IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A14-48

Enzalutamide (new therapeutic indication) – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Enzalutamid (neues Anwendungsgebiet) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 March 2015). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Enzalutamide (new therapeutic indication) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

19 December 2014

Internal Commission No.:

A14-48

Address of publisher:

Institute for Quality and Efficiency in Health Care
Im Mediapark 8 (KölnTurm)
50670 Cologne
Germany

Tel.: +49 (0)221 – 35685-0
Fax: +49 (0)221 – 35685-1
E-Mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Christian Doehn, Urologikum Lübeck, Lübeck, Germany

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

IQWiG employees involved in the dossier assessment[2]:

- Helmut Hörn
- Christiane Balg
- Andreas Gerber-Grote
- Petra Kohlepp
- Ulrike Lampert
- Christoph Schürmann
- Ulrike Seay
- Volker Vervölgyi

Keywords: enzalutamide, prostatic neoplasms, benefit assessment

[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables[3]

Page

[3] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
ADT	androgen deprivation therapy
AE	adverse event
BPI-SF	Brief Pain Inventory-Short Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group performance status
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life-5 Dimensions
FACT-P	Functional Assessment of Cancer Therapy-Prostate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LH-RH	luteinizing hormone-releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
rPFS	radiographic progression-free survival
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TI	therapeutic indication
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of a therapeutic indication newly approved in November 2014 for the drug enzalutamide. The assessment was based on a dossier compiled by the company. The dossier was sent to IQWiG on 19 December 2014.

Research question

The aim of the present report was to assess the added benefit of enzalutamide versus the appropriate comparator therapy (ACT) for treatment of adult men with metastatic castration-resistant prostate cancer (mCRPC) who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy (ADT) in whom chemotherapy is not yet clinically indicated.

The G-BA specified the following options for the ACT:

- watchful waiting while maintaining ongoing conventional ADT

  or, if applicable,

- combined maximal androgen blockade with a non-steroidal anti-androgen (flutamide, bicalutamide)

  or

- abiraterone acetate while maintaining ongoing ADT

The company concurred with the G-BA's specification and chose watchful waiting while maintaining conventional ADT from the options mentioned. The present benefit assessment was conducted in comparison with the option chosen by the company from the options of ACT specified by the G-BA.

The assessment was conducted based on patient-relevant outcomes and on the evidence provided by the company in the dossier.

Results

One relevant study was available for the benefit assessment: the approval study PREVAIL.

Study characteristics

The PREVAIL study was a multicentre, randomized, double-blind, placebo-controlled, 2-arm parallel group study. Chemotherapy-naive adult patients with mCRPC with asymptomatic or mildly symptomatic course of disease after failure of ADT were enrolled in the study.

1717 patients were randomized in a ratio of 1:1, 872 patients to the enzalutamide arm and 845 patients to the placebo arm.

The patients in the enzalutamide arm received 160 mg enzalutamide once daily. The patients in the placebo arm received placebo once daily. Continued conventional ADT was required in both treatment arms. Treatment in the control arm of the study was evaluated as sufficient operationalization of the ACT (watchful waiting).

The randomized study treatment was continued until at least one of the following criteria for discontinuation occurred:

- withdrawal of the patient's consent
- safety concerns (e.g. non-acceptable toxicity)
- occurrence of confirmed radiographic progression or of a skeletal-related complication **and** initiation of cytotoxic chemotherapy or a study treatment for treatment of the prostate cancer in another study

If a patient did not receive cytotoxic chemotherapy or another study treatment for treatment of the prostate cancer on occurrence of confirmed radiographic progression or of a skeletal-related complication, the randomized study treatment was not discontinued. However, in this case the patient could receive hormonal therapies including other anti-androgens and abiraterone or biologic anti-tumour treatment as concomitant treatment in addition to the randomized study treatment.

After the end of the randomized study treatment, the patients first underwent a follow-up of up to 28 days to record severe pain measured by means of initiation of opiate treatment and to record adverse events (AEs), and then a long-term follow-up every 12 weeks until the end of the study. Overall survival and radiographic progression-free survival (rPFS) were co-primary outcomes. The median treatment duration with the study medication was 16.6 months in the enzalutamide arm and 4.6 months in the placebo arm. This resulted in markedly different observation periods in the 2 study arms for the outcomes "severe pain measured by means of initiation of opiate treatment", "health-related quality of life" and "AEs". These differences were considered in the assessment of the risk of bias of these outcomes and in the choice of the types of analyses.

One interim analysis and a final analysis were planned in the study for overall survival. The interim analysis was conducted after 540 deaths and was considered as the final analysis because of the good efficacy. The results from this analysis were used for the benefit assessment.

Risk of bias

The risk of bias of the PREVAIL study at study level was rated as low.

At outcome level, the risk of bias for the outcomes "overall survival", "time to first skeletal-related complication" was rated as low. The risk of bias was rated as high for the following outcomes: severe pain measured by means of initiation of opiate treatment, health-related quality of life (Functional Assessment of Cancer Therapy-Prostate [FACT-P]), severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), serious AEs (SAEs), discontinuation due to AEs and hot flush.

Results

Mortality

Treatment with enzalutamide + ADT produced a statistically significant prolongation of overall survival compared with placebo + ADT.

In addition, there was an indication of an effect modification by the characteristic "age" for the outcome "overall survival" (interaction test $p = 0.17$). It was therefore also advisable to consider the results for patients aged < 75 years and ≥ 75 years separately. Treatment with enzalutamide + ADT resulted in a statistically significant prolongation of overall survival in comparison with placebo + ADT in both age groups. Hence for both age groups, there was an indication of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for the outcome "overall survival". The extent was different in the 2 age groups, however.

Morbidity

The time to first skeletal-related complication was statistically significantly longer under treatment with enzalutamide + ADT than under placebo + ADT. This resulted in an indication of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for the outcome "skeletal-related complications".

There were no evaluable data for the outcome "pain (Brief Pain Inventory-Short Form [BPI-SF])". Hence there was no hint of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT; an added benefit is therefore not proven.

Since other evaluable data for recording pain were lacking, the time to initiation of opiate treatment was used in the present benefit assessment as operationalization for the occurrence of severe pain. The time to severe pain measured by means of initiation of opiate treatment was statistically significantly longer under treatment with enzalutamide + ADT than under placebo + ADT. This resulted in a hint of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for this outcome.

There were no evaluable data for the outcome "health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])". Hence there was no hint of an added

benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT; an added benefit is therefore not proven.

Health-related quality of life

Under treatment with enzalutamide + ADT, the time to worsening of health-related quality of life (measured with the FACT-P) was statistically significantly longer than under placebo + ADT. This resulted in a hint of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for the outcome "health-related quality of life (FACT-P)".

Adverse events

Both for severe AEs (CTCAE grade ≥ 3) and for SAEs, the time to first event was statistically significantly longer under treatment with enzalutamide + ADT than under placebo + ADT. This resulted in a hint of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for the outcomes "severe AEs (CTCAE grade ≥ 3)" and "SAEs".

Under treatment with enzalutamide + ADT, the time to treatment discontinuation due to AEs was statistically significantly longer than under placebo + ADT. Although the results of this outcome also had a high risk of bias, there was an indication of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT. The results for this outcome had a high risk of bias because of the differences in observation periods in the 2 treatment arms. However, since more events occurred in the placebo arm, which had the shorter observation period, it is not assumed that the observed direction of effect was caused by bias alone. Hence the quality of the certainty of results could be considered as high so that there was an indication of an added benefit.

The patients had their first hot flush statistically significantly earlier under treatment with enzalutamide + ADT than under placebo + ADT. This resulted in a hint of greater harm from enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for the outcome "hot flush".

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

Overall, positive effects and one negative effect remain. Positive effects were shown in the outcome categories "mortality", "serious/severe symptoms/late complications", "health-related quality of life", "serious/severe AEs" and "non-serious/non-severe AEs". The negative effect was shown in the outcome category "non-serious/non-severe AEs". Since there was an indication of an effect modification by the subgroup characteristic "age" for the outcome "overall survival", the overall assessment of added benefit was conducted separately for patients aged < 75 years and ≥ 75 years.

Added benefit for patients aged < 75 years

There is an indication of a minor added benefit for the outcome "overall survival" for patients aged < 75 years. Irrespective of age, there is also a hint of a major added benefit for health-related quality of life, a hint of major added benefit for serious/severe symptoms/late complications, and at most indications of considerable added benefit for AEs. The hint of considerably greater harm from the outcome "hot flush" was more than outweighed by the indication and the hints of lesser harm of considerable extent from the other outcomes regarding harm. Hence in the overall conclusion, the extent of added benefit is not reduced.

Due to the available data, it was necessary to balance between an indication of considerable and a hint of major added benefit. Because of the higher certainty of results of an "indication", there was overall an indication of a considerable added benefit for patients aged < 75 years.

Added benefit for patients aged ≥ 75 years

There is an indication of a major added benefit for the outcome "overall survival" for patients aged ≥ 75 years. This effect is initially decisive for the overall conclusion on added benefit. In addition, there were at most indications of an added benefit, with the extent being at most major, for serious/severe symptoms/late complications and health-related quality of life and AEs. The hint of considerably greater harm from the outcome "hot flush" was more than outweighed by the indication and the hints of lesser harm of considerable extent from the other outcomes regarding harm. Hence in the overall conclusion, the extent of added benefit is not reduced.

Hence there is an indication of a major added benefit for patients aged ≥ 75 years.

[4] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

Summary

Table 2 presents a summary of the extent and probability of the added benefit of enzalutamide.

Table 2: Enzalutamide – extent and probability of added benefit

Therapeutic indication	**ACT[a]**	**Subgroup**	**Extent and probability of added benefit**
Treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated	▪ **watchful waiting while maintaining ongoing conventional ADT** or, if applicable, ▪ combined maximal androgen blockade with a non-steroidal anti-androgen (flutamide, bicalutamide) or ▪ abiraterone acetate while maintaining ongoing ADT	Age < 75 years	Indication of considerable added benefit
		Age ≥ 75 years	Indication of major added benefit
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee; SPC: Summary of Product Characteristics			

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of enzalutamide versus the ACT for treatment of adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated.

The G-BA specified the following options for the ACT:

- watchful waiting while maintaining ongoing conventional ADT

  or, if applicable,

- combined maximal androgen blockade with a non-steroidal anti-androgen (flutamide, bicalutamide)

  or

- abiraterone acetate while maintaining ongoing ADT

The company concurred with the G-BA's specification and chose watchful waiting while maintaining ongoing conventional ADT from the options mentioned. The present benefit assessment was conducted in comparison with the option chosen by the company from the options of ACT specified by the G-BA.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- list of studies on enzalutamide (studies completed up to 20 October 2014)
- bibliographical literature search on enzalutamide (last search on 24 October 2014)
- search in trial registries for studies on enzalutamide (last search on 20 October 2014)

To check the completeness of the study pool:

- search in trial registries for studies on enzalutamide (last search on 15 January 2015)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in Table 3 was included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
PREVAIL (MD3100-03)	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. ADT: androgen deprivation therapy; RCT: randomized controlled trial; vs.: versus			

The study pool for the benefit assessment of enzalutamide corresponded to that of the company. Study PREVAIL (MD3100-03) [3] is hereinafter referred to as "PREVAIL".

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

Table 4 and Table 5 describe the study used for the benefit assessment.

Table 4: Characteristics of the studies included – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PREVAIL	RCT, double-blind, parallel	Chemotherapy-naive adult mCRPC patients with asymptomatic or mildly symptomatic course of disease after failure of ADT	Enzalutamide + ADT (N = 872) placebo + ADT (N = 845)	Screening: up to 28 days before randomization Treatment until occurrence of a criterion for discontinuation[b] Follow-up: until death or discontinuation of study participation	Worldwide at 207 study centres: United States, Canada, United Kingdom, France, Spain, Germany, Denmark, Sweden, Finland, Italy, Poland, Netherlands, Belgium, Austria, Russia, Lithuania, Slovakia, Israel, Australia, Singapore, South Korea, Japan 28 Sep 2010 – 16 Sep 2013 (data cut-off of the interim analysis) Follow-up ongoing	Primary outcomes: overall survival, radiographic progression-free survival Secondary outcomes: skeletal-related complications, health-related quality of life, pain, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Criteria for discontinuation: occurrence of confirmed radiographic progression or of a skeletal-related complication **and** initiation of cytotoxic chemotherapy or a study treatment for treatment of prostate cancer.

ADT: androgen deprivation therapy; AE: adverse event; mCRPC: metastatic castration resistant prostate cancer; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study	Intervention	Comparison	Concomitant treatment
PREVAIL	Enzalutamide 160 mg once daily (4 capsules of 40 mg) + continued conventional ADT (LH-RH analogues) or surgical castration	Placebo once daily (4 capsules) + continued conventional ADT (LH-RH analogues) or surgical castration	**Concomitant treatment permitted, particularly:** ▪ bisphosphonates or other approved bone-targeted agents for the treatment of metastatic prostate cancer ▪ corticosteroids up to 10 mg/day prednisone equivalent ▪ supportive treatment: ▫ blood transfusion ▫ pain therapy ▫ radiotherapy ▫ vaccine therapy ▫ palliative surgery for the treatment of skeletal-related complications ▪ on radiographic progression or a skeletal-related complication: ▫ hormonal therapy including other anti-androgens and abiraterone ▫ biologic anti-tumour treatment

ADT: androgen deprivation therapy; LH-RH: luteinizing hormone-releasing hormone; RCT: randomized controlled trial; vs.: versus

The PREVAIL study was a randomized, double-blind, placebo-controlled, 2-arm parallel group study. It was conducted in Australia, Europe, North America and East Asia. Chemotherapy-naive adult patients with mCRPC with asymptomatic or mildly symptomatic course of disease after failure of ADT were enrolled in the study.

1717 patients were randomized in a ratio of 1:1, 872 patients to the enzalutamide arm and 845 patients to the placebo arm. The patients enrolled in the study were considered overall to have met the criteria of the new therapeutic indication for enzalutamide (see Section 2.7.2.4.1 of the full dossier assessment). This concurs with the company's assessment.

The patients in the enzalutamide arm received 160 mg enzalutamide once daily. The patients in the placebo arm received placebo once daily. The treatment regimen of the randomized study treatment with enzalutamide concurs with the description in the Summary of Product Characteristics (SPC) [4].

Patients without surgical castration had to receive ADT with a luteinizing hormone-releasing hormone (LH-RH) analogue in addition to the study medication. The ADT had to have started at least 4 weeks before the start of the randomized study treatment, and its dose had to be maintained at a stable level in the course of the study. After randomization, approximately 95% of the 872 patients in the enzalutamide arm, and approximately 96% of the 845 patients in the placebo arm received ADT; 4.6 versus 5.0% of the patients had been surgically

castrated at the start of the study, according to the European Public Assessment Report (EPAR). The use of corticosteroids up to 10 mg/day prednisone equivalent was allowed. Bisphosphonate preparations or other approved bone-targeted agents for the treatment of metastatic prostate cancer were allowed with their dose having to be maintained at a stable level in the course of the study. Hence the placebo arm of the PREVAIL study can be considered to be an adequate operationalization of the ACT watchful waiting while maintaining conventional ADT.

The randomized study treatment was continued until at least one of the following criteria for discontinuation occurred:

- withdrawal of the patient's consent
- safety concerns (e.g. non-acceptable toxicity)
- occurrence of confirmed radiographic progression or of a skeletal-related complication **and** initiation of cytotoxic chemotherapy or a study treatment for treatment of the prostate cancer in another study

If a patient did not receive cytotoxic chemotherapy or another study treatment for treatment of the prostate cancer on occurrence of confirmed radiographic progression or of a skeletal-related complication, the randomized study treatment was not discontinued. However, in this case the patient could receive hormonal therapies including other anti-androgens and abiraterone or biologic anti-tumour treatment as concomitant treatment in addition to the randomized study treatment.

The randomized study treatment of a patient could be unblinded in the course of the study in case knowledge of treatment was required. However, this only applied to 20 patients in total.

After the end of the randomized study treatment, the patients first underwent a follow-up of up to 28 days to record severe pain measured by means of initiation of opiate treatment and to record AEs, and then a long-term follow-up every 12 weeks until the end of the study. Overall survival and rPFS were co-primary outcomes.

The analysis of 3 data cut-offs was planned for the study, one analysis in which only the outcome "rPFS" was analysed, one interim analysis, and one final analysis for the outcome "overall survival". The time point of the interim analysis for overall survival with the data cut-off on 16 September 2013 was relevant for the present benefit assessment. This was conducted after 540 deaths had occurred. Since the outcome criteria of the study had already been reached at this time point, the data monitoring committee decided on 21 October 2013 to end the study because of good efficacy. Consequently, the interim analysis was considered as the final analysis, and all other outcomes were analysed; the final analysis originally planned was not conducted. Blinding of the study was lifted on 3 December 2013, i.e. after the relevant data cut-off. Only then the patients of the placebo arm were allowed to switch to treatment with enzalutamide, which started in January 2014, according to the EPAR [5]. From

the EPAR, an analysis with the 15 January 2014 data cut-off was available for overall survival. This is only presented as additional information, however, because the survival status on 15 January 2014 was probably not recorded for all patients, according to the EPAR.

Table 6 shows the planned duration of follow-up of the patients for the included outcomes with evaluable data.

Table 6: Planned duration of follow-up – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Outcome	**Planned follow-up**
Overall survival	Until the end of participation in the study
Skeletal-related complications	Continuously until the end of participation in the study
Severe pain measured by means of initiation of opiate treatment	Continuously until 28 days after the end of the randomized study treatment or until the day before initiation of cytotoxic chemotherapy or study treatment in another study, depending on what occurred earlier
Health-related quality of life (FACT-P)	Start of study, Week 5, Week 13 and then every 12 weeks until the end of the randomized study treatment
AEs	Continuously until 28 days after the end of the randomized study treatment or until the day before initiation of cytotoxic chemotherapy or study treatment in another study, depending on what occurred earlier
ADT: androgen deprivation therapy; AE: adverse event; FACT-P: Functional Assessment of Cancer Therapy-Prostate; RCT: randomized controlled trial; vs.: versus	

Of the included outcomes with evaluable data, only overall survival and skeletal-related complications were recorded up to the end of study participation. All other outcomes included were recorded up to the end of the randomized study treatment or up to 28 days afterwards.

Table 7 shows the characteristics of the patients in the study included.

Table 7: Characteristics of the study populations – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study characteristics category	**Enzalutamide + ADT N = 872**	**Placebo + ADT N = 845**
PREVAIL		
Age [years]		
Median [min; max]	72.0 [43.0; 93.0]	71.0 [42.0; 93.0]
Duration of the disease[a] [months]		
Median [min; max]	62.7 [0.2; 326.6]	64.6 [0.1; 275.4]
BPI-SF pain score (question 3)[b], n (%)		
0-1	569 (65.3)	567 (67.1)
2-3	275 (31.5)	262 (31.0)
≥ 4	15 (1.7)	11 (1.3)
Missing	13 (1.5)	5 (0.6)
ECOG PS at start of study, n (%)		
0	584 (67.0)	585 (69.2)
1	288 (33.0)	260 (30.8)
Location of the metastases at start of study, n (%)		
Bone	348 (39.9)	335 (39.6)
Soft tissue	124 (14.2)	149 (17.6)
Bone and soft tissue	393 (45.1)	355 (42.0)
None	7 (0.8)	6 (0.7)
Study discontinuations[c], n (%)	246 (28.2)	313 (37.0)

a: Time to randomization since first diagnosis or since first treatment.
b: Assessment of the worst pain within the last 24 hours on an 11-point scale from 0 (no pain) to 10 (worst pain imaginable).
c: Data cut-off 16 September 2013.
ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; ECOG PS: Eastern Cooperative Oncology Group performance status; max: maximum; min: minimum; N: number of randomized patients; n: number of patients in the category; RCT: randomized controlled trial; vs.: versus

Patient characteristics were largely comparable in the 2 treatment arms. Median age was 72 years in the enzalutamide arm, and 71 years in the placebo arm; the median of disease duration was 62.7 versus 64.6 months. Approximately 97% of the patients had a BPI-SF pain score of ≤ 4 and therefore were asymptomatic or mildly symptomatic. More than 99% of the patients had metastases at the start of the study. All patients had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1 at the start of the study.

Table 8 shows the median treatment duration of the patients and the median follow-up period for overall survival and AEs.

Table 8: Information on the course of the study – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study characteristics category	**Enzalutamide + ADT N = 872**	**Placebo + ADT N = 845**
PREVAIL		
Treatment duration [months][a]:		
Median [min; max]	16.6 [0.2; 35.6]	4.6 [0.1; 31.7]
Observation period [months]:		
Overall survival		
Median [min; max]	20.7 [0.7; 35.5]	19.1 [0.6; 35.5]
Adverse events[a]		
Median [min; max]	17.1 [0.7; 35.7]	5.4 [0.7; 31.7]
Further outcomes	ND	ND
a: Information was only available for the safety population (871 vs. 844 patients) and not for the ITT population.		
ADT: androgen deprivation therapy; ITT: intention to treat; max: maximum; min: minimum; N: number of patients in the ITT population; ND: no data; RCT: randomized controlled trial; vs.: versus		

In the enzalutamide arm, the median treatment duration was 16.6 months and thus approximately 3.5 times as long as in the placebo arm (4.6 months), whereas the median follow-up period for AEs was approximately 3 times as long in the enzalutamide arm (17.1 months) as in the placebo arm (5.4 months). In contrast, the median follow-up period for the outcome "overall survival" (20.7 versus 19.1 months) hardly differed.

Due to the large differences in treatment and observation periods, only analyses using survival time analyses were included in the benefit assessment (see Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment).

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study	**Adequate random sequence generation**	**Allocation concealment**	**Blinding**		**Reporting independent of the results**	**No additional aspects**	**Risk of bias at study level**
			Patient	**Treating staff**			
PREVAIL	Yes	Yes	Yes	Yes	Yes	Yes	Low
ADT: androgen deprivation therapy; RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level for the PREVAIL study was rated as low. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - skeletal-related complications
  - pain (BPI-SF)
  - severe pain measured by means of initiation of opiate treatment
  - health status (EQ-5D VAS)
- Health-related quality of life
  - health-related quality of life (FACT-P)
- Adverse events
  - severe AEs (CTCAE grade ≥ 3)
  - serious adverse events (SAEs)
  - discontinuation due to AEs
  - hot flush

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.7.2.4.3 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study	Outcomes									
	Overall survival	Skeletal-related complications	Pain (BPI-SF)	Severe pain measured by means of initiation of opiate treatment	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	Severe AEs (CTCAE grade ≥ 3)	SAEs	Discontinuation due to AEs	Hot flush
PREVAIL	Yes	Yes	No[a]	Yes	No[a]	Yes	Yes	Yes	Yes	Yes

a: No evaluable results were available in the company's dossier; for reasons, see Section 2.7.2.4.3 of the full dossier assessment.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

Table 11 shows the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study	Study level	Outcomes									
		Overall survival	Skeletal-related complications	Pain (BPI-SF)	Severe pain measured by means of initiation of opiate treatment	Health status (EQ-5D VAS)	Health-related quality of life (FACT-P)	Severe AEs (CTCAE grade ≥ 3)	SAEs	Discontinuation due to AEs	Hot flush
PREVAIL	L	L	L	–[a]	H[b, c]	–[a]	H[d]	H[b]	H[b]	H[b]	H[b]

a: No evaluable results.
b: The observation period was limited to the treatment period + up to 28 days and was importantly different between the treatment arms (medians:17.1 months in the enzalutamide arm, and 5.4 months in the placebo arm).
c: The recording of the outcome was not planned in the study so that it cannot be excluded that reporting in Module 4 A was conducted on the basis of the results.
d: The observation period was limited to the treatment period and was importantly different between the treatment arms (medians: 16.6 months in the enzalutamide arm, and 5.6 months in the placebo arm).
ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias was rated as low for the outcomes “overall survival” and “skeletal-related complications”, which concurs with the company’s assessment.

The risk of bias was rated as high for the outcome “severe pain measured by means of initiation of opiate treatment”. This assessment deviated from that of the company, which rated the risk of bias as low.

The risk of bias was rated as high for the outcome “health-related quality of life (FACT-P)”. The company included this outcome on the basis of a different operationalization.

The risk of bias was rated as high for the outcomes “severe AEs (CTCAE grade ≥ 3)”, “SAEs”, “discontinuation due to AEs” and “hot flush”. This assessment deviated from that of the company, which in each case rated the risk of bias as low.

Moreover, when interpreting the AEs, it should be borne in mind that some of the AEs in the PREVAIL study represent aspects of benefit (e.g. pain or skeletal-related complications), which might already have been recorded with the included outcomes on morbidity. A check of the events that had occurred was therefore carried out to see whether the results on AEs were substantially affected by those AEs explained by the aspects of benefit. The influence of these events was considered to be irrelevant, however.

Due to the potentially important bias due to differences in observation period for the outcomes on time to initiation of opiate treatment, time to worsening of quality of life measured with the FACT-P, and time to occurrence of AEs (SAEs, severe AEs, discontinuation due to AEs, and hot flush), further subgroup analyses for these outcomes are not conclusive and were therefore not conducted for these outcomes.

The assessment of the risk of bias is justified in Section 2.7.2.4.2 of the full dossier assessment.

2.4.3 Results

Table 12, Table 13, Table 14 and Table 15 summarize the results on the comparison of enzalutamide and watchful waiting in patients in the therapeutic indication. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations. The Kaplan-Meier curves of survival time analyses on overall survival, on the combined events of skeletal-related complications, on severe pain measured by means of initiation of opiate treatment, and on the total score of health-related quality of life (FACT-P) are presented in Figure 1, Figure 2, Figure 3 and Figure 4. All remaining Kaplan-Meier curves of the survival time analyses can be found in Appendix A, and the supplementary tables on AEs in Appendix C of the full dossier assessment. The assessment was based on hazard ratios. Since the differences in hazard ratios not always appear in the medians, the 25% quantiles from the Kaplan-Meier curves were additionally read and presented as supplementary information.

Table 12: Results (mortality) – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study outcome category outcome data cut-off	Enzalutamide + ADT N	Enzalutamide + ADT Median survival time in months [95% CI] Patients with event n (%) 25% quantile in months[b]	Placebo + ADT N	Placebo + ADT Median survival time in months [95% CI] Patients with event n (%) 25% quantile in months[b]	Enzalutamide + ADT vs. placebo + ADT HR [95% CI][a]	 p-value
PREVAIL						
Mortality						
Overall survival						
16 Sep 2013	872	32.4 [30.1; NA] 241 (27.6) 21.8	845	30.2 [28.0; NA] 299 (35.4) 17.1	0.71 [0.60; 0.84]	< 0.001
15 Jan 2014	872	NA [31.7; NA] 299 (34.3)	845	31.0 [28.9; NA] 357 (42.2)	0.73 [0.63; 0.85]	ND

a: Cox regression model without adjustment for further covariables.
b: The 25% quantile was read from the Kaplan-Meier curves.
ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; ND: no data; RCT: randomized controlled trial; vs.: versus

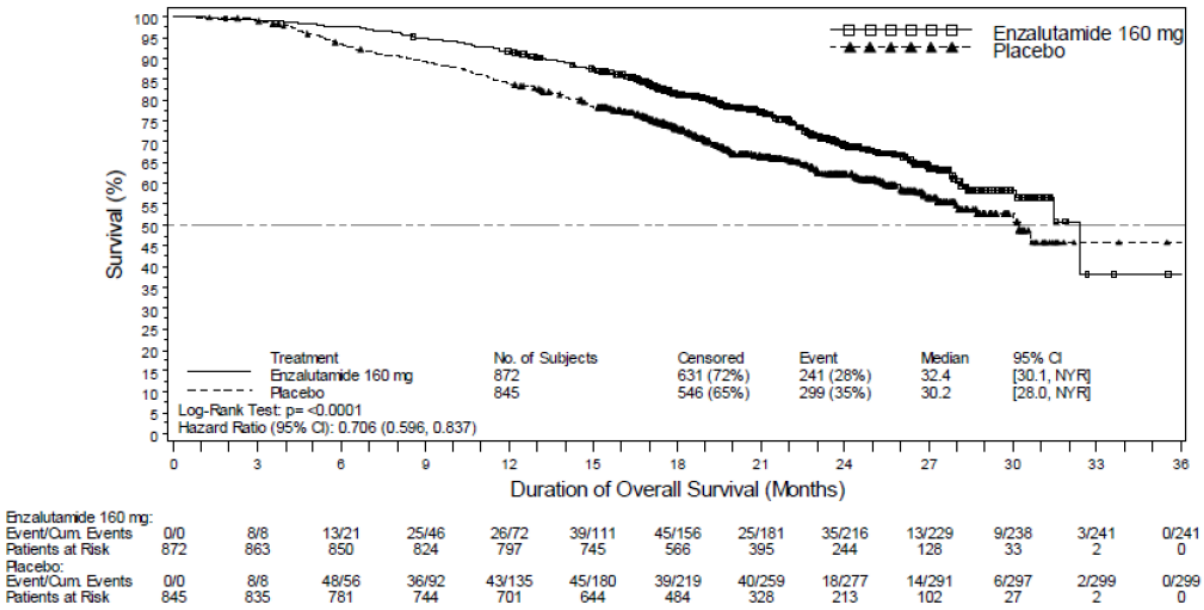


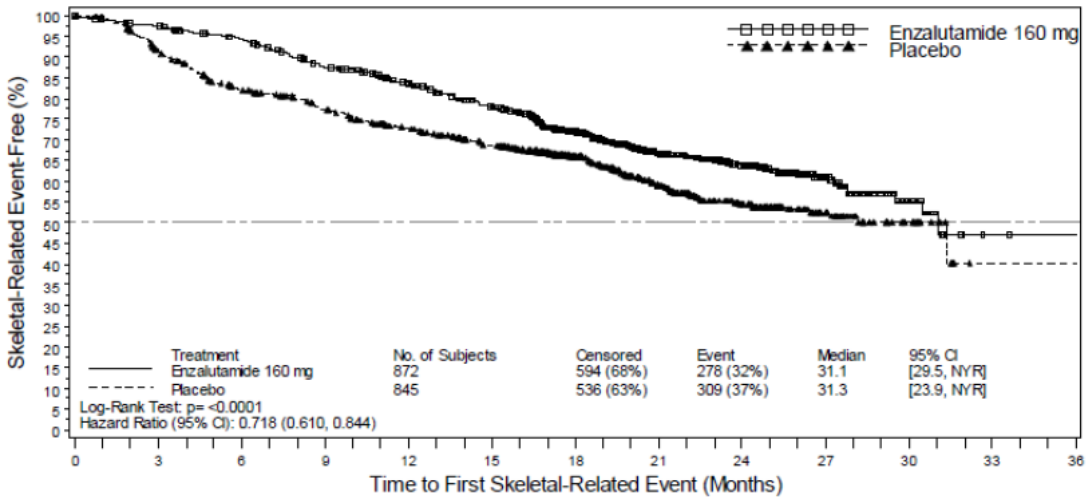
Figure 1: Survival time curve (mortality: overall survival) – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT, PREVAIL study

Table 13: Results (morbidity) – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study outcome category outcome	Enzalutamide + ADT N	Enzalutamide + ADT Median in months [95% CI] Patients with event n (%) 25% quantile in months[b]	Placebo + ADT N	Placebo + ADT Median in months [95% CI] Patients with event n (%) 25% quantile in months[b]	Enzalutamide + ADT vs. placebo + ADT HR [95% CI][a]	 p-value
PREVAIL						
Morbidity						
Skeletal-related complications: time to first event						
All skeletal-related complications	872	31.1 [29.5; NA] 278 (31.9) 16.5	845	31.3 [23.9; NA] 309 (36.6) 10.1	0.72 [0.61; 0.84]	< 0.001
Radiation of bone	872	NA [31.1; NA] 181 (20.8)	845	31.3 [31.3; NA] 208 (24.6)	0.69 [0.57; 0.84]	< 0.001
Bone surgery	872	NA [NA; NA] 11 (1.3)	845	NA [NA; NA] 11 (1.3)	0.81 [0.35; 1.88]	0.63
Pathological bone fracture	872	NA [NA; NA] 39 (4.5)	845	NA [NA; NA] 31 (3.7)	1.00 [0.63; 1.61]	0.98
Spinal cord compression	872	NA [NA; NA] 39 (4.5)	845	NA [NA; NA] 40 (4.7)	0.79 [0.51; 1.22]	0.28
Change of antineoplastic therapy to treat bone pain	872	NA [NA; NA] 16 (1.8)	845	NA [NA; NA] 29 (3.4)	0.45 [0.25; 0.83]	0.01
Pain (BPI-SF)	No evaluable data					
Time to severe pain measured by means of initiation of opiate treatment	872	NA [22.5; NA] 330 (37.8) 10.0	845	15.7 [12.1; 21.5] 307 (36.3) 3.8	0.57 [0.49; 0.67]	< 0.001
Health status (EQ-5D VAS)	No evaluable data					

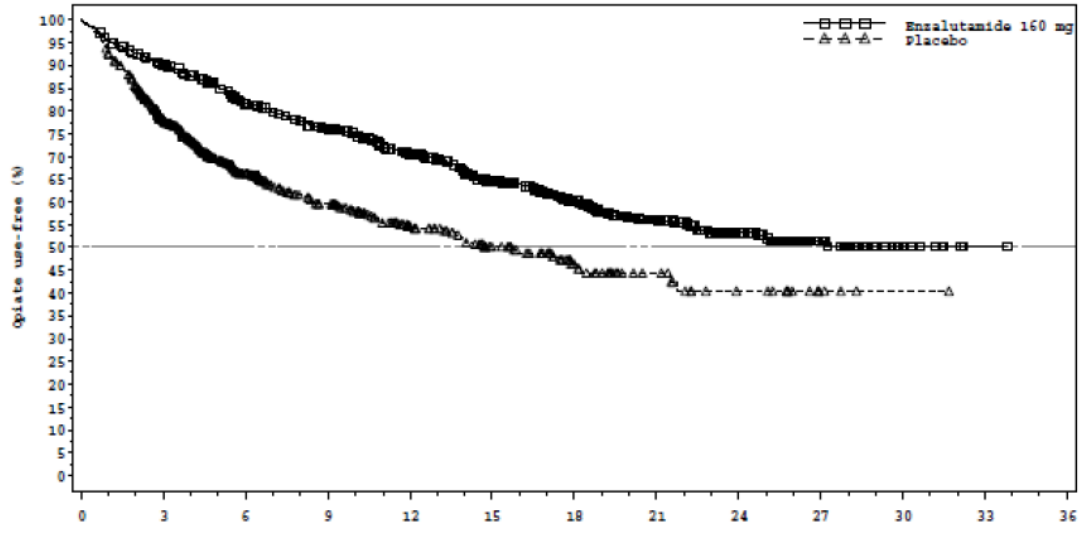
a: Cox regression model without adjustment for further covariables.
b: The 25% quantile was read from the Kaplan-Meier curves.

ADT: androgen deprivation therapy; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus



Enzalutamide 160 mg:													
Event/Cum. Events	0/0	21/21	30/51	55/106	32/138	46/184	42/226	27/253	11/264	6/270	6/276	2/278	0/278
Patients at Risk	872	843	797	732	674	605	447	286	183	90	24	1	0
Placebo:													
Event/Cum. Events	0/0	73/73	73/146	39/185	32/217	28/245	16/261	29/290	13/303	3/306	2/308	1/309	0/309
Patients at Risk	845	750	644	585	520	463	319	198	118	59	18	0	0

Figure 2: Survival time curve (morbidity: time to first skeletal-related complication) – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT, PREVAIL study



Enzalutamide 160 mg													
Event/Cum. Events	0/0	86/86	71/157	43/200	41/241	38/279	24/303	16/319	7/326	3/329	1/330	0/330	0/330
Patients at Risk	872	766	661	593	496	388	272	160	94	47	13	1	0
Placebo													
Event/Cum. Events	0/0	180/180	70/250	25/275	14/289	9/298	5/303	2/305	2/307	0/307	0/307	0/307	0/307
Patients at Risk	845	558	296	202	121	83	49	26	15	4	1	0	0

Figure 3: Survival time curve (morbidity: time to severe pain measured by means of initiation of opiate treatment) – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT, PREVAIL study

Table 14: Results (health-related quality of life) – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study outcome category outcome	Enzalutamide + ADT N	Enzalutamide + ADT Median in months [95% CI] Patients with event n (%) 25% quantile in months[b]	Placebo + ADT N	Placebo + ADT Median in months [95% CI] Patients with event n (%) 25% quantile in months[b]	Enzalutamide + ADT vs. placebo + ADT HR [95% CI][a]	 p-value
PREVAIL						
Health-related quality of life						
Time to worsening of health-related quality of life measured with the FACT-P						
Total score[c]	872	11.3 [11.1; 13.9] 456 (52.3) 2.8	845	5.6 [5.5; 5.6] 409 (48.4) 2.6	0.623 [0.54; 0.72]	< 0.001
Physical well-being[d]	872	8.7 [8.3; 11.1] 542 (62.2)	845	5.6 [5.5; 5.6] 409 (48.4)	0.75 [0.65; 0.85]	< 0.001
Social well-being[d]	872	24.9 [16.5; NA] 369 (42.3)	845	8.5 [6.0; 13.8] 316 (37.4)	0.73 [0.62; 0.86]	< 0.001
Emotional well-being[d]	872	19.4 [16.6; 24.9] 369 (42.3)	845	11.0 [8.2; 11.4] 295 (34.9)	0.66 [0.57; 0.78]	< 0.001
Functional well-being[d]	872	8.5 [8.3; 11.1] 514 (58.9)	845	3.1 [2.9; 5.6] 425 (50.3)	0.71 [0.62; 0.81]	< 0.001
Prostate-cancer-specific subscale[d]	872	5.7 [5.6; 8.3] 565 (64.8)	845	2.8 [2.8; 3.0] 480 (56.8)	0.69 [0.60; 0.78]	< 0.001

a: Cox regression model without adjustment for further covariables.
b: The 25% quantile was read from the Kaplan-Meier curves.
c: A decrease of score by ≥ 10 points was considered as worsening.
d: A decrease of score by ≥ 3 points was considered as worsening.

ADT: androgen deprivation therapy; CI: confidence interval; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

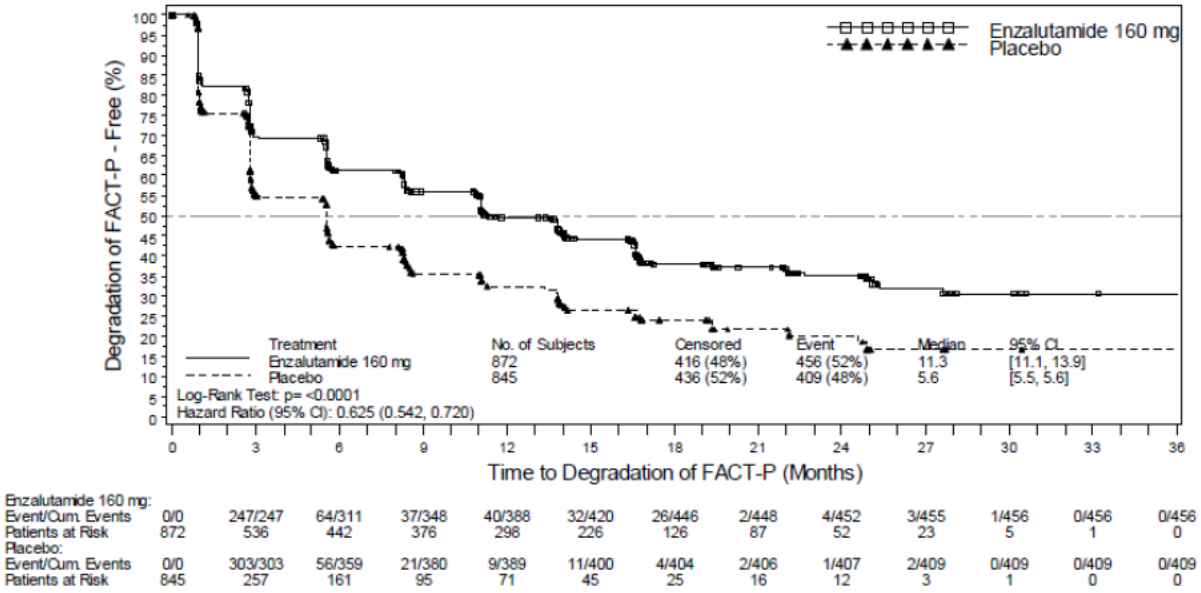


Figure 4: Survival time curve (health-related quality of life: time to worsening according to FACT-P, total score) – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT, PREVAIL study

Table 15: Results (AEs) – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study outcome category outcome	Enzalutamide + ADT N	Enzalutamide + ADT Median in months [95% CI] Patients with event n (%) 25% quantile in months[b]	Placebo + ADT N	Placebo + ADT Median in months [95% CI] Patients with event n (%) 25% quantile in months[b]	Enzalutamide + ADT vs. placebo + ADT HR [95% CI][a]	 p-value
PREVAIL						
AEs, time to (first) event						
Overall rate AEs	871	0.79 [0.62; 0.89] 844 (96.9) 0.5	844	0.76 [0.66; 0.89] 787 (93.2) 0.5		
Severe AEs (CTCAE grade ≥ 3)	871	22.3 [19.0; 28.3] 374 (42.9) 8.1	844	13.3 [11.1; 18.2] 313 (37.1) 3.6	0.66 [0.57; 0.77]	< 0.001
SAEs	871	NA [28.3; NA] 279 (32.0) 12.5	844	23.3 [16.1; NA] 226 (26.8) 6.6	0.63 [0.53; 0.76]	< 0.001
Discontinuation due to AEs	871	NA [NA; NA] 148 (17.0) NA	844	NA [21.1; NA] 216 (25.6) 7.0	0.35 [0.28; 0.44]	< 0.001
Hot flush	871	NA [NA; NA] 174 (20.0) NA	844	NA [NA; NA] 67 (7.9) NA	2.29 [1.73; 3.05]	< 0.001

a: Cox regression model without adjustment for further covariables.
b: The 25% quantile was read from the Kaplan-Meier curves.

ADT: androgen deprivation therapy; AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The particular requirements for derivation of proof from a single study are not met by the PREVAIL study (see Section 2.7.2.8.1 of the full dossier assessment). Hence, at most "indications", e.g. of an added benefit, could be derived from the data. This deviates from the company's assessment, which considered the PREVAIL study suitable for deriving proof.

As described in Section 2.3.2, the data of the data cut-off on 16 September 2013 were presented as decisive for the derivation of the added benefit also for overall survival.

Mortality

Overall survival

Treatment with enzalutamide + ADT produced a statistically significant prolongation of overall survival compared with placebo + ADT.

In addition, there was an indication of an effect modification by the characteristic "age" for the outcome "overall survival" (interaction test p = 0.17). It was therefore also advisable to consider the results for patients aged < 75 years and ≥ 75 years separately. In both age groups, the subgroup analyses resulted in an indication of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT. The extent was different in the 2 age groups, however (see Table 17).

This assessment deviates from that of the company, which on the basis of the total population, derived proof of added benefit for this outcome and did not consider the indication of effect modification by age.

Morbidity

Skeletal-related complications

The time to first skeletal-related complication was statistically significantly longer under treatment with enzalutamide + ADT than under placebo + ADT. This resulted in an indication of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for the outcome "skeletal-related complications".

This assessment deviates from that of the company, which, on the basis of the PREVAIL study, derived proof of added benefit for this outcome.

Pain (BPI-SF)

There were no evaluable data for the outcome "pain (BPI-SF)". Hence there was no hint of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT; an added benefit is therefore not proven.

This assessment deviates from that of the company, which derived proof of added benefit based on different analyses of the BPI-SF.

Severe pain measured by means of initiation of opiate treatment

Since other evaluable data for recording pain were lacking, the time to initiation of opiate treatment was used in the present benefit assessment as operationalization for the occurrence of severe pain.

The time to severe pain measured by means of initiation of opiate treatment was statistically significantly longer under treatment with enzalutamide + ADT than under placebo + ADT. This resulted in a hint of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for this outcome.

This assessment deviates from that of the company, which derived proof of added benefit for this outcome.

Health status (EQ-5D VAS)

There were no evaluable data for the outcome "health status (EQ-5D VAS)". Hence there was no hint of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT; an added benefit is therefore not proven.

This assessment concurred with that of the company, which also derived no added benefit for this outcome.

Health-related quality of life

Health-related quality of life (FACT-P)

Under treatment with enzalutamide + ADT, the time to worsening of health-related quality of life (measured with the FACT-P) was statistically significantly longer than under placebo + ADT. The risk of bias for this outcome was assessed as high. This resulted in a hint of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for the outcome "health-related quality of life (FACT-P)".

This assessment deviates from that of the company, which derived no added benefit for this outcome on the basis of the analysis of changes in mean values between randomization and Week 13 or Week 25.

Adverse events

Severe adverse events (CTCAE grade ≥ 3) and serious adverse events

Both for severe AEs (CTCAE grade ≥ 3) and for SAEs, the time to first event was statistically significantly longer under treatment with enzalutamide + ADT than under placebo + ADT. The risk of bias for both outcomes was assessed as high. This resulted in a hint of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for the outcomes "severe AEs (CTCAE grade ≥ 3)" and "SAEs".

This assessment deviates from that of the company, which derived proof of added benefit for each of these 2 outcomes.

Discontinuation due to adverse events

Under treatment with enzalutamide + ADT, the time to treatment discontinuation due to AEs was statistically significantly longer than under placebo + ADT. Although the results of this outcome had a high risk of bias, there was an indication of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT. The results for this outcome had a high risk of bias because of the differences in observation periods in the 2 treatment arms. However, since more events occurred in the placebo arm, which had the shorter observation period, it is not assumed that the observed direction of effect was caused by bias alone. Hence the quality of the certainty of results could

be considered as high so that there was an indication of an added benefit (see Section 2.7.2.4.2 of the full dossier assessment).

This assessment deviates from that of the company, which derived proof of added benefit for this outcome.

Hot flush

The patients had their first hot flush statistically significantly earlier under treatment with enzalutamide + ADT than under placebo + ADT. The risk of bias for this outcome was assessed as high. This resulted in a hint of greater harm from enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for the outcome "hot flush".

This assessment deviates from that of the company, which presented the results for this outcome in Module 4 A, but did not mention them in the derivation of the added benefit.

2.4.4 Subgroups and other effect modifiers

In order to uncover possible effect differences between patient groups, the following subgroup characteristics were included:

- age (< 75 years versus ≥ 75 years)
- geographical region (Germany versus Europe versus United States versus rest of the world for the outcomes "overall survival" and "skeletal-related complications")
- visceral metastases (lungs and/or liver) at the time point of screening (yes versus no)

The prerequisite for proof of differing effects is a statistically significant homogeneity and/or interaction test ($p < 0.05$). An indication of differing effects results from a p-value between 0.05 and 0.2. The interaction tests for the subgroup characteristics "age" and "visceral metastases" were available from the dossier, whereas the interaction tests for the subgroup characteristic "geographical region" were calculated by the Institute using the additional analyses presented by the company.

There was no proof ($p < 0.05$) of an effect modification from any of the subgroup analyses. Table 16 shows the results of the subgroup analyses for subgroup characteristics for which an indication of an effect modification was provided. The Kaplan-Meier curves of survival time analyses can be found in Appendix B of the full dossier assessment.

Table 16: Subgroups (survival time): outcome "overall survival" by age – RCT, direct comparison: enzalutamide + ADT vs. watchful waiting + ADT

Study outcome characteristic subgroup	Enzalutamide + ADT		Placebo + ADT		Enzalutamide + ADT vs. placebo + ADT	
	N	Median survival time in months [95% CI] Patients with event n (%) 25% quantile in months[b]	N	Median survival time in months [95% CI] Patients with event n (%) 25% quantile in months[b]	HR [95% CI][a]	p-value
PREVAIL						
Overall survival						
Age						
< 75 years	555	31.5 [30.1; NA] 141 (25.4) 22.7	553	NA [30.0; NA] 170 (30.7) 18.4	0.77 [0.62; 0.96]	0.02
≥ 75 years	317	32.4 [27.7; NA] 100 (31.5) 19.9	292	25.1 [22.6; 28.0] 129 (44.2) 14.1	0.61 [0.47; 0.79]	< 0.001
					Interaction:	0.17

a: Cox regression model without adjustment for further covariables.
b: The 25% quantile was read from the Kaplan-Meier curves.
ADT: androgen deprivation therapy; CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: number of patients with event; NA: not achieved; RCT: randomized controlled trial; vs.: versus

Mortality

Overall survival

For overall survival, there was an indication of an effect modification by the subgroup characteristic "age".

Treatment with enzalutamide + ADT resulted in a statistically significant prolongation of overall survival in comparison with placebo + ADT in both age groups. Hence for both age groups, there was an indication of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining ongoing conventional ADT, for the outcome "overall survival". The extent was different in the 2 age groups, however (see Table 17).

This assessment deviates from that of the company, which, on the basis of the total population, derived proof of added benefit for this outcome and did not consider the indication of effect modification.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 led to indications or hints of an added benefit of enzalutamide in comparison with watchful waiting, in each case while maintaining conventional ADT for the outcomes “overall survival”, “skeletal-related complications”, “severe pain measured by means of initiation of opiate treatment” and “health-related quality of life (FACT-P)”. For AEs, there were indications or hints of lesser harm and a hint of greater harm of enzalutamide in comparison with watchful waiting, in each case while maintaining conventional ADT.

In addition, there was an indication of an effect modification by the subgroup characteristic “age” for the outcome “overall survival”.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 17). In the overall assessment, it was investigated whether different conclusions on the extent of added benefit arise for the individual patient groups.

Table 17: Extent of added benefit at outcome level: enzalutamide + ADT vs. watchful waiting + ADT

Outcome category **outcome** **effect modifier** **subgroup**	**Enzalutamide + ADT vs. watchful waiting + ADT** **median of time to event** **25% quantile[a] of time to event** **effect estimate [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Mortality		
Overall survival: time to event		
Age		
< 75 years	Median [months]: 31.5 vs. NA 25% quantile [months]: 22.7 vs. 18.4 HR: 0.77 [0.62; 0.96] p = 0.02 probability: "indication"	Outcome category: survival time $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
≥ 75 years	Median [months]: 32.4. vs. 25.1 25% quantile [months]: 19.9 vs. 14.1 HR: 0.61 [0.47; 0.79] p < 0.001 probability: "indication"	Outcome category: survival time $CI_u < 0.85$ added benefit, extent: "major"
Morbidity		
Skeletal-related complications: time to first event	Median [months]: 31.1. vs. 31.3 25% quantile [months]: 16.5 vs. 10.1 HR: 0.72 [0.61; 0.84] p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
Pain (BPI-SF)	No evaluable data	Lesser benefit/added benefit not proven
Severe pain measured by means of initiation of opiate treatment: time to event	Median [months]: NA vs. 15.7 25% quantile [months]: 10.0 vs. 3.8 HR: 0.57 [0.49; 0.67] p < 0.001 probability: "hint"	Outcome category: serious/severe symptoms/late complications $CI_u < 0.75$ added benefit, extent: "major"
Health status (EQ-5D VAS)	No evaluable data	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-P: time to worsening	Median [months]: 11.3. vs. 5.6 25% quantile [months]: 2.8 vs. 2.6 HR: 0.62 [0.54; 0.72] p < 0.001 probability: "hint"	Outcome category: health-related quality of life $CI_u < 0.75$ added benefit, extent: "major"

(continued)

Table 17: Extent of added benefit at outcome level: enzalutamide + ADT vs. watchful waiting + ADT (continued)

Outcome category **outcome**	**Enzalutamide + ADT vs. watchful waiting + ADT** **median of time to event** **25% quantile[a] of time to event** **effect estimate [95% CI]** **p-value** **probability[b]**	**Derivation of extent[c]**
Adverse events		
Severe AEs (CTCAE-grade ≥ 3): time to first event	Median [months]: 22.3. vs. 13.3 25% quantile [months]: 8.1 vs. 3.6 HR: 0.66 [0.57; 0.77] p < 0.001 probability: "hint"	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
SAEs: time to first event	Median [months]: NA vs. 23.3 25% quantile [months]: 12.5 vs. 6.6 HR: 0.63 [0.53; 0.76] p < 0.001 probability: "hint"	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ lesser harm, extent: "considerable"
Discontinuation due to AEs: time to event	Median [months]: NA vs. NA 25% quantile [months]: NA vs. 7.0 HR: 0.35 [0.28; 0.44] p < 0.001 probability: "indication"[d]	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ lesser harm, extent: "considerable"
Hot flush: time to first event	Median [months]: NA vs. NA 25% quantile [months]: NA vs. NA HR: 2.29 [1.73; 3.05] HR: 0.44 [0.33; 0.58][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm, extent: "considerable"

a: The 25% quantile was read from the Kaplan-Meier curves.
b: Probability given if statistically significant differences are present.
c: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
d: Despite the longer observation period, the event "discontinuation due to AEs" occurred less frequently in the enzalutamide arm than in the placebo arm.
e: Institute's calculation: reversed direction of effect to enable use of limits to derive the added benefit.

ADT: androgen deprivation therapy; AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of CI; CTCAE: Common Terminology Criteria for Adverse Events; EQ-5D: European Quality of Life-5 Dimensions; FACT-P: Functional Assessment of Cancer Therapy-Prostate; HR: hazard ratio; NA: not achieved; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of enzalutamide + ADT compared with watchful waiting + ADT

Positive effects	Negative effects
Mortality ▪ Overall survival ▫ age (< 75 years) indication of an added benefit – extent: “minor” ▫ age (≥ 75 years) indication of an added benefit – extent: “major”	
Serious/severe symptoms/late complications ▪ Skeletal-related complications indication of an added benefit – extent: “considerable” ▪ Severe pain measured by means of initiation of opiate treatment hint of an added benefit – extent: “major”	
Health-related quality of life: ▪ FACT-P hint of an added benefit – extent: “major”	
Serious/severe adverse events ▪ Severe AEs (CTCAE grade ≥ 3) hint of lesser harm – extent: “considerable” ▪ SAEs hint of lesser harm – extent: “considerable”	
Non-serious/non-severe adverse events ▪ Discontinuation due to AEs indication of lesser harm – extent: “considerable”	Non-serious/non-severe adverse events ▪ Hot flush: hint of greater harm – extent: “considerable”
ADT: androgen deprivation therapy; AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACT-P: Functional Assessment of Cancer Therapy-Prostate; SAE: serious adverse event	

Overall, positive effects and one negative effect remain. Positive effects were shown in the outcome categories “mortality”, “serious/severe symptoms/late complications”, “health-related quality of life”, “serious/severe AEs” and “non-serious/non-severe AEs”. The negative effect was shown in the outcome category “non-serious/non-severe AEs”. Since there was an indication of an effect modification by the subgroup characteristic “age” for the outcome “overall survival”, the overall assessment of added benefit was conducted separately for patients aged < 75 years and ≥ 75 years.

Added benefit for patients aged < 75 years

There is an indication of a minor added benefit for the outcome “overall survival” for patients aged < 75 years. In addition, and irrespective of age, there are hints of major added benefit for

serious/severe symptoms/late complications and health-related quality of life, an indication of considerable added benefit for serious/severe symptoms/late complications, and at most indications of considerable added benefit for AEs. The hint of considerably greater harm from the outcome "hot flush" was more than outweighed by the indication and the hints of lesser harm of considerable extent from the other outcomes regarding harm. Hence in the overall conclusion, the extent of added benefit is not reduced.

Due to the available data, it was necessary to balance between an indication of considerable and a hint of major added benefit. Because of the higher certainty of results of an "indication", there was overall an indication of a considerable added benefit for patients aged < 75 years.

Added benefit for patients aged ≥ 75 years

There is an indication of a major added benefit for the outcome "overall survival" for patients aged ≥ 75 years. This effect is initially decisive for the overall conclusion on added benefit. In addition, there were at most indications of an added benefit, with the extent being at most major, for serious/severe symptoms/late complications and health-related quality of life and AEs. The hint of considerably greater harm from the outcome "hot flush" was more than outweighed by the indication and the hints of lesser harm of considerable extent from the other outcomes regarding harm. Hence in the overall conclusion, the extent of added benefit is not reduced.

Hence there is an indication of a major added benefit for patients aged ≥ 75 years.

Summary

In summary, for adult men with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated, there is an indication of considerable added benefit for men aged < 75 years, and an indication of major added benefit for men aged ≥ 75 years, of enzalutamide versus the ACT, watchful waiting while maintaining ongoing conventional ADT.

Table 19 presents a summary of the extent and probability of the added benefit of enzalutamide.

Table 19: Enzalutamide – extent and probability of added benefit

Therapeutic indication	ACT[a]	Subgroup	Extent and probability of added benefit
Treatment of adult men with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated	▪ **watchful waiting while maintaining ongoing conventional ADT** or, if applicable, ▪ combined maximal androgen blockade with a non-steroidal anti-androgen (flutamide, bicalutamide) or ▪ abiraterone acetate while maintaining ongoing ADT	Age < 75 years	Indication of considerable added benefit
		Age ≥ 75 years	Indication of major added benefit
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACT: appropriate comparator therapy; ADT: androgen deprivation therapy; G-BA: Federal Joint Committee			

This deviates from the company's approach, which derived proof of a major added benefit.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.6 List of included studies

PREVAIL

Astellas Pharma. Additional analyses for study: PREVAIL; a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy; study MDV3100-03 [unpublished]. 2014.

Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371(5): 424-433.

Medivation. PREVAIL: a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy [online]. In: PharmNet.Bund Klinische Prüfungen. [Accessed: 20 October 2014]. URL: http://www.pharmnet-bund.de/dynamic/de/klinische-pruefungen/index.htm.

Medivation. A safety and efficacy study of oral MDV3100 in chemotherapy-naive patients with progressive metastatic prostate cancer (PREVAIL): full text view [online]. In: ClinicalTrials.gov. 16 October 2014 [accessed: 15 January 2015]. URL: https://www.clinicaltrials.gov/ct2/show/study/NCT01212991.

Medivation. PREVAIL: a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy [online]. In: EU Clinical Trials Register. [Accessed: 15 January 2015]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2010-020821-41.

Medivation. PREVAIL: a multinational phase 3, randomized, double-blind, placebo-controlled efficacy and safety study of oral MDV3100 in chemotherapy-naïve patients with progressive metastatic prostate cancer who have failed androgen deprivation therapy; study MDV3100-03; clinical study report [unpublished]. 2014.

Medivation. A safety and efficacy study of oral MDV3100 in chemotherapy-naive patients with progressive metastatic prostate cancer (PREVAIL): study results [online]. In: ClinicalTrials.gov. 16 October 2014 [accessed: 15 January 2015]. URL: https://www.clinicaltrials.gov/ct2/show/results/NCT01212991.

Theeuwes A. Statistical analysis plan for the AMNOG process: enzalutamide MDV3100-03 (PREVAIL) study [unpublished]. 2014.

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General Methods: version 4.1 [online]. 28 November 2013 [accessed: 1 August 2014]. URL: https://www.iqwig.de/download/IQWiG_General_Methods_Version_%204-1.pdf.

2. Institute for Quality and Efficiency in Health Care. Ticagrelor: benefit assessment according to §35a Social Code Book V; extract; commission no. A11-02 [online]. 29 September 2011 [accessed: 5 May 2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf.

3. Beer TM, Armstrong AJ, Rathkopf DE, Loriot Y, Sternberg CN, Higano CS et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med 2014; 371(5): 424-433.

4. Astellas. Xtandi 40 mg Weichkapseln: Fachinformation [online]. January 2015 [accessed: 5 March 2015]. URL: http://www.fachinfo.de.

5. European Medicines Agency. Xtandi: European public assessment report; variation EMEA/H/C/002639/II/0008 [online]. 23 October 2014 [accessed: 21 January 2015]. URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/002639/WC500180617.pdf.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-48-enzalutamid-neues-anwendungsgebiet-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6548.html.