

Horizon Scanning in Oncology

Darolutamide for the
treatment of patients with
nonmetastatic castration-
resistant prostate cancer
(CRPC)



Ludwig Boltzmann Institut
Health Technology Assessment

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Health Technology Assessment

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Authors: Dr. med. Eleen Rothschedl
Internal review: Priv.-Doz. Dr. phil. Claudia Wild; Nicole Grössmann, MSc
External review: Prof. Dr. Christian Schwentner
Urologische Klinik, Diakonie Klinikum Stuttgart

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The HTA Core Model® for Rapid Relative Effectiveness for Pharmaceuticals, developed within EUnetHTA (www.eunetha.eu), has been utilised when producing the contents and/or structure of this work. A working version (unpublished) of V3.0 of the Model was used. Use of the HTA Core Model® does not guarantee the accuracy, completeness, quality or usefulness of any information or service produced or provided by using the Model.

CONTACT INFORMATION

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Responsible for Contents:

Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)
Garnisongasse 7/20, A-1090 Vienna
<http://hta.lbg.ac.at/>

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Abstract

Introduction

Castration-resistant prostate cancer (CRPC) is a type of prostate cancer that keeps growing even when the testosterone level is reduced to very low levels. Darolutamide is a nonsteroidal androgen receptor (AR) antagonist with a molecular structure that differs from other AR antagonists. To date, darolutamide is neither approved by the European Medicines Agency (EMA) nor by the U.S. Food and Drug Administration (FDA) for any 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 95 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 ARAMIS trial

The ARAMIS trial aimed to investigate the efficacy and safety of darolutamide compared to placebo in men with nonmetastatic CRPC. The trial is currently ongoing; thus, presented data are primary- and interim results. The primary analysis of median metastasis-free survival (MFS) showed a gain of 22 months in patients who received darolutamide compared to patients who received placebo (HR for metastasis or death in the darolutamide group was 0.41). This beneficial treatment effect of darolutamide was observed across all pre-specified subgroups. An interim analysis of OS showed a lower risk of death with darolutamide as compared to placebo (HR for death was 0.71); however, median OS data have not been reached in either group. Progression-free survival (PFS, an exploratory endpoint) was statistically significantly longer (36.8 months) in patients of the darolutamide group than in patients of the placebo group (14.8 months). In patients receiving darolutamide, the time to pain progression and the time to prostate-specific antigen (PSA) progression were prolonged by 14.9 months and 25.9 months, respectively. Health-related quality of life (HRQoL) and disease specific quality of life (QoL) were evaluated by the use of five different questionnaires. Overall, patient-reported QoL was similar between the two treatment groups.

Conclusion

The ARAMIS trial showed that darolutamide provides a prolongation of MFS in patients with nonmetastatic CRPC and was associated with better outcomes regarding disease progression as compared to placebo. However, the presented data are the primary and interim analysis; final results of all endpoints are lacking. Hence, the actual clinical benefit of darolutamide is not yet proven. In this regard, more data concerning efficacy, safety and long-term results is required, as well as a direct comparison with other AR antagonists to determine the optimal treatment for affected patients. Darolutamide is currently not approved, but may provide an additional treatment option for patients with nonmetastatic CRPC.

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1 Research questions

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

EUnetHTA
HTA Core Model®

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

2 Drug description

Generic/Brand name/ATC code:

Darolutamide/-/L02BB06

B0001: What is darolutamide?

**darolutamide:
nonsteroidal AR
antagonist**

Darolutamide (developmental code names: ODM-201, BAY-1841788) is a nonsteroidal androgen receptor (AR) antagonist with a molecular structure that differs from other AR antagonists. Darolutamide and its active metabolite inhibit testosterone-induced translocation of AR to the nucleus. This mechanism prevents the binding to and the transcription of genes that regulate the proliferation of prostate cancer cells, resulting in an inhibition of growth in AR-expressing prostate cancer cells [2, 3].

**total daily dose of
1,200 mg**

**ADT therapy continued
throughout the trial**

Patients of the ARAMIS trial received darolutamide at a dose of 600 mg given as two 300 mg tablets twice daily (total daily dose of 1,200 mg) with food, or matching placebo tablets which were indistinguishable from darolutamide tablets. Throughout the trial, patients continued to receive a luteinising hormone (LH)-releasing hormone agonist or antagonist for androgen-deprivation therapy (ADT).

**interaction with other
drugs unlikely**

According to the ARAMIS trial protocol [4], the interaction of darolutamide (at therapeutic dose level, based on nonclinical data) with other drugs is unlikely. Plasma concentration of drugs that are primary metabolised or activated by P450 CYP2C9 or drugs that are sensitive substrates to P-glycoprotein (P-gp) inhibition might be affected by darolutamide. Medicinal products that are sensitive substrates for P-gp, such as digoxin, should be used with caution when co-administered with darolutamide. If patients are treated with both darolutamide and drugs metabolised by CYP2C9 with a narrow therapeutic index, they should be monitored for possible increased therapeutic effects. In patients who are treated with warfarin, International Normalized Ratio (INR) monitoring should be conducted.

**decreased fertility and
developmental toxicity
expected**

Although no stand-alone developmental and reproductive toxicity studies have been conducted with darolutamide, decreased fertility in males and developmental toxicity would be expected on the basis of the known pharmacologic effects of antiandrogens. It also has to be considered that the ARAMIS trial patients received gonadotropin-releasing hormone (GnRH) agonist or antagonist treatment throughout the trial, which affects fertility [4].

A0022: Who manufactures darolutamide?

Bayer HealthCare and Orion Pharma.

3 Indication

A0007: What is the target population in this assessment?

Darolutamide is indicated in patients with nonmetastatic castration-resistant prostate cancer (CRPC) and a PSA doubling time (PSADT) of ten months or less.

men with nonmetastatic PSA and PSADT \leq 10 months

4 Current regulatory status

A0020: For which indications has darolutamide received marketing authorisation?

To date, darolutamide is neither approved by the European Medicines Agency (EMA) nor by the U.S. Food and Drug Administration (FDA) for any indication.

NOT approved by the EMA and the FDA

Based on data from the ARAMIS trial, the manufacturer submitted a marketing authorisation application to the EMA for darolutamide for the treatment of patients with nonmetastatic CRPC in March 2019 [5]. The submission of a New Drug Application to the FDA for darolutamide was initiated in December 2018; the rolling submission¹ was completed in February 2019 [6, 7].

EMA: marketing authorisation submitted, FDA: rolling submission completed

5 Burden of disease

A0002: What is prostate cancer?

Prostate cancer is the most frequent cancer in men in Austria [8] and is among the most common cancers worldwide [9]. The majority of prostate cancers are adenocarcinomas, developing from the gland cells. Other types of prostate cancers, including sarcomas, small cell carcinomas, neuroendocrine tumours (other than small cell carcinomas) and transitional cell carcinomas, are rare.

most common cancer in men in Austria

CRPC is a type of prostate cancer that keeps growing even when the testosterone level is reduced to very low levels [10]. CRPC is defined as a castrate serum testosterone <50 ng/dl or 1.7 nmol/l and has either one of the following progression characteristics:

CRPC grows despite low testosterone levels

- ❖ Biochemical progression: three consecutive rises in PSA one week apart (resulting in two 50% increases over the nadir) and PSA >2 ng/ml, or

¹ In the course of a rolling submission, which is a dose in waves, completed sections - as opposed to the entire application - are submitted for review by the sponsors (e.g., the nonclinical portion in the first wave, followed by a chemistry, manufacturing and control wave, and a final wave containing clinical data).

- ❖ Radiologic progression: the appearance of two or more new lesions on bone scan or a soft tissue lesion using the Response Evaluation Criteria in Solid Tumours (RECIST) [11].

**no radiological findings
in men with
nonmetastatic CRPC**

Patients with nonmetastatic CRPC show rising PSA and castrate testosterone levels, with no radiological findings of metastatic disease on computed tomography (CT) and bone scan [12].

A0004: What is the natural course of prostate cancer?

**77% of prostate cancers
are diagnosed at the
local stage**

According to data from the US population, 77% of prostate cancers are diagnosed at a local stage (confined to primary site), 12% are diagnosed at a regional stage (spread to regional lymph nodes) and 6% of prostate cancer cases are diagnosed at a distant stage, when the cancer has already metastasized (4% of prostate cancer cases remain unstaged) [13].

**Austria: 5-year relative
survival rate of 91.5%**

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

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

A0023: How many people belong to the target population?

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

In Austria, 5,245 men per year (2016) are newly diagnosed with prostate cancer. The age-standardised incidence rate for the European Standard Population (2013) is 138.3 per 100,000 men per year (2016) [8].

**median age at diagnosis:
66 years**

Since there is a lack of European data regarding age at diagnosis and detailed incidence as well as prevalence data, information from the US is reported in the following. In the US, the incidence and prevalence of nonmetastatic CRPC was estimated at 50,000–60,000 men per year and 100,000 men, respectively, with a 34% annual progression to metastatic CRPC; overall mortality was 16% [14]. According to data from the US, prostate cancer is most frequently diagnosed among men between the ages of 65 and 74 years; the median age at diagnosis is 66 years [13].

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

**mostly diagnosed at
asymptomatic, local
stage**

Most cases of prostate cancer are diagnosed at the local stage when patients are asymptomatic. Patients rarely present with nonspecific urinary symptoms including haematuria or haemospermia that are usually associated with non-malignant conditions [9].

**symptoms of metastatic
disease**

Patients with metastatic disease at the time of diagnosis may present with bone pain; other symptoms are weight loss, weakness or pain caused by spinal cord compression or due to pathologic fractures, fatigue due to anaemia, renal or urinary symptoms (haematuria, inability to void, incontinence) as well as symptoms that are associated with chronic renal failure. A clinical sign that can be associated with prostate cancer is an elevation of PSA on laboratory testing. However, PSA is not specific for malignancy, since an elevation may

also be caused by a number of benign conditions. Although PSA is not specific for prostate cancer, the measurement of the PSA level is the most commonly used and most valuable test to detect prostate cancer at an early stage. Further clinical signs that may indicate the presence of prostate cancer are abnormal findings on the digital rectal examination (DRE). A DRE may enable the detection of prostate nodules, indurations or asymmetries potentially associated with prostate cancer. However, only tumours that are localised in the posterior and lateral aspects of the prostate gland can be detected by a DRE; tumours in other parts of the gland are not reachable or not palpable, such as small, stage T1 cancers [9].

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

The risk for the development of clinically significant prostate cancer is related to the following factors [9, 15-18]:

- | | |
|---|--|
| <ul style="list-style-type: none">❖ Age: Increasing age is the most important risk factor for the development of prostate cancer. The disease is rare in men younger than 40 years, but its incidence increases progressively thereafter.❖ 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.❖ 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.❖ 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.❖ 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).❖ Findings on DRE including prostate nodules, indurations or asymmetries.❖ Other factors including diet, hormone levels and obesity may have some effect on the incidence of prostate cancer; however, the role of these factors appears to be limited. | <p>risk factors:</p> <p>increasing age</p> <p>African Americans:
higher risk</p> <p>strong inherited
component</p> <p>elevated PSA level</p> <p>f/t PSA ratio</p> <p>suspicious findings on
DRE</p> <p>other factors: limited
role</p> |
|---|--|

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

no consistent PSA threshold	An elevation in PSA levels or an abnormality on DRE can be a signs of prostate cancer that warrant additional evaluation. There is no consistent PSA threshold for defining an abnormal PSA value [9].
final diagnosis is based on histological examination	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.
grading system	The Gleason grade for the two most prevalent differentiation patterns is used to create the Gleason score and is now used in the new grading (grade group) system; the latter provides a more accurate risk stratification. Due to the fact that 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 [9, 19].
EAU-ESTRO-ESUR-SIOG recommendations	According to the EAU-ESTRO-ESUR-SIOG ² Guidelines on Prostate Cancer [20], frequent post-treatment PSA surveillance leads to earlier detection of disease progression in nonmetastatic CRPC. Approximately one third of patients with a rising PSA develop bone metastases within two years. However, there is no evidence available demonstrating a benefit for immediate treatment. A consensus statement by the Prostate Cancer Radiographic Assessments for Detection of Advanced Recurrence (RADAR) group suggested the conduction of a bone scan and a CT when the PSA level has reached 2 ng/ml. If the results are negative, the imaging procedures should be repeated when the PSA has reached 5 ng/ml and then again after every doubling of the PSA level based on PSA measurement every three months for asymptomatic patients. If patients are symptomatic, they should undergo relevant investigation [20].
differential diagnosis	For prostate cancer, differential diagnosis should be considered. Lower urinary tract symptoms including frequency, urgency, nocturia, and hesitancy occur commonly among men and are usually related to benign conditions rather than to prostate cancer. An elevation of the PSA level can be caused by transient conditions, such as prostatitis or perineal trauma, and by persistent causes such as benign prostate hyperplasia (BPH) [9].

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

6 Current treatment

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

For the treatment of localised prostate cancer, the following approach is recommended [21]:

- ❖ Localised prostate cancer – low risk: Affected patients have major chances to be cured by surgery or radiotherapy, but there is also a risk for overtherapy. Therapeutic options include:
 - Active surveillance
 - Radical prostatectomy
 - Percutaneous radiation therapy of the prostate gland (74–80 Gray)
 - Iodine-125 low dose rate (LDR) brachytherapy (145 Gray)
 - Watchful waiting (palliative approach)

For all these options, observational studies showed a prostate cancer-specific survival rate of 90% to 97% after ten years.

- ❖ Localised prostate cancer – intermediate risk: In this heterogeneous group of patients there is a major chance for a cure, although there is also a risk for overtherapy. Treatment options include:
 - Percutaneous radiotherapy
 - With 74–80 Gray or
 - In combination with LDR brachytherapy or
 - In combination with endocrine therapy for four to six months
 - Active surveillance (application of advanced criteria)
 - Watchful waiting (palliative approach)
- ❖ Localised prostate cancer – high risk: Due to the high risk of disease progression, a curative approach is recommended. In case of contraindications, a palliative approach (based on symptoms) is recommended. Possible treatment options include:
 - Radical prostatectomy
 - Percutaneous radiation therapy of the prostate gland
 - In combination with endocrine therapy for six months or, preferably, 24–36 months or
 - In combination with high dose rate (HDR) brachytherapy, possibly with endocrine therapy
 - Watchful waiting (palliative approach).

According to the National Comprehensive Cancer Center Guidelines [22], for patients with CRPC and no signs of distant metastasis, observation can be considered if PSADT is >10 months. For patients with a PSADT <10 months, secondary hormone therapy (apalutamide or enzalutamide may be considered) provides an option, because the androgen receptor may remain active. Patients with progressive disease despite combined androgen blockade can discontinue the antiandrogen to exclude an “antiandrogen withdrawal response”. Antiandrogen withdrawal is a potential therapeutic manoeuvre for patients with progressive prostate cancer [22, 23].

treatment recommendations for low-, intermediate- and high-risk localised prostate cancer

NCCN guidelines

7 Evidence

<p>systematic literature search in 5 databases: 63 hits</p>	<p>A literature search was conducted on 19 April 2019 in four databases: the Cochrane Library, Embase, Ovid Medline and PubMed. Search terms were “darolutamide”, “ODM-201”, “castration-resistant prostate cancer”, “CRPC”, “prostatic neoplasms, castration-resistant” and “nonmetastatic”. The manufacturer was also contacted and submitted eight references (two of these had already been identified by systematic literature search). A manual search identified 37 additional references (web documents and journal articles).</p>
<p>manual search: 37 additional references</p>	
<p>overall: 95 references included: 2 studies</p>	<p>Overall, 95 references were identified. Included in this reported are:</p> <ul style="list-style-type: none"> ❖ Primary and interim analysis data from ARAMIS, a multinational, double-blind, placebo-controlled phase III trial to evaluate the efficacy and safety of darolutamide in patients with nonmetastatic CRPC [4, 24, 25] and ❖ ARADES, an open-label phase 1 dose escalation and randomised phase II dose expansion trial, assessing the activity and safety of darolutamide in patients with metastatic CRPC [26].
<p>study level risk of bias assessed based on EUnetHTA internal validity for RCTs</p>	<p>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) [27]. Evidence was assessed based on the adequate generation of the randomisation sequence, allocation concealment, blinding of patient and treating physician, selective outcome reporting and other aspects that may increase the risk of bias. Study quality details are reported in Table 5 of the Appendix.</p>
<p>applicability of study results</p>	<p>The external validity of the included trials 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) [28].</p>
<p>magnitude of meaningful clinical benefit assessed based on ESMO-MCBS</p>	<p>To evaluate the magnitude of “meaningful clinical benefit” that can be expected from a new anti-cancer treatment, the Magnitude of Clinical Benefit Scale developed by the European Society for Medical Oncology (ESMO-MCBS) was used [29]. In addition, an adapted version (due to perceived limitations) of the ESMO-MCBS was applied [30]. Details of the magnitude of the clinically meaningful benefit scale are reported in Table 3.</p>

7.1 Quality assurance

<p>internal and external review</p>	<p>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:</p> <ul style="list-style-type: none"> ❖ 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?

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.

quality assurance
method

7.2 Clinical efficacy and safety – phase III studies

The ARAMIS trial [4, 24, 25] is a multinational, randomised, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of darolutamide compared to placebo in men with nonmetastatic CRPC. Patients were enrolled between September 2014 and March 2018; a total of 1,509 patients underwent randomisation and were assigned in a 2:1 ratio to either the darolutamide group (n = 955) or the placebo group (n = 554). Randomisation was stratified according to PSA doubling time (≤ 6 months or ≥ 6 months) and the use of osteoclast-targeted therapy at randomisation (yes/no). Patients were eligible to participate in the ARAMIS trial if they had a histologically or cytologically confirmed adenocarcinoma of the prostate, CRPC, a baseline PSA level of at least 2 ng per millilitre, a PSADT of ten months or less and an Eastern Cooperative (ECOG) performance status of 0 or 1. Patients with detectable metastases or a history of metastatic disease were excluded; patients with previous seizures or conditions predisposing to a seizure were allowed to participate. Detailed inclusion- and exclusion criteria can be found in Table 5 **Fehler! Verweisquelle konnte nicht gefunden werden..**

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

Patients of both groups had a median age of 74 years; 1,194 patients were White, 52 patients were of African descent. The median time from initial diagnosis was 86.2 months in patients of the darolutamide group and 84.2 months in patients of the placebo group. 17% of darolutamide group patients and 29% of placebo group patients showed a presence of lymph nodes on central imaging review. The median PSADT was 4.4 months (darolutamide group) compared to 4.7 months (placebo group); the median serum testosterone level was 0.6 nmol/l in patients of either group. The majority of patients had an ECOG performance status of 0, in particular 68% in the darolutamide group and 71% in the placebo group. A small number of patients, 3% in the darolutamide group and 6% in the placebo group, used a bone-sparing agent. 19% of patients in either group received one previous hormonal therapy agent, 76% of patients in either group were previously treated with two or more hormonal therapy agents. Detailed patient characteristics can be found in Table 5 **Fehler! Verweisquelle konnte nicht gefunden werden..**

patient characteristics:

median age of 74 years

median PSADT:
darolutamide 4.4
months
placebo 4.7 months

<p>darolutamide: 600 mg twice daily (2 x 300 mg tablet), total daily dose of 1,200 mg</p>	<p>Patients of the darolutamide group received the study drug at a dose of 600 mg given as two 300 mg tablets twice daily with food, resulting in a total daily dose of 1,200 mg. Patients of the placebo group received matching placebo tablets. Study treatment was administered until protocol-defined progression, discontinuation of the regimen due to adverse events (AEs) or withdrawal of consent. Throughout the trial, patients continued to receive ADT.</p>
<p>MFS: primary endpoint</p>	<p>Metastasis-free survival (MFS) was the primary endpoint of the ARAMIS trial, defined as the time from randomisation to confirmed evidence of distant metastasis on imaging or death from any cause, whichever occurred first. Secondary endpoints were overall survival (OS), the time to pain progression, the time to cytotoxic chemotherapy and the time to first symptomatic skeletal event. Exploratory endpoints were progression-free survival (PFS) and the time to PSA progression, to first prostate cancer-related invasive procedures and to initiation of subsequent antineoplastic therapy.</p>
<p>median follow-up: 17.9 months, median duration of treatment: 14.8 months (darolutamide group) vs. 11.0 months (placebo group)</p>	<p>The data collection cut-off date for the primary analysis was on September 3, 2018. The median follow-up time was 17.9 months; the median duration of treatment was 14.8 months in patients of the darolutamide group and 11.0 months in patients of the placebo group. 64% (darolutamide group) and 36% (placebo group) were still receiving the trial regimen at the time of data cut-off. 35.5% of patients (darolutamide group) and 63.9% of patients (placebo group) discontinued study treatment. 29.5% of darolutamide group patients and 36.7% of placebo group patients who discontinued the trial regimen received subsequent approved therapy for metastatic CRPC; most frequently used subsequent treatments were docetaxel, abiraterone acetate and enzalutamide. Clinical efficacy data are presented in Table 1; AE data are presented in Table 2.</p>
<p>trial is ongoing, primary- and interim analysis presented</p>	<p>The ARAMIS trial is ongoing until June 2020 (estimated study completion date); hence, primary and interim analyses are presented.</p>

7.2.1 Clinical efficacy

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

lower risk of death with darolutamide at the time of interim analysis, median OS not reached

OS was a secondary endpoint of the ARAMIS trial. An interim analysis of OS was performed after 136 deaths, showing a lower risk of death in patients receiving darolutamide than in patients receiving placebo; hazard ratio (HR) for death was 0.71, confidence interval (CI) 0.50–0.99, $p = 0.045$. Median duration of OS has not been reached [24].

D0006: How does darolutamide affect progression (or recurrence) of nonmetastatic CRPC?

MFS prolonged with darolutamide: 40.4 vs. 18.4 months

MFS was the primary endpoint of the ARAMIS trial. The primary analysis conducted after the occurrence of death or metastasis in 437 patients, showed a median MFS of 40.4 months in patients of the darolutamide group versus 18.4 months in the placebo group (HR for metastasis or death in the darolutamide group was 0.41, 95% CI 0.34–0.50, $p < 0.001$). The superiority of darolutamide regarding MFS was observed across all pre-specified subgroups [24].

The median time to pain progression, a secondary endpoint of the ARAMIS trial, was prolonged in patients of the darolutamide group: 40.3 months as compared to 25.4 months in the placebo group (HR 0.65, 95%CI 0.53–0.79, $p < 0.001$). The median time to the first cytotoxic chemotherapy (another secondary endpoint) was not reported in darolutamide group patients, and was 38.2 months in placebo group patients (HR 0.43, 95% CI 0.31–0.60, $p < 0.001$). The median time to the first symptomatic skeletal event (secondary endpoint) was not reported in patients of either group, HR was 0.43, 95% CI 0.22–0.84, $p = 0.01$ [24].

median time to pain progression prolonged with darolutamide

Median PFS was 36.8 months in patients receiving darolutamide and 14.8 months in patients receiving placebo (HR for disease progression or death was 0.38, 95% CI 0.32–0.45, $p < 0.001$) [24].

darolutamide: median PFS +22 months

D0005: How does darolutamide affect symptoms and findings (severity, frequency) of nonmetastatic CRPC?

The median time to PSA progression was 33.2 months in the darolutamide group and 7.3 months in the placebo group (HR for PSA progression or death was 0.13, 95% CI 0.11–0.16, $p < 0.001$). Regarding the time to first prostate cancer-related invasive procedure and the time to initiation of subsequent antineoplastic therapy, the median duration of these endpoints was not reported from both treatment groups. HR for the time to first prostate cancer-related invasive procedure was 0.39, 95% CI 0.25–0.61, $p < 0.001$. HR for the time to initiation of subsequent antineoplastic therapy was 0.33, 95% CI 0.23–0.47, $p < 0.001$ [24].

median time to PSA progression +25.9 months

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

The occurrence of fatigue or asthenic conditions was higher in patients who received darolutamide (15.8%) than in patients receiving placebo (11.4%); more patients in the darolutamide group (2.9%) than patients in the placebo group (0.9%) experienced rash. There was no higher incidence with darolutamide regarding falls, seizures or change in mental status.

higher rate of fatigue/asthenic conditions and rash with darolutamide

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

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

To evaluate the generic health-related (HRQoL) and the disease-specific quality of life (QoL) of the ARAMIS trial patients, the following questionnaires were used: the Brief Pain Inventory Short-Form (BPI-SF), the Functional Assessment of Cancer Therapy-Prostate (FACT-P), the prostate cancer-specific subscale of the FACT-P (FACT-P PCS), the generic EuroQol Group 5-dimension 3-level (EQ-5D-3L) and the European Organisation for Research and Treatment of Cancer quality of life questionnaire urinary symptoms subscale (EORTC-QLQ-PR25). Analyses showed similar results for patient-reported QoL in both groups. Differences in least-squares mean (LSM), time-adjusted, area-under-the-curve (AUC) scores were statistically significant for BPI-SF (pain severity and pain interference scores), FACT-P (Physical Well-Being, Emotional Well-Being, PCS, General, FACT-P total and Trial Outcome Index), and the EORTC-QLQ-PR25 urinary symptoms subscale were in

QoL assessed by the use of BPI-SF, FACT-P, FACT-P PCS, EQ-5D-3L, EORTC-QLQ-PR25

patient-reported QoL: similar in both groups

differences in LSM time-adjusted AUC scores favoured darolutamide, but clinically meaningful thresholds were not reached

favour of darolutamide. However, the clinically meaningful thresholds were not reached [24, 25].

Table 1: Efficacy results of ARAMIS trial [24, 25]

Descriptive statistics and estimate variability	Treatment group	Darolutamide	Placebo
	Number of subject	955	554
	Median MFS, months	40.4	18.4
	Median OS, months	NR	NR
	Median time to pain progression, months	40.3	25.4
	Median PFS, months	36.8	14.8
	Median time to PSA progression, months	33.2	7.3
	BPI-SF pain interference	1.1	1.3
	BPI-SF pain severity	1.3	1.4
	FACT-P (total)	112.9	111.6
	FACT-P PCS	32.4	31.8
	EORTC-QLQ-PR25 (urinary symptoms subscale)	23.7	26.4
	EQ-5D-3L Index Score	0.8	0.8
	EQ-5D-3L VAS	73.3	72.7
	Effect estimate per comparison	Comparison groups	
Median MFS		HR for metastasis or death	0.41
		95% CI	0.34–0.50
		p-value	<0.001
Median OS		HR for death	0.71
		95% CI	0.50–0.99
		p-value	0.045
Median time to pain progression		HR	0.65
		95% CI	0.53–0.79
		p-value	<0.001
Median PFS		HR	0.38
		95% CI	0.32–0.45
		p-value	<0.001
Median time to PSA progression		HR	0.13
		95% CI	0.11–0.16
		p-value	<0.001
BPI-SF pain interference		Difference	-0.2
		MID	2
BPI-SF pain severity		Difference	-0.2
		MID	2
FACT-P (total)		Difference	1.3
		MID	10
FACT-P PCS		Difference	0.6
	MID	3	
EORTC-QLQ-PR25 (urinary symptoms subscale)	Difference	-2.7	
	MID	8	

	EQ-5D-3L Index Score	Difference	0.01
		MID	-
	EQ-5D-3L Visual Analogue Scale	Difference	0.6
		MID	-

Abbreviations: BPI-SF = Brief Pain Inventory Short-Form, CI = confidence interval, EORTC-QLQ-PR25 = European Organisation for Research and Treatment of Cancer Quality of Life, EQ-5D-3L = EuroQol 5-dimensions 3-levels, FACT-P = Functional Assessment of Cancer Therapy-Prostate, HR = hazard ratio, MFS = Metastasis-free survival, MID = minimally important difference, NR = not reported, OS = overall survival, PCS = prostate cancer subscale, PFS = progression-free survival, PSA = prostate-specific antigen, VAS = visual analogue scale

7.2.2 Safety

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

AEs of any grade were reported from 83.2% of darolutamide group patients and 76.9% of placebo group patients; AEs of grade 3 or 4 were reported in 24.7% (darolutamide group) and 19.5% (placebo group) of patients. 24.8% of darolutamide group patients and 20.0% of placebo group patients experienced serious AEs of any grade. 15.8% and 12.6% of patients had serious AEs of grade 3 or 4 in the darolutamide group and placebo group, respectively. 3.9% of darolutamide group patients and 3.2% of placebo group patients had a grade 5 AE; one death in the darolutamide group and two deaths in placebo group patients were considered to be related to the study treatment.

The most common AEs occurring in $\geq 5\%$ of patients were fatigue (12.1%), back pain (8.8%) and arthralgia (8.1%) in darolutamide group patients and arthralgia (9.2%), back pain (9.0%) and fatigue (8.7%) in placebo group patients. The most frequent AEs of special interest (any grade) were fatigue or asthenic conditions (15.8%), bone fracture (4.2%) and falls, including accident (4.2%) in patients of the darolutamide group and fatigue or asthenic conditions (11.4%), falls, including accident (4.7%), and dizziness, including vertigo (4.0%), in placebo group patients.

Among patients of the darolutamide group, 8.9% of them discontinued treatment due to AEs of any grade and 3.4% of patients stopped the trial regimen due to AEs of grade 3 or 4. In the placebo group, AEs of any grade led to discontinuation in 8.7% of patients, and 4.3% of patients discontinued receiving the study drug due to AEs of grade 3 or 4.

AEs grade ≥ 3 : 24.7% in darolutamide group vs. 19.5% in placebo group
1 death in darolutamide group and 2 deaths in placebo group considered to be related to study treatment

most common AEs in the darolutamide group: fatigue, back pain, arthralgia

study treatment discontinuation due to AEs in 8.9% (darolutamide group) and 8.7% (placebo group)

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

Massard et al. reported that darolutamide was well tolerated in an open-label phase I trial when patients initially received a single 600 mg dose of darolutamide (tablet or capsules) and 600 mg twice daily (capsules) in the extension phase. All treatment-related AEs were grade 1 and none of the patients required dose reductions [4, 31]. Within the scope of the ARADES trial, different dosage regimens of darolutamide treatment were assessed. Darolutamide was well tolerated up to the highest prespecified dose of 1,800 mg per day; a maximum tolerated dose was not reached. The most frequently reported AEs were of grade 1 or 2 and the AE profile did not differ between dose levels [26].

different dosages up to 1,800 mg darolutamide/day were well tolerated in previous phase I/II trials

**ARAMIS trial:
interruption of
treatment
(≤28 days)/ dose
reduction allowed**

According to the ARAMIS trial protocol, patients who are affected by a treatment-related grade ≥ 3 AE that cannot be ameliorated by the use of an adequate medical intervention should interrupt the trial regimen until the AE improves to grade ≤ 2 . If the treatment interruption lasts longer than 28 days, the patient must be withdrawn from the study. If it is considered necessary for the safety of a trial participant, the dose of the trial regimen can be reduced to 300 mg twice daily. If a patient experiences an AE of grade ≥ 3 after one dose reduction despite medical intervention, withdrawal from study treatment is required [4].

**decreased fertility
expected**

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

On the basis of the known pharmacologic effects of antiandrogens, decreased fertility is expected in men who receive darolutamide. In addition, it has to be considered that ARAMIS trial participants continue to receive ADT throughout the trial, which also affects fertility [4].

Table 2: Most frequent adverse events [24]

Adverse event (according to NCI CTCAE version 4.03)	Darolutamide (n = 954)		Placebo (n = 554)	
	Any grade n (%)	Grade 3 or 4 n (%)	Any grade n (%)	Grade 3 or 4 n (%)
Any adverse event	794 (83.2)	236 (24.7)	426 (76.9)	108 (19.5)
Serious adverse event	237 (24.8)	151 (15.8)	111 (20.0)	70 (12.6)
Grade 5 adverse event	37 (3.9)	-	18 (3.2)	-
Adverse event leading to discontinuation of the trial regimen	85 (8.9)	32 (3.4)	48 (8.7)	24 (4.3)
Adverse events that occurred in ≥5% of patients in either group				
Fatigue	115 (12.1)	4 (0.4)	48 (8.7)	5 (0.9)
Back pain	84 (8.8)	4 (0.4)	50 (9.0)	1 (0.2)
Arthralgia	77 (8.1)	3 (0.3)	51 (9.2)	2 (0.4)
Diarrhoea	66 (6.9)	0 (0)	31 (5.6)	1 (0.2)
Hypertension	63 (6.6)	30 (3.1)	29 (5.2)	12 (2.2)
Constipation	60 (6.3)	0 (0)	34 (6.1)	0 (0)
Pain in an extremity	55 (5.8)	0 (0)	18 (3.2)	1 (0.2)
Anaemia	53 (5.6)	8 (0.8)	25 (4.5)	2 (0.4)
Hot flush	50 (5.2)	0 (0)	23 (4.2)	0 (0)
Nausea	48 (5.0)	2 (0.2)	32 (5.8)	0 (0)
Urinary tract infection	47 (4.9)	6 (0.6)	28 (5.1)	3 (0.5)
Urinary retention	33 (3.5)	15 (1.6)	36 (6.5)	11 (2.0)
Adverse events of interest				
Fatigue or asthenic conditions	151 (15.8)	6 (0.6)	63 (11.4)	6 (1.1)
Bone fracture	40 (4.2)	9 (0.9)	20 (3.6)	5 (0.9)
Falls, including accident	40 (4.2)	8 (0.8)	26 (4.7)	4 (0.7)
Seizure, any event	2 (0.2)	0 (0)	1 (0.2)	0 (0)
Rash	28 (2.9)	1 (0.1)	5 (0.9)	0 (0)
Weight decrease, any event	34 (3.6)	0 (0)	12 (2.2)	0 (0)
Dizziness, including vertigo	43 (4.5)	2 (0.2)	22 (4.0)	1 (0.2)
Cognitive disorder	4 (0.4)	0 (0)	1 (0.2)	0 (0)
Memory impairment	5 (0.5)	0 (0)	7 (1.3)	0 (0)
Change in mental status	0 (0)	0 (0)	1 (0.2)	0 (0)
Hypothyroidism	2 (0.2)	0 (0)	0 (0)	0 (0)
Cerebral ischaemia	13 (1.4)	7 (0.7)	8 (1.4)	4 (0.7)
Coronary-artery disorder	31 (3.2)	16 (1.7)	14 (2.5)	2 (0.4)
Heart failure	18 (1.9)	5 (0.5)	5 (0.9)	0 (0)

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

7.3 Clinical effectiveness and safety – further studies

<p>ARADES: phase I dose escalation and randomised phase II dose expansion trial</p>	<p>The ARADES trial [26], an open-label, multicentre study with a non-randomised phase I dose escalation part, a phase II randomised dose expansion part and a long-term follow up was conducted to assess darolutamide in patients with progressive metastatic CRPC. Eligible patients had histologically confirmed adenocarcinoma of the prostate, progressive metastatic disease and a PSA higher than 2 ng/ml. Patients with seizure were not excluded; three patients had a history of seizures.</p>
<p>phase I endpoint: safety and tolerability</p>	<p>In the phase I part of the trial, the 24 enrolled patients received darolutamide orally at a starting daily dose of 200 mg, which was increased to 400 mg, 600 mg, 1,000 mg, 1,400 mg and 1,800 mg. The primary endpoint of the phase I part was safety and tolerability. In the phase II part of the study, 110 patients received one of three daily doses of darolutamide: 200 mg, 400 mg or 1,400 mg; the primary endpoint of this study phase was the proportion of patients with a PSA response (50% or greater decrease in serum PSA) at week 12. The median time of darolutamide administration was 24.8 months in phase I and 11.0 months in phase II of the ARADES trial. The most common reason for discontinuation of the trial regimen was disease progression; 4% of the patients discontinued due to the occurrence of an AE. Safety analyses showed that in the phase I part 93% of the AEs were of grade 1–2. Three patients reported eight AEs of grade 3, including fracture, muscle injury, laceration, paralytic ileus, pain, presyncope, urinary retention and vomiting; one patient had a grade 4 event (lymphoedema). None of the grade 3–4 AEs were deemed to be related to the administration of darolutamide. Fourteen of the phase I patients entered phase II.</p>
<p>phase II endpoint: PSA response rate</p>	
<p>tolerable safety profile, no seizures</p>	
<p>approx. 1/3 of patients had PSA response at 12 weeks</p>	<p>The phase II analyses showed that 29% of patients in the 200 mg group, 33% of patients in the 400 mg group and 33% of patients in the 1,400 mg group had a PSA response at 12 weeks. Analyses among the safety population (n = 124) showed that the most common treatment-emergent AEs were fatigue or asthenia in 12% of patients, hot flush in 5% of patients, and decreased appetite in 4% of patients. One patient experienced a treatment-emergent grade 3 event (fatigue). No treatment-emergent grade 4 AEs occurred and no seizures were reported. Limitations of the ARADES trial include the open-label design, small sample sizes, the lack of control groups and the absence of QoL measurement [26].</p>
<p>limitations: open-label, small sample sizes, no control group, no QoL measurement</p>	

8 Estimated costs

A0021: What is the reimbursement status of darolutamide?

no cost information available

Due to the fact that darolutamide is not approved throughout the European Union or the US, no cost information is available.

9 Ongoing research

Currently, the ARAMIS trial (NCT02200614) is the only phase III trial evaluating darolutamide in patients with nonmetastatic CRPC. The estimated study completion date is 30 June 2020 [32].

However, the following two trials are aiming to assess darolutamide in patients with metastatic prostate cancer:

- ❖ The ARASENS trial (NCT02799602) is a phase III trial assessing the efficacy and safety of darolutamide in combination with standard ADT therapy and docetaxel in patients with metastatic hormone-sensitive prostate cancer. The estimated study completion date is August 2022 [33].
- ❖ ODENZA (NCT03314324) is a prospective, randomised, open-label cross-over phase II trial assessing patient preference between darolutamide and enzalutamide by questionnaire in patients with metastatic CRPC. The estimated study completion date is January 2022 [32].

There are several other phase I and phase II studies assessing darolutamide in prostate cancer, and one phase II trial evaluating darolutamide in female breast cancer [32, 34].

ARAMIS is the only ongoing phase III trial for the assessed indication

ARASENS and ODENZA: darolutamide in metastatic prostate cancer

several ongoing phase I/II trials

10 Discussion

Darolutamide, a novel nonsteroidal androgen receptor, is not currently approved by the EMA or by the FDA for any indication. Based on data from the ARAMIS trial, the manufacturer submitted a marketing authorisation application to the EMA for darolutamide for the treatment of patients with nonmetastatic CRPC in March 2019 [5]; in the US, the submission of a New Drug Application to the FDA for darolutamide was initiated in December 2018; the rolling submission was completed in February 2019 [6].

darolutamide is currently not approved by the EMA or the FDA

MFS: +22 months with darolutamide	The ARAMIS trial is aiming to investigate the efficacy and safety of darolutamide compared to placebo in men with nonmetastatic CRPC. The trial is currently ongoing; thus, presented data are primary and interim results. The primary analysis of median MFS showed a gain of 22 months in patients who received darolutamide compared to patients who received placebo (HR for metastasis or death in the darolutamide group was 0.41). This beneficial treatment effect of darolutamide was observed across all pre-specified subgroups. An interim analysis of OS showed a lower risk of death with darolutamide as compared to placebo (HR for death was 0.71); however, median OS data have not been reached in either group. PFS – an exploratory endpoint – was statistically significantly longer (36.8 months) in patients of the darolutamide group than in patients of the placebo group (14.8 months). In patients receiving darolutamide, the time to pain progression and the time to PSA progression were prolonged by 14.9 months and 25.9 months, respectively. HRQoL and disease-specific QoL were evaluated by the use of five different questionnaires. Even though differences in LSM time-adjusted AUC scores were consistently favouring darolutamide and were statistically significant for BPI-SF, FACT-P and the EORTC-QLQ-PR25 urinary symptoms subscale and the clinically meaningful thresholds were not reached. Overall, patient-reported QoL was similar between the two treatment groups.
PFS: +22 months with darolutamide	
patient-reported QoL was similar between the 2 groups	
final analysis and long-term efficacy data for OS and QoL are needed	Due to the ongoing status of the ARAMIS trial, no final analysis regarding clinically meaningful outcomes, including OS and QoL, is available. However, to prove the clinical benefit of darolutamide, final analysis and long-term efficacy data for OS and QoL are required. MFS is a newly established surrogate parameter and was recently used as a primary endpoint supporting drug approval [35, 36]. Although Xie et al. deemed MFS to be a strong surrogate for OS in clinically localised prostate cancer [37], it needs to be demonstrated whether a benefit in MFS implies a benefit in OS.
MFS: surrogate parameter	
higher rate of AEs in darolutamide group patients	AEs of grade 3 or 4 occurred in 24.7% (darolutamide group) and 19.5% (placebo group) of patients; most common were hypertension and urinary retention, occurring in 3.1% and 1.6% in darolutamide group patients and in 2.2% and 2.0% of placebo group patients, respectively. 15.8% of darolutamide group patients and 12.6% of patients experienced serious AEs. One death in the darolutamide group and two deaths in the placebo group were considered to be treatment-related. The percentage of patients who discontinued the trial regimen due to AEs was similar in either group [24].
CNS-related AEs: lower risk due to lower brain-blood barrier penetration?	Preclinical studies showed that darolutamide had a tenfold lower blood-brain barrier penetration than enzalutamide, suggesting a lower risk of inducing Central Nervous System (CNS)–related AEs, as compared to enzalutamide [38]. In contrast to other trials evaluating AR antagonists, patients with a history of seizures or conditions predisposing to seizures were allowed to participate in the ARAMIS trial; analysis showed that the incidence of seizures was 0.2% in both treatment groups and none of the patients with previous seizures had a seizure during the trial. ARAMIS trial analysis showed similar incidences of seizure, dizziness, cognitive disorders and memory impairment in the two treatment groups, potentially caused by a lower blood-brain barrier penetration of darolutamide. However, there is no evidence to confirm this potential benefit of darolutamide. Although safety data from the ARADES trial [26] has been substantiated by the results of the ARAMIS trial, no mature data regarding long-term safety and potential long-term toxicities is available.

To date, ARAMIS is the only phase III trial assessing darolutamide in patients with nonmetastatic CRPC; the trial is ongoing until 30 June 2020. Further evidence in terms of efficacy and safety of darolutamide may be provided by the ARASENS [33] trial and the ODENZA trial [32], even though both trials evaluate darolutamide in patients with metastatic CRPC. To fully elucidate the role of darolutamide in patients with nonmetastatic CRPC, a direct comparison of darolutamide, enzalutamide and apalutamide is required.

An issue to discuss is the potential advantage of an intervention at the a-symptomatic, nonmetastatic stage of CRPC rather than at a later stage of the disease. Mateo et al. [39] stated that long-term toxicities of earlier and therefore longer drug administration and the associated economic implications have to be considered in case of treatment intensification at an early, nonmetastatic stage of CRPC. Studies have evaluated the impact of an earlier treatment on healthcare costs by considering the drug costs and the benefits of a delay in disease progression, AEs that are drug- and disease-related, as well as the economic benefit of an improved QoL, are required. To achieve this, the implementation of prospective trials to directly compare earlier to later intervention is needed [39].

The ARAMIS trial was conducted as a double-blind study; adequate generation of randomisation sequence and allocation concealment were described, and reasons for discontinuations were reported. Since the trial is currently ongoing, final data analysis is lacking. Hence, the reporting bias cannot be assessed by now. Other aspects that increase the risk of bias are the funding of ARAMIS trial by the manufacturers and their participation in the data analysis. Overall, a low risk of bias was detected. In terms of applicability, it needs to be noted that patients with African American descent were underrepresented in the ARAMIS trial (52 of 1,509 patients). Since the incidence of prostate cancer is higher in African Americans than in other ethnic groups, the applicability of results is limited. Final analysis of data of all primary, secondary and exploratory endpoints is lacking; hence, the applicability of the results in terms of outcomes is limited. Furthermore, the wide range of exclusion criteria, particularly the exclusion of patients with clinically significant cardiovascular diseases including uncontrolled hypertension, severe/unstable angina pectoris or congestive heart failure New York Heart Association (NYHA) Class III or IV, may limit the applicability of the results.

We applied the ESMO-MCBS in order to assess whether darolutamide satisfies the criteria for a “meaningful clinical benefit” (score 4 or 5). Both the original v1.1 as well as the adapted version of the MCBS were used. Given the non-curative treatment setting of darolutamide, the lack of an evaluation form for the study endpoint MFS and the immature OS data, PFS (Form 2b) was the basis for the ESMO-MCBS assessment. The application of the scale to the ARAMIS study resulted in a grade 3 in both the original and the adapted version of the ESMO-MCBS, respectively. Therefore, darolutamide leads to no “meaningful clinical benefit” according to the original scale or the adapted framework. However, the result of this evaluation has to be taken with caution, since PFS was not even a secondary study endpoint, but rather an exploratory one.

The costs for darolutamide treatment are not yet known. Once the cost information on darolutamide is available, a direct comparison of darolutamide, enzalutamide and apalutamide treatment will be feasible. At any rate, additional costs for the continuation of ADT incur.

ARAMIS is ongoing until 06/2020

direct comparison with enzalutamide and apalutamide required

prospective trials needed to compare early vs. later intervention

low risk of bias

limitations of applicability

ESMO-MCBS: grade 3 (original & adapted scale);

no mature OS data, PFS not a secondary endpoint → no meaningful clinical benefit

no cost information available

**MFS prolongation, but
clinical benefit not yet
proven**

The ARAMIS trial showed that darolutamide provides a prolongation of MFS in patients with nonmetastatic CRPC and was associated with better outcomes regarding disease progression as compared to placebo. However, the presented data are the primary and interim analysis; final results of all endpoints are lacking. Hence, the actual clinical benefit of darolutamide is not yet proven. In this regard, more data concerning efficacy, safety and long-term results is required, as well as a direct comparison with other AR antagonists, to determine the optimal treatment for affected patients. Darolutamide is currently not approved, but may provide an additional treatment option for patients with nonmetastatic CRPC.

Table 3: Benefit assessment based on original ESMO-MCBS and adapted benefit assessment based on adapted ESMO-MCBS [29, 30]

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		
Adapt-ed ESMO-MCBS	Darolutamide	Nonmetastatic CRPC	NC	MFS ₃	2b	>6 months	+22	0.38 (0.32–0.45)	HR ≤0.65 AND Gain >3 months	3	+5.2 grade 3–4 AEs, +0.2 discontinuation	ND	x	3
Original ESMO-MCBS	Darolutamide	Nonmetastatic CRPC	NC	MFS ₃	2b	>6 months	+22	0.38 (0.32–0.45)	HR ≤0.65 AND Gain >3 months	3	x	ND	x	3

Abbreviations: AJ = Adjustments, CI = confidence interval, CRPC = castration-resistant prostate cancer, ESMO-MCBS = European Society for Medical Oncology-Magnitude of Clinical Benefit Scale, FM = final adjusted magnitude of clinical benefit grade, HR = hazard ratio, m = months, MG = median gain, MFS = metastasis-free survival, ND = no difference, PE = primary endpoint, PM = preliminary magnitude of clinical benefit grade, QoL = quality of life

DISCLAIMER

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

³ PFS was used since there is no form available to evaluate MFS. However, PFS was not even a secondary endpoint, but rather an exploratory one.

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12 Appendix

Table 4: Administration and dosing of darolutamide [4]

	Technology	Comparator
Administration mode	The tablets should be taken with food and a glass (about 250 ml) of water, milk or juice (not grape juice). The tablets should be swallowed whole.	Matching placebo twice daily with food.
Description of packaging	The active ingredient darolutamide will be provided as 300 mg film-coated tablets for oral administration. The tablets are blue oval-shaped tablets embossed with a code 'OR-300'. Each tablet contains approximately 180 mg lactose	Placebo film-coated tablets will be provided as a reference product. The tablets are blue oval-shaped tablets embossed with a code 'OR-300'. Each tablet contains approximately 180 mg lactose. The placebo tablets will be indistinguishable from darolutamide-201 tablets.
Total volume contained in packaging for sale	-	-
Dosing	Darolutamide was administered to ARAMIS trial patients at a total daily dose of 1200 mg (2 x 300 mg tablets twice daily)	Placebo tablets were administered to patients of the control group in the same manner as in patients of the darolutamide group.
Median treatment duration	ARAMIS trial: 14.8 months in the darolutamide group	ARAMIS trial: 11.0 months in the placebo group
Contraindications	-	-
Drug interactions	According to the ARAMIS trial protocol [4], the interaction of darolutamide (at therapeutic dose level, based on nonclinical data) with other drugs is unlikely. Plasma concentration of drugs that are primary metabolised or activated by P450 CYP2C9 or drugs that are sensitive substrates to P-glycoprotein (P-gp) inhibition might be affected by darolutamide. Medicinal products that are sensitive substrates for P-gp, such as digoxin should be used with caution when co-administered with darolutamide. If patients are treated with both darolutamide and drugs metabolised by CYP2C9 with a narrow therapeutic index, they should be monitored for possible increased therapeutic effects. In patients who are treated with warfarin, International Normalized Ratio (INR) monitoring should be conducted.	-

Table 5: Characteristics of ARAMIS trial

Title: Darolutamide in nonmetastatic, castration-resistant prostate cancer [4, 24, 25]			
Study identifier	NCT02200614, EudraCT Number: 2013-003820-36		
Design	Multinational, randomised, double-blind, placebo-controlled, phase III trial		
	Duration of main phase:	Enrolment: between September 2014 and March 2018 Data-collection cut-off date for the primary analysis: 3 September 2018 Median follow-up time: 17.9 months	
Hypothesis	Superiority		
Funding	Bayer HealthCare and Orion Pharma		
Treatment groups	Intervention (n = 955)	Patients received darolutamide 600 mg given as two 300 mg tablets twice daily (a daily dose of 1200 mg) with food until protocol-defined progression, discontinuation of the regimen because of AEs, or withdrawal of consent. Patients continued to receive ADT (luteinising hormone-releasing hormone agonist or antagonist) throughout the trial.	
	Placebo (n = 554)	Patients received matching placebo for darolutamide (2 tablets) orally with food. Patients continued to receive ADT (luteinising hormone-releasing hormone agonist or antagonist) throughout the trial.	
Endpoints and definitions	Metastasis-free survival (primary endpoint)	MFS	Defined as the time from randomisation to confirmed evidence of distant metastasis on imaging or death from any cause, whichever occurred first.
	Overall survival (secondary endpoint)	OS	Defined as time from randomisation to date of death from any cause.
	Time to pain progression (secondary endpoint)	-	Defined as either an increase of ≥ 2 points from baseline in the score assessed with the BPI-SF questionnaire or initiation of opioid treatment for cancer pain, whichever occurred first.
	Time to first symptomatic skeletal event (secondary endpoint)	SSE	Defined as external-beam radiation therapy to relieve skeletal symptoms, new symptomatic pathologic bone fracture, occurrence of spinal cord compression, or tumour-related orthopaedic surgical intervention.
	Time to first cytotoxic chemotherapy (secondary endpoint)	-	Defined as time from randomisation to initiation of the first cytotoxic chemotherapy.
	Progression-free survival (exploratory endpoint)	PFS	Defined as the time from randomisation to evidence of any radiographic disease progression, including local relapse or new pathologic lymph nodes, or death from any cause, whichever occurred first.
	Time to first prostate cancer-related invasive procedure (exploratory endpoint)	-	Defined as time from randomisation to date of first prostate cancer-related invasive procedure. Prostate cancer-related invasive procedure is defined as any procedure needed for alleviation of symptoms, signs or findings caused by progression of prostate cancer (e.g., catheterisation of the bladder, percutaneous drainage of hydronephrosis, palliative electroresection of the prostate, etc.).
	Time to initiation of subsequent antineoplastic therapy (exploratory endpoint)	-	Defined as time from randomisation to initiation of first antineoplastic therapy.

Title: Darolutamide in nonmetastatic, castration-resistant prostate cancer [4, 24, 25]			
Study identifier	NCT02200614, EudraCT Number: 2013-003820-36		
	Time to PSA progression (exploratory endpoint)	-	<p>PSA progression is defined according to the Consensus Guidelines of the PCWG2.</p> <ul style="list-style-type: none"> ✱ For patients with declines from baseline at week 16, the PSA progression is defined as the date that a $\geq 25\%$ PSA increase and an absolute increase of ≥ 2 ng/ml above the nadir is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later. ✱ For patients with no decline from baseline at week 16, the PSA progression is defined as the date that a $\geq 25\%$ PSA increase in PSA along with an absolute increase of ≥ 2 ng/ml above the baseline is documented, which is confirmed by a second consecutive value obtained 3 or more weeks later. <p>Early increases in PSA values before the 16 weeks are not considered as PSA progression.</p>
	PSA response (exploratory endpoint)	-	Defined as a decline of at least 50% from baseline in the PSA level, according to PCWG2 criteria.
	Deterioration in ECOG performance status(exploratory endpoint)	-	Defined as an increase to a score of 3 or higher.
	Quality of life	QoL	-
Database lock	Entire database will be locked after all data for the follow-up period of the study have been entered and queries resolved.		
Results and analysis			
Analysis description	<p>Primary analysis</p> <p>The sample size was calculated on the basis of the primary end point, metastasis-free survival. Assuming a HR of 0.71 for death or metastasis in the darolutamide group, we calculated that a sample of 1,500 patients (randomly assigned in a 2:1 ratio to receive darolutamide or placebo) with approximately 385 primary end-point events would provide the trial with 91% power to detect a significant difference in MFS with the use of a log-rank test at a two-sided significance level of 0.05. The full ITT population, which was made up of all patients who underwent randomisation, was included in the analysis of the primary end point; patients with metastases at baseline were counted as having an event at randomisation. Subgroup analyses of MFS and OS were performed to determine the effect of demographic or baseline characteristics. Randomisation stratification factors were used to adjust analyses of the primary and all secondary efficacy end points. Data from patients without events were censored at the last assessment date. Kaplan–Meier curves, including median survival times and their 95% CIs, were calculated; the HR was calculated with a Cox proportional-hazards model. Secondary and exploratory end points were analysed with the same methods as the primary end point, with the exception of the percentage of patients with PSA response and percentage of patients with deterioration in ECOG performance status, which were analysed with the Cochran–Mantel–Haenszel test. Secondary end points were evaluated in a hierarchical order, with a significance level of 0.05 split between the primary analysis and final analysis (planned to occur after 240 deaths from any cause) of secondary endpoints. The end point of OS was used to determine the alpha spend and significance threshold for each of the secondary end points. For QoL variables, an analysis of covariance model was used to compare the time-adjusted AUC between groups, with covariates for baseline scores and randomisation stratification factors. The least-squares mean and 95% confidence interval was estimated for each group and for the difference between the groups. Statistical analysis and generation of patient data listings were performed with the use of SAS for Windows, version 9.2 (SAS Institute). Incomplete data on event occurrence dates were imputed as the earliest possible date.</p>		

Title: Darolutamide in nonmetastatic, castration-resistant prostate cancer [4, 24, 25]		
Study identifier	NCT02200614, EudraCT Number: 2013-003820-36	
Analysis population	Inclusion	<ul style="list-style-type: none"> ✱ Males aged ≥ 18 years ✱ Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features ✱ CRPC defined as 3 rising PSA levels after the nadir taken at least 1 week apart during ADT. If the patient has a history of antiandrogen use, the most recent PSA value must be obtained at least 4 weeks after anti-androgen withdrawal. ✱ Castrate level of serum testosterone < 1.7 nmol/l (50 ng/dl) on GnRH agonist or antagonist therapy or after bilateral orchiectomy at screening or Day 1 visit. Patients who have not undergone bilateral orchiectomy must continue GnRH therapy during the study. ✱ PSADT of ≤ 10 months and PSA ≥ 2 ng/ml at screening. ✱ ECOG performance status of 0-1. ✱ Blood counts at screening: haemoglobin ≥ 9.0 g/dl, absolute neutrophil count $\geq 1500/\mu\text{l}$ ($1.5 \times 10^9/\text{l}$), platelet count $\geq 100,000/\mu\text{l}$ ($100 \times 10^9/\text{l}$) (patient must not have received any growth factor or blood transfusion within 7 days of the haematology laboratory obtained at screening). ✱ Screening values of serum ALT and AST $\leq 2.5 \times \text{ULN}$, total bilirubin $\leq 1.5 \times \text{ULN}$ (except patients with a diagnosis of Gilbert's disease), creatinine $\leq 2.0 \times \text{ULN}$. ✱ Sexually active patients, unless surgically sterile, must agree to use condoms as an effective barrier method and refrain from sperm donation during the study treatment and for 3 months after the end of the study treatment.

Title: Darolutamide in nonmetastatic, castration-resistant prostate cancer [4, 24, 25]				
Study identifier		NCT02200614, EudraCT Number: 2013-003820-36		
Analysis population (continuation)	Exclusion	<ul style="list-style-type: none"> ✘ History of radiographically documented metastatic disease at any time or presence of detectable metastases by blinded central reading within 42 days prior to start of study treatment. Presence of pelvic lymph nodes <2 cm in short axis below the aortic bifurcation is allowed. ✘ Symptomatic local-regional disease that requires medical intervention including moderate/severe urinary obstruction or hydronephrosis due to prostate cancer. ✘ Acute toxicities of prior treatments and procedures not resolved to grade ≤ 1 or baseline before randomisation. ✘ Prior treatment with: <ul style="list-style-type: none"> • second-generation AR antagonists such as enzalutamide and apalutamide, or darolutamide or other investigational AR antagonists • CYP17 enzyme inhibitors, such as abiraterone acetate, TAK-700; or • oral ketoconazole for longer than 28 days. ✘ Use of oestrogens or 5-α reductase inhibitors (finasteride, dutasteride) within 28 days before randomisation and AR antagonists (bicalutamide, flutamide, nilutamide, cyproterone acetate) at least 28 days before screening. ✘ Prior chemotherapy or immunotherapy for prostate cancer, except adjuvant/neoadjuvant treatment completed >2 years before randomisation. ✘ Use of systemic corticosteroid with dose greater than the equivalent 10 mg of prednisone/day within 28 days before randomisation. ✘ Radiation therapy (EBRT), brachytherapy, or radiopharmaceuticals) within 12 weeks before randomisation. ✘ Severe or uncontrolled concurrent disease, infection or comorbidity that, in the opinion of the investigator, would make the patient inappropriate for enrolment. ✘ Treatment with an osteoclast-targeted therapy (bisphosphonate or denosumab) to prevent skeletal-related events within 12 weeks before randomisation. Patients receiving osteoclast-targeted therapy to prevent bone loss at a dose and schedule indicated for osteoporosis may continue treatment at the same dose and schedule. ✘ Known hypersensitivity to the study treatment or any of its ingredients. ✘ Major surgery within 28 days before randomisation. ✘ Any of the following within 6 months before randomisation: stroke, myocardial infarction, severe/unstable angina pectoris, coronary/peripheral artery bypass graft; congestive heart failure NYHA Class III or IV. ✘ Uncontrolled hypertension as indicated by a systolic blood pressure \geq 160 mmHg or diastolic blood pressure \geq 100 mmHg at screening. ✘ Prior malignancy. Adequately treated basal cell or squamous cell carcinoma of skin or superficial bladder cancer that has not spread behind the connective tissue layer (i.e., pTis, pTa, and pT1) is allowed, as well as any other cancer for which treatment has been completed \leq 5 years ago and from which the patient has been disease-free. ✘ Gastrointestinal disorder or procedure that expects to interfere significantly with absorption of study treatment. ✘ Active viral hepatitis, active HIV, or chronic liver disease. ✘ Treatment with any investigational drug within 28 days before randomisation. ✘ Any condition that, in the opinion of the investigator, would impair the patient's ability to comply with the study procedures. ✘ Unable to swallow study medications and comply with study requirements. 		
	Characteristics		Intervention n = 955	Control n = 554
		Median age (range), years	74 (48-95)	74 (50-92)
	Geographic region, n (%)			
	North America	108 (11)	76 (14)	
	Asia-Pacific	119 (12)	67 (12)	
	Rest of the World	728 (76)	411 (74)	
	Median time from initial diagnosis (range), months	86.2 (2.6-337.5)	84.2 (0.5-344.7)	

Title: Darolutamide in nonmetastatic, castration-resistant prostate cancer [4, 24, 25]			
Study identifier	NCT02200614, EudraCT Number: 2013-003820-36		
Analysis population (continuation)	Presence of lymph nodes on central imaging review, n (%)		
	Yes	163 (17)	158 (29)
	No	792 (83)	396 (71)
	Median serum PSA level (range), ng/ml	9.0 (0.3-858.3)	9.7 (1.5-885.2)
	PSA doubling time Median (range), months	4.4 (0.7-11.0)	4.7 (0.7-13.2)
	≤6 months, n (%)	667 (70)	371 (67)
	≥6 months, n (%)	288 (30)	183 (33)
	Median serum testosterone level (range), nmol/litre	0.6 (0.2-25.9)	0.6 (0.2-7.3)
ECOG performance status, n (%)	0	650 (68)	391 (71)
	1	305 (32)	163 (29)
Use of bone-sparing agent, n (%)	Yes	31 (3)	32 (6)
	No	924 (97)	522 (94)
Previous hormonal therapy agents received, n (%)	One	177 (19)	103 (19)
	Two or more	727 (76)	420 (76)
	Not applicable	51 (5)	31 (6)
Applicability of evidence			
Population	Patients of African American descent were underrepresented in the ARAMIS trial (52/1509 patients). Since the incidence of prostate cancer is higher in African Americans than in other ethnic groups, the applicability of results is limited.		
Intervention	Darolutamide is not approved; hence there are no approved licenses or other treatment recommendations available.		
Comparators	In the ARAMIS trial, a placebo was selected as a comparator. A direct comparison to the androgen-receptor inhibitors apalutamide and enzalutamide would be of interest.		
Outcomes	There is evidence that MFS was significantly longer with darolutamide compared to placebo in men with nonmetastatic CRPC. However, the reported data are primary and interim analysis data; since the ARAMIS trial is ongoing, final analysis data are lacking.		
Setting	The ARAMIS trial was conducted in 36 countries worldwide at 409 centres. No issue of setting applicability was identified.		

Abbreviations: ADT = androgen-deprivation therapy, AE = adverse event, ALT = alanine transaminase, AR = androgen receptor, AST = Aspartate transaminase, AUC = area under the curve, BPI-SF = Brief Pain Inventory Short-Form, CI = confidence interval, CRPC = castration-resistant prostate cancer, ECOG = Eastern Cooperative Oncology Group, GnRH = gonadotropin releasing hormone, HIV = human immunodeficiency virus, HR = hazard ratio, ITT = intention-to-treat, MFS = metastasis-free survival, NYHA = New York Heart Association PCWG2 = Prostate Cancer Clinical Trials Working Group 2, PFS = progression-free survival, PSA = prostate-specific antigen, PSADT = PSA doubling time, QoL = Quality of life, SEE = symptomatic skeletal event, ULN = upper limit normal

Table 6: Risk of bias assessment on study level is based on EUnetHTA (Internal validity of randomised controlled trials) [4, 24, 27]

Criteria for judging risk of bias		Risk of bias
Adequate generation of randomisation sequence: Randomisation will be performed centrally blocking by centre according to the design of the study using a 2-step procedure. Firstly, a separate master randomisation schedule and study treatment package list will be created using randomly permuted blocks. Secondly, randomly permuted blocks from the master randomisation schedule are assigned to the study centres.		yes
Adequate allocation concealment: An IRT (also called IVRS) system assigns patients to receive either darolutamide or matching placebo using allocation ratio 2:1, respectively.		yes
Blinding:	Patient	Yes
	Treating physician	yes
Selective outcome reporting unlikely: Since the ARAMIS trial is ongoing, only data from the primary analysis and the interim analysis are available; final analysis data are lacking. No median OS data was reported. Reasons for discontinuations have been reported.		Unclear
No other aspects which increase the risk of bias: The trial was funded by Bayer HealthCare and Orion Pharma. The data were collected by the investigators, analysed by statisticians who were employed by the sponsors, and interpreted by the authors, including employees of the sponsors. Bayer HealthCare provided funding for medical writing and editing assistance.		No
Risk of bias – study level		low

Abbreviations: IRT = interactive response technology, IVRS = interactive voice response system