide group) compared to 13.2 µg/l (bicalutamide group); approximately half of the patients had a high Gleason score category (8–10) at initial diagnosis. At the time of study entry, disease stage (per case report form) was M0 in 35.4% and 34.8%, M0/N0 (non-nodal) in 30.8% and 30.3%, M0/N1 (nodal) in 4.5% and 4.5%, M1 (bone metastases on bone scan or soft-tissue metastases above the aortic bifurcation) in 64.6% and 65.2% of enzalutamide-group and placebo-group patients respectively. Progression-free survival (PFS) was the primary endpoint of the STRIVE trial.

median PFS in enzalutamide-group patients: + 13.7 months

median PFS in patients with nonmetastatic CRPC not reached in enzalutamide group

superiority of enzalutamide in key secondary endpoints

The median time on treatment was 14.7 months for the enzalutamide group versus 8.4 months for the bicalutamide group. Median PFS in patients who received enzalutamide was 19.4 months compared to 5.7 months in bicalutamide-group patients. In patients with nonmetastatic CRPC, median PFS was not reached in patients of the enzalutamide group versus 8.6 months in bicalutamide-group patients (HR 0.24, 95% CI, 0.14–0.42). Patients with metastatic CRPC had a median PFS of 16.5 months (enzalutamide group) compared to 5.5 months in the bicalutamide group. Analyses of key secondary endpoints including time to PSA progression, PSA response of ≥ 50% and radiographic PFS (rPFS) showed statistical(ly significant) superiority of enzalutamide over bicalutamide (in both the nonmetastatic and metastatic subgroups). In patients with both nonmetastatic and metastatic CRPC, enzalutamide was associated with a decrease in the risk of radiographic progression to death when compared to bicalutamide. The risk of PSA progression was reduced by 81% in enzalutamide-group patients.

similar rates in both groups in grade ≥ 3 AEs, serious AEs and AEs leading to death

The rates of grade ≥ 3 AEs, serious AEs and AEs leading to death were similar in patients of both groups. In 8% of patients (enzalutamide group) and 6% of patients (bicalutamide group), the occurrence of one or more AEs was the primary reason for discontinuation of the trial regimen. The AEs reported more frequently with enzalutamide treatment than with bicalutamide were fatigue, back pain, hot flashes, falls, hypertension, dizziness and decreased appetite. More frequently reported AEs in patients of the bicalutamide group than in enzalutamide-group patients included constipation, diarrhoea, anaemia and urinary tract infection. One patient (with a previously undisclosed history of multiple seizures before study entry) who received enzalutamide was affected by seizure.

8 Estimated costs

A0021: What is the reimbursement status of enzalutamide?

In Austria, 112 (4x28) enzalutamide (Xtandi®) 40-mg soft capsules are available at an ex-factory price of € 2,895.35 [33].

112 (4x28) Xtandi® capsules = € 2,895.35

The recommended dose for the treatment of patients with (metastatic) CRPC is 160 mg enzalutamide (four 40-mg soft capsules) administered orally once daily; 28 days of enzalutamide treatment would cost € 2,895.35.

€ 2,895.35 for 28 days of enzalutamide treatment

In the PROSPER trial, the median duration of trial regimen was 18.4 months in patients of the enzalutamide group, which would result in costs of € 53,274.44. However, median MFS of PROSPER trial patients who received enzalutamide was 36.6 months and the time to first use of subsequent antineoplastic therapy was 39.6 months [23]. Hence, a median duration of enzalutamide therapy of more than 35 months should be assumed, amounting to costs of more than € 100,000 for enzalutamide treatment.

median treatment duration of 35 months should be assumed, amounting to costs of more than € 100,000

9 Ongoing research

In October 2018, a search in databases www.clinicaltrials.gov and http://www.clinicaltrialsregister.eu was conducted. Two ongoing phase III trials, assessing enzalutamide in patients with nonmetastatic prostate cancer, were identified, one of which is the PROSPER trial discussed above:

PROSPER is the only ongoing phase III study for the assessed indication

- **NCT02003924** (EudraCT number: 2012-005665-12, PROSPER): The estimated study completion date is May 2020.
- **NCT02319837:** EMBARK is a phase III study of enzalutamide plus leuprolide, enzalutamide monotherapy and placebo plus leuprolide in patients with high-risk nonmetastatic prostate cancer who have progressed after radical prostatectomy or radiotherapy or both [34], which may provide further general safety and efficacy information about enzalutamide treatment. The estimated study completion date is July 2023.

comparison with leuprolide in pre-treated patients

One further trial (study phase not available) was identified: JCASTRE-Zero ("Japanese Research for Patients with Non-metastatic Castration Resistant Prostate Cancer – Enzalutamide"), which is a trial investigating the efficacy and safety of enzalutamide in patients with nonmetastatic CRPC, with an estimated enrolment of 60 patients (single-group assignment) and an estimated study completion date in September 2021.

JCASTRE-Zero: small sample size, unknown study phase

10 Discussion

approved for the assessed indication by the FDA, not by the EMA

Enzalutamide (Xtandi®) is an androgen receptor inhibitor approved by the FDA in July 2018 for the treatment of patients with both nonmetastatic and metastatic CRPC [4]. To date, enzalutamide has not yet been approved by the EMA for the assessed indication.

PROSPER trial: 71% lower risk of metastasis or death with enzalutamide

statistically significant delay of PSA progression + time to first use of subsequent antineoplastic therapy with enzalutamide

median OS not reached in either group

The PROSPER trial [21-23] investigated the efficacy and safety of enzalutamide versus placebo in patients with nonmetastatic CRPC and a rapidly rising PSA level. Analyses showed that patients of the enzalutamide group had a statistically significant benefit in median MFS (HR 0.29, 95% CI, 0.24–0.35, $p < 0.001$); hence, patients who received enzalutamide had a 71% lower risk of metastasis or death than patients who received the placebo. Patients of the enzalutamide group also had a statistically significant delay regarding the median time to PSA progression (HR 0.07, 95% CI, 0.05–0.08, $p < 0.001$) and the median time to first use of subsequent antineoplastic therapy (HR 0.21, 95% CI, 0.17–0.26, $p < 0.001$). For OS, only data from the first interim analysis is available; at that point of time, 11% of the patients of the enzalutamide group and 13% of placebo-group patients had died. Median OS was not reached in either treatment group. Between randomisation and 112 days after discontinuation of the trial regimen, 15% of patients (enzalutamide group) and 2% of patients (placebo group) died without evidence of radiographic progression. The median time to FACT-P score degradation was equal in both groups; for HRQoL or pain no statistically significant or clinically meaningful difference (over 96 weeks) has been reported [32].

OS results of interim analyses, trial ongoing

QoL results not complete

MFS as surrogate for OS?

apalutamide: MFS as primary endpoint supported approval

Due to the fact that the PROSPER trial is ongoing until May 2020, no final analyses are available. The clinically most meaningful aspect for patients, the OS data as well as final analyses of QoL-related secondary endpoints including results of the EQ-5D-5L and the QLQ-PR25, are lacking. To confirm the clinical benefit of enzalutamide, final and long-term OS data as well as a full statistical evaluation of QoL data are required. Since Xie et al. defined MFS as a strong surrogate for OS in clinically localised prostate cancer [35], this raises the question whether the same applies to patients with nonmetastatic CRPC. In this context, it is noteworthy that the FDA approval of apalutamide for the treatment of patients with nonmetastatic CRPC in February 2018 was based on the results of the SPARTAN trial showing a statistically significant improvement in MFS in patients receiving apalutamide. Hence, this was the first use of MFS as a primary endpoint supporting drug approval [36, 37]. However, the quality of this surrogate endpoint should be proven in further trials and supported by a long-term survival benefit.

lack of OS benefit

Patients with nonmetastatic CRPC are usually strictly asymptomatic (except for side effects of androgen-deprivation therapy); the major challenge is to keep patients in this health state as long as possible by delaying the onset of the first bone metastasis [38]. However, according to an expert's opinion [39], the clinical benefit of a treatment – without proven OS benefit – needs to be demonstrated when asymptomatic patients are intended to be treated. This corresponds to Wilson et al. [40], who stated that trial endpoints should show clinically meaningful improvements regarding the survival of patients or their QoL.

higher rates of AEs with enzalutamide

There was a high rate of AEs of any grade in both treatment groups; one third of enzalutamide-group patients had an AE of grade 3 or higher. Serious AEs were more frequent among patients of the enzalutamide group than in placebo-group patients (24% vs. 18%); 3% of enzalutamide patients had an AE that led to death compared to 1% in the placebo group. No cases of PRES were reported in patients of either group during the trial; however, there were neurologic AEs – considered serious and drug-related – that occurred within 180 days after initiation of the study drug. The occurrence of one or more AEs led to the discontinuation of the trial regimen in 10% of enzalutamide-group patients and in 6% of placebo-group patients. 15% of patients in the enzalutamide group discontinued the study treatment due to disease progression, as did 44% of placebo-group patients.

no PRES reported

more phase III data required

Data from EMBARK, a three-armed trial with one treatment group, assessing enzalutamide monotherapy in patients with high-risk nonmetastatic prostate cancer progressing after radical prostatectomy or radiotherapy or both, as well as the JCASTRE trial [29], may provide further information. However, the number of patients receiving enzalutamide in the course of these two trials is rather small. Further phase III data to establish the efficacy and safety of enzalutamide is needed. The EAU and the NCCN both recommend to consider apalutamide for the treatment of patients with nonmetastatic CRPC and a PSADT shorter than ten months [10, 20]. While apalutamide is not yet approved in Europe, the Committee for Medicinal Products for Human Use (CHMP) has adopted a positive opinion, recommending the granting of a marketing authorisation for apalutamide for the treatment of nonmetastatic CRPC [41]. Consequently, a direct comparison of enzalutamide versus apalutamide would be needed to determine the optimal treatment for this patient population.

direct comparison of enzalutamide and apalutamide

ESMO-MCBS evaluations were not applicable

Given the lack of applicable and evaluable study endpoints of the PROSPER trial, ESMO-MCBS could not be applied to assess whether enzalutamide satisfies the criteria for a "meaningful clinical benefit" (score 4 or 5).

low risk of bias detected

Regarding the external and internal validity of the PROSPER trial, it is noticeable that the trial was conducted as a double-blind study; adequate generation of randomisation sequence and adequate allocation concealment were described in the protocol and the risk of performance bias is low. Although reasons for discontinuations were reported, selective outcome reporting was considered unclear, owing to the fact that not all pre-specified endpoints from the protocol have been reported yet. However, this may be due to the ongoing status of the PROSPER trial. Overall, a low risk of bias was detected but additional aspects that may potentially have an effect on the risk of bias were identified: the trial was funded by the co-developers of enzalutamide, the sponsors were involved in trial design, protocol writing and data analyses (see Table 6). In terms of applicability, no issue regarding population or setting applicability was found. However, there was a wide range of exclusion criteria for participants in the PROSPER trial. In particular, the exclusion of patients with certain clinically significant cardiovascular diseases (including e.g. myocardial infarction within six months before screening, uncontrolled angina within three months before screening, congestive heart failure New York Heart Association class 3 or 4 or uncontrolled hypertension) may limit the applicability of enzalutamide. Since final OS data and several QoL data are lacking, the applicability of the results in terms of outcomes is limited.

€ 2,895.35 for 28 days, more than € 100,000 for ≥ 35 months of enzalutamide treatment

The costs for 28 days of enzalutamide treatment are € 2,895.35 (ex-factory price)[33]. Since the median MFS of PROSPER trial patients who received enzalutamide was 36.6 months and the time to first use of subsequent antineoplastic therapy was 39.6 months [23], a median duration of enzalutamide therapy of more than 35 months should be assumed, increasing the costs to more than € 100,000. Additionally, costs for GnRH analogues may incur.

clinical benefit of enzalutamide treatment needs to be proven

The administration of enzalutamide in patients with nonmetastatic CRPC and a rapidly rising PSA prolonged MFS and delayed PSA progression as well as the use of subsequent antineoplastic therapy. However, the clinical benefit of enzalutamide reflected in OS prolongation and an improvement of the patients' QoL has not been established. Final analyses of the PROSPER trial and further ongoing studies may provide information about whether prolonged MFS also implies prolongation of OS. At any rate, the benefits of enzalutamide treatment need to be weighed against the risks, always considering the patients' QoL. Additionally, a direct comparison of enzalutamide and apalutamide is needed to verify the optimal treatment for this patient population.

Table 3: Benefit assessment based on ESMO-MCBS v1.1 and an adapted version of ESMO-MCBS [27, 28]

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	nonmet-astatic CRPC	NC	MFS	-	-	-	-	-	-	-	-	-	**NA**[2]
Original ESMO-MCBS	Enzalutamide	nonmet-astatic CRPC	NC	MFS	-	-	-	-	-	-	-	-	-	**NA**[2]

Abbreviations: AJ = Adjustments, CI = confidence interval, CRPC = castration-resistant prostate cancer, ESMO = European Society for Medical Oncology, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, NC = non-curative setting, 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. For this reason, we report the adjustments separately.

[2] An ESMO-MCBS score cannot be assessed since none of the available study endpoints was applicable or evaluable.

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12 Appendix

Table 4: Administration and dosing of enzalutamide (Xtandi®) [3, 22, 33]

	Technology	Comparator
Administration mode	Xtandi® is for oral use. The soft capsules should not be chewed, dissolved or opened but should be swallowed whole with water, and can be taken with or without food.	The corresponding placebo consists of Labrasol filled in matching capsules.
Description of packaging	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 and 57.8 mg of sorbitol.	-
Total volume contained in packaging for sale	Xtandi® 40-mg soft capsules 4x28	-
Dosing	The recommended dose is 160 mg enzalutamide (four 40-mg soft capsules) as a single oral daily dose.	Placebo capsules, identical in appearance to enzalutamide capsules, will be administered to patients in the control arm in the same manner as in patients of the enzalutamide arm
Median treatment duration	PROSPER trial: median treatment duration (enzalutamide group) of 18.4 months	PROSPER trial: median treatment duration (placebo group) of 11.1 months
Contraindications	✪ Hypersensitivity to the active substance 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 ✪ Women who are or may become pregnant	-
Drug interactions	Potential for other medicinal products to affect enzalutamide exposures: CYP2C8 inhibitors, CYP3A4 inhibitors, CYP2C8 and CYP3A4 inducers. Potential for enzalutamide to affect exposures to other medicinal products: enzyme induction, CYP1A2 and CYP2C8 substrates, P-gp substrates, BCRP, MRP2, OAT3 and OCT1 substrates, medicinal products which prolong the QT interval Effect of food on enzalutamide exposures: no clinically significant effect on the extent of exposure to enzalutamide.	-

Table 5: Characteristics of the PROSPER trial

Title: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer [21-23]			
Study identifier	NCT02003924, EudraCT number: 2012-005665-12		
Design	International, double-blind, randomised, placebo-controlled phase III trial		
	Duration of main phase:		Enrolment: 26 November 2013 to 28 June 2017 Time of data cut-off: 28 June 2017 Median follow-up: 18.5 months (enzalutamide group) and 15.1 months (placebo group)
Hypothesis	Superiority The trial was originally designed to enrol approximately 1,560 patients in order to detect at least 574 primary end-point events and at least 480 deaths. On the basis of efficacy results in the subgroup of patients with nonmetastatic disease in the STRIVE trial, the planned enrolment was reduced to 1,440 patients in order to detect at least 440 primary end-point events and to uncouple the final analysis of the primary endpoint from the final analysis of overall survival. This change provided the trial with 90% power to detect a target hazard ratio of 0.72.		
Funding	Pfizer and Astellas Pharma		
Treatments groups	Intervention (n = 933)		Patients received enzalutamide orally as four 40-mg soft gelatin capsules once daily with or without food. The trial regimen was continued until radiographic progression, as assessed by central independent blinded radiographic review.
	Control (n = 468)		Patients received placebo capsules (identical in appearance to enzalutamide capsules) in the same manner as intervention-group patients.
Endpoints and definitions	Metastasis-free survival (primary endpoint)	MFS	Defined as the time from randomisation to radiographic progression (as determined by central review at any time) or as the time to death from any cause during the period from randomisation to 112 days after the discontinuation of the trial regimen without evidence of radiographic progression, whichever occurred first.
	Overall survival	OS	Defined as the time from randomisation to death due to any cause.
	Time to pain progression	-	Assessed by using BPI-SF. Pain progression is defined as a 2-point or more increase from baseline in the question 3 pain score. Time to this event is defined as the time from randomisation to onset of pain progression.
	Time to opiate use for prostate cancer pain	-	Opiate use for prostate cancer pain is derived from the indication associated with the new use of an opiate for pain. Time to this event is defined as the time from randomisation to the new use of an opiate for prostate cancer pain.
	Time to pain progression or opiate use for prostate cancer pain	-	Defined as the time from randomisation to the earliest onset of pain progression or new use of an opiate for prostate cancer pain.
	Time to first use of cytotoxic chemotherapy	-	Defined as the time from randomisation to first use of cytotoxic chemotherapy for prostate cancer.
	Time to first use of new antineoplastic therapy	-	Defined as the time from randomisation to first use of new antineoplastic therapy for prostate cancer.
	Time to PSA progression (secondary endpoint)	-	Defined as the time from randomisation to the date of the first PSA value demonstrating progression, which is subsequently confirmed. For patients with PSA decline at week 17, the PSA progression date is defined as the date that a $\geq$ 25% increase and an absolute increase of $\geq$ 2 µg/L (2 ng/mL) above the nadir (or baseline for patients with no PSA decline by week 17) is documented, which is confirmed by a second consecutive value obtained at least 3 weeks later.

Title: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer [21-23]			
Study identifier	NCT02003924, EudraCT number: 2012-005665-12		
	PSA response rate (secondary endpoint)	-	PSA response will be calculated as a decline from baseline in PSA (ng/mL) to the maximum PSA response with thresholds at 50% and 90%. Additionally, PSA response will be assessed as a decline to undetectable levels, where undetectable is defined as below the limit of quantification of the centrally assessed PSA results. A PSA response must be confirmed by a second consecutive value at least 3 weeks later. A stratified Cochran-Mantel-Haenszel mean score test will be used to compare response rates between treatment groups.
	Time to functional status deterioration	-	Time to functional status deterioration as assessed by the FACT-P questionnaire is defined as the time from randomisation to the occurrence of a 10-point decrease from baseline in the FACT-P global score.
	Quality of life (secondary endpoint)	QoL	Assessed by the EQ-5D-5L Health Questionnaire and QLQ-PR25 Module
	Safety	-	Safety analyses include all patients who receive one dose or partial dose of the study drug (safety population). Safety is evaluated by the frequency of serious AEs, frequency and severity of AEs, frequency of study-drug discontinuation due to AEs, and frequency of new clinically significant changes in clinical laboratory values and vital signs.
Database lock	NR		
Results and analysis			
Analysis description	**Primary analysis** The primary endpoint was analysed in the ITT population at a type I error rate of 0.05 (two-sided). Key secondary endpoints of the time to PSA progression and the time to first use of subsequent antineoplastic therapy and the first interim analysis of OS were evaluated at the time of the primary analysis. To maintain the family-wise two-sided type I error rate at 0.05, a parallel testing strategy between OS (with an allocated type I error rate of 0.03) and the remaining key secondary endpoints (with an allocated type I error rate of 0.02 with sequential testing in hierarchical order) was used. If the differences in the remaining key secondary endpoints were significant at the 0.02 level, OS was to be allocated an overall type I error rate of 0.05. The first interim analysis for OS was conducted at the 0.001 significance level. The final analysis of overall survival has not yet been performed (see the protocol). The trial groups were compared with the use of a log-rank test with stratification according to the same factors that were used in randomisation. The Kaplan–Meier method was used to estimate medians. A stratified Cox regression model was used to estimate hazard ratios and 95% confidence intervals.		

Title: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer [21-23]		
Study identifier	NCT02003924, EudraCT number: 2012-005665-12	
Analysis population	Inclusion	✲ Patients aged 18 years or older ✲ Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation, signet-cell, or small-cell features ✲ Ongoing androgen deprivation therapy with a GnRH agonist/antagonist or prior bilateral orchiectomy (medical or surgical castration) ✲ Testosterone ≤ 50 ng/dL (≤ 1.73 nmol/L) at screening ✲ For patients receiving bisphosphonates or denosumab, dose must be stable for at least four weeks before randomisation ✲ Progressive disease on androgen deprivation therapy at enrolment defined as a minimum of 3 rising PSA values (PSA1 < PSA2 < PSA3) assessed by a local laboratory (local PSA) with an interval of ≥ 1 week between each determination ✲ The most recent local PSA and the screening PSA assessed by the central laboratory (central PSA) should be ≥ 2 µ g/L (2 ng/mL). In the event of prior androgen receptor inhibitor use, the most recent local PSA and the central PSA assessed at screening must be obtained at least four weeks after the last dose of the androgen receptor inhibitor. ✲ PSA doubling time ≤ 10 months ✲ No prior or present evidence of metastatic disease as assessed by CT/MRI for soft tissue disease and whole-body radionuclide bone scan for bone disease. If the screening bone scan shows a lesion suggestive of metastatic disease, the patient will be eligible only if a second imaging modality (plain film, CT or MRI) does not show bone metastasis. If the imaging results are equivocal or consistent with metastasis, the patient is not eligible for enrolment. Patients with soft-tissue pelvic disease may be eligible if lesions do not qualify as target lesions (e.g. lymph nodes below aortic bifurcation are permissible if the short axis of the largest lymph node is < 15 mm). ✲ Asymptomatic prostate cancer ✲ Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 ✲ Estimated life expectancy ≥ 12 months ✲ Able to swallow the study drug and comply with study requirements ✲ Contraception required (see the protocol)
	Exclusion	✲ Prior cytotoxic chemotherapy, aminoglutethimide, ketoconazole, abiraterone acetate, or enzalutamide for the treatment of prostate cancer or participation in a clinical trial of an investigational agent that inhibits the androgen receptor or androgen synthesis (unless treatment was placebo) ✲ Treatment with hormonal therapy (e.g. androgen receptor inhibitors, oestrogens, 5-alpha reductase inhibitors) or biologic therapy for prostate cancer (other than approved bone-targeting agents and GnRH agonist/antagonist therapy) within four weeks of randomisation ✲ Use of an investigational agent within four weeks of randomisation ✲ Known or suspected brain metastasis or active leptomeningeal disease ✲ History of another invasive cancer within three years of randomisation, with the exception of fully treated cancers with a remote probability of recurrence in the opinion of both the medical monitor and the investigator ✲ Absolute neutrophil count < 1,000/µ L, platelet count < 100,000/µ L or haemoglobin < 10 g/dL (6.2 mmol/L) at screening. NOTE: may not have received growth factors or blood transfusions within seven days before obtaining the haematology values at screening ✲ Total bilirubin ≥ 1.5 times the ULN (except patients with a diagnosis of Gilbert's disease); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 2.5 times ULN at screening ✲ Creatinine > 2 mg/dL (177 µ mol/L) at screening ✲ Albumin < 3.0 g/dL (30 g/L) at screening ✲ History of seizure or any condition that may predispose to seizure (e.g. prior cortical stroke or significant brain trauma). History of loss of consciousness or transient ischemic attack within 12 months of randomisation. ✲ Clinically significant cardiovascular disease (for detailed information, see the protocol) ✲ Gastrointestinal disorder affecting absorption (e.g. gastrectomy, active peptic ulcer disease within three months before randomisation) ✲ Major surgery within four weeks of randomisation ✲ Hypersensitivity reaction to the active pharmaceutical ingredient or any of the capsule components, including Labrasol, butylated hydroxyanisole, and butylated hydroxytoluene ✲ Any concurrent disease, infection, or comorbid condition that interferes with the ability of the patient to participate in the trial, which places the patient at undue risk, or complicates the interpretation of data, in the opinion of the investigator or medical monitor

Title: Enzalutamide in men with nonmetastatic, castration-resistant prostate cancer [21-23]				
Study identifier	NCT02003924, EudraCT number: 2012-005665-12			
	Characteristics		Intervention n = 933	Control n = 468
		Median age (range), years	74 (50–95)	73 (53–92)
		ECOG performance status score, n (%) 0 1 Missing data	 747 (80) 185 (20) 1 (< 1)	 382 (82) 85 (18) 1 (< 1)
		Serum PSA value, ng/mg Median (range)	 11.1 (0.8–1071.1)	 10.2 (0.2–467.5)
		PSA doubling time Median (range), months Distribution, n (%) < 6 months ≥ 6 months Missing data	 3.8 (0.4–37.4) 715 (77) 217 (23) 1 (< 1)	 3.6 (0.5–71.8) 361 (77) 107 (23) 0
		Use of bone-targeting agent, n (%) No Yes	 828 (89) 105 (11)	 420 (90) 48 (10)
Applicability of evidence				
Population	The PROSPER trial population was highly selected: men with nonmetastatic CRPC with a rapidly rising PSA level. No issue regarding population applicability was identified.			
Intervention	The mode of administration and dosing used for enzalutamide is consistent with the (FDA-) approved license [4]. Patients received the trial regimen until radiographic progression (as assessed by central independent blinded radiographic review).			
Comparators	In the PROSPER trial, a placebo was selected as comparator. Apalutamide, which is an antiandrogen related to the same drug class as enzalutamide, may be appropriate for direct comparison.			
Outcomes	There is evidence that enzalutamide lowered the risk of metastasis or death by 71% when compared to the placebo. Since final OS data (PROSPER trial is ongoing) and several QoL data are lacking, the applicability of the results in terms of outcomes is limited.			
Setting	The PROSPER trial is an international multicentre study (300 sites in 32 countries). No information was found regarding the ethnicity of participating patients. No issue regarding setting applicability was found.			

Abbreviations: AE = adverse event, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BPI-SF = Brief Pain Inventory Short Form, CT = computed tomography, ECOG = Eastern Cooperative Oncology Group, EQ-5D-5L = European Quality of Life-5 Dimensions-5 Levels, FACT-P = Functional Assessment of Cancer Therapy-Prostate, GnRH = gonadotropin-releasing hormone, ITT = intention-to-treat, MFS = metastasis-free survival, NR = not reported, OS = overall survival, PSA = prostate-specific antigen, QLQ-PR25 = Quality of Life Questionnaire-Prostate 25 module, ULN = upper limit normal

Table 6: Risk of bias assessment on study level based on EUnetHTA (internal validity of randomised controlled trials) [22, 23, 25]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: Patients were randomly assigned; according to the protocol, randomisation was planned to be conducted centrally		Yes
Adequate allocation concealment: According to the protocol, study-site personnel was planned to access the IXRS to assign a screening identification number to a potential study participant. Study-site personnel was planned to access the IXRS to randomly assign patients to blinded study treatment after receiving approval by the medical monitor (signed randomisation authorisation form or email correspondence).		Yes
Blinding: double-blinded	**Patient:** blinded	Yes
	Treating physician: blinded	Yes
Selective outcome reporting unlikely: Since the trial is still ongoing, not all of the pre-specified endpoints from the protocol have been reported yet. Reasons for discontinuations have been reported.		Unclear
No other aspects which increase the risk of bias: The trial was funded by Pfizer and Astellas Pharma (co-developers of enzalutamide). The trial was designed and the protocol was written by the first and last authors along with employees of the sponsors. The data analyses were performed by the sponsors and were provided to all the authors, who wrote the manuscript and made the decision to submit it for publication.		No
Risk of bias – study level		Low

Abbreviation: IXRS = interactive voice/web recognition system