AUSTRALIAN PRODUCT INFORMATION
XTANDI® (ENZALUTAMIDE) SOFT CAPSULES

1 NAME OF THE MEDICINE

Enzalutamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

XTANDI is provided as liquid-filled soft gelatin capsules for oral administration. Each soft capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl macrogolglycerides.

Excipient(s) with known effect
Each soft capsule contains 57.8 mg of sorbitol.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Capsule, soft

Supplied as white to off-white oblong soft gelatin capsules imprinted with “ENZ” in black ink on one side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

XTANDI is indicated for:

- the treatment of patients with non-metastatic hormone-sensitive prostate cancer (nmHSPC) with biochemical recurrence at high-risk for metastasis (high-risk BCR).
- the treatment of patients with metastatic hormone-sensitive prostate cancer.
- the treatment of patients with non-metastatic castration-resistant prostate cancer (see PROSPER, section 5.1 Clinical trials).
- the treatment of patients with metastatic castration resistant prostate cancer following failure of androgen deprivation therapy in whom chemotherapy is not yet indicated.
- the treatment of patients with metastatic castration-resistant prostate cancer who have previously received docetaxel.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended dose of XTANDI is 160 mg (four 40 mg capsules) as a single oral daily dose. XTANDI can be taken with or without food. XTANDI should be taken at the same time each day.

In patients with castration-resistant prostate cancer or metastatic hormone-sensitive prostate cancer, medical castration with a luteinising hormone-releasing hormone (LHRH) analogue should be continued during treatment of patients not surgically castrated.

Patients with nmHSPC with high-risk BCR may be treated with XTANDI with or without androgen deprivation therapy. For patients who receive XTANDI with or without androgen deprivation therapy, treatment can be suspended if PSA is undetectable (< 0.2 ng/mL) after 36 weeks of therapy. Treatment should be reinitiated when PSA has increased to ≥ 2.0 ng/mL for patients who had prior radical prostatectomy or ≥ 5.0 ng/mL for patients who had prior primary radiation therapy (Refer to section 5.1 - PHARMACODYNAMIC PROPERTIES).

If a patient misses taking XTANDI at the usual time, the prescribed dose should be taken as close as possible to the usual time. If a patient misses a dose for a whole day, treatment should be resumed the following day with the daily dose.

If a patient experiences a ≥ Grade 3 toxicity or an intolerable adverse reaction, withhold dosing for one week or until symptoms improve to ≤ Grade 2, then resume at the same or a reduced dose (120 mg or 80 mg) if warranted.

Method of administration

Swallow capsules whole with a sufficient amount of water. Do not chew, dissolve, or open the capsules.

XTANDI should not be handled by persons other than the patient or their caregivers. Based on its mechanism of action and embryo-fetal toxicity observed in mice, XTANDI may harm a developing foetus. Women who are or may become pregnant should not handle damaged or opened enzalutamide capsules without protection, e.g., gloves (Refer to Section 4.6 – FERTILITY, PREGNANCY AND LACTATION).

Keep out of the reach of children.

Concomitant use with strong CYP2C8 inhibitors:

The concomitant use of strong CYP2C8 inhibitors should be avoided if possible. If patients must be co-administered a strong CYP2C8 inhibitor, reduce the dose of XTANDI to 80 mg once daily. If co-administration of the strong CYP2C8 inhibitor is discontinued, the XTANDI dose should be returned to the dose used prior to initiation of the strong CYP2C8 inhibitor (Refer to Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Patients with Hepatic Impairment:

No dose adjustment is required for patients with mild, moderate or severe hepatic impairment (Child-Pugh Class A, B or C, respectively).

Patients with Renal Impairment:

No dose adjustment is necessary for patients with mild or moderate renal impairment (Refer to Section 5.2 – PHARMACOKINETIC PROPERTIES – Pharmacokinetic Characteristics in Special

Populations). Caution is advised in patients with severe renal impairment or end-stage renal disease (Refer to Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Use in renal impairment).

4.3 CONTRAINDICATIONS

XTANDI is contraindicated in patients with known hypersensitivity to enzalutamide or to any of the excipients in the formulation (Refer to Section 6.1 – List of excipients).

XTANDI is contraindicated in women who are, or may become, pregnant (Refer to Section 4.2 – Dose and method of administration and Section 4.6 – FERTILITY, PREGNANCY AND LACTATION – Use in pregnancy).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

XTANDI capsules should only be prescribed by a medical practitioner who is experienced with the treatment of prostate cancer and the use of antineoplastic endocrine therapies.

The following are clinically significant: seizures (see Risk of Seizure below and Section 4.8 - Adverse effects (Undesirable effects)), **Posterior Reversible Encephalopathy Syndrome (PRES)** (see Posterior Reversible Encephalopathy Syndrome below and Section 4.8 – Adverse effects (Undesirable effects)) and **drug interactions** (Refer to Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

Risk of Seizure

Use of enzalutamide has been associated with seizure. Caution should be used in administering XTANDI to patients with a history of seizures or other predisposing factors including, but not limited to, underlying brain injury, stroke, primary brain tumours or brain metastases, or alcoholism. In addition, the risk of seizure may be increased in patients receiving concomitant medicines that lower the seizure threshold. Permanently discontinue XTANDI in patients who develop a seizure during treatment.

Because of the risk of seizure associated with XTANDI use, patients should be advised of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been rare reports of PRES in patients receiving XTANDI. PRES is a rare, reversible, neurological disorder which can present with rapidly evolving symptoms including seizure, headache, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of XTANDI in patients who develop PRES is recommended.

Falls and Fall-Related Injuries

In the combined data of five randomised clinical trials, falls or injuries related to falls occurred in 12.0% of patients treated with XTANDI compared to 5.5% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fall-related injuries were more severe in patients treated with XTANDI and included non-pathologic fractures, joint injuries, and haematomas. Androgen deprivation therapy has been known to cause bone loss. For patients who fall or have a concomitant recognised risk of falling, it is recommended that the physicians consider additional supportive therapy when appropriate.

Hypersensitivity Reactions

Hypersensitivity reactions manifested by symptoms including, but not limited to, face oedema, tongue oedema, lip oedema, pharyngeal oedema, and rash have been observed with enzalutamide (see Section 4.8 – Adverse effects (Undesirable effects)). Advise patients who experience any symptoms of hypersensitivity to discontinue enzalutamide and promptly seek medical care.

Androgen Deprivation Therapy May Prolong the QT Interval

In patients with a history of or risk factors for QT prolongation and in patients receiving concomitant medicinal products that might prolong the QT interval, physicians should assess the benefit risk ratio including the potential for *Torsade de pointes* prior to initiating XTANDI.

Recent Cardiovascular Disease

The phase 3 studies excluded patients with recent myocardial infarction (in the past 6 months) or unstable angina (in the past 3 months), New York Heart Association (NYHA) Class III or IV heart failure except if Left Ventricular Ejection Fraction (LVEF) ≥ 45%, bradycardia or uncontrolled hypertension. This should be taken into account if XTANDI is prescribed in these patients.

Hypertension

In the combined data from five randomised placebo-controlled clinical trials, hypertension was reported in 14.2% of patients receiving XTANDI and 7.4% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

Risk of Second Malignancy

Across the clinical trial program, the crude incidence of treatment emergent adverse events (TEAEs) corresponding to second primary malignancies (SPM) in the enzalutamide group and placebo/active surveillance group was 3.5% and 2.0%, and the median duration of treatment for patients with SPM was 30.6 months and 14.5 months, respectively. The incidence rate per 100 patient-years of any event of SPM for patients treated with enzalutamide was similar to those in the placebo/active surveillance group (2.0 vs 1.9) in the clinical trial setting.

Use with Chemotherapy

The safety and efficacy of concomitant use of XTANDI with cytotoxic chemotherapy has not been established.

Contraception in Males and Females

As it is not known whether XTANDI or its metabolites are present in semen, and there were severe teratogenic effects observed in the animal studies, a condom is required during and for 3 months after treatment with XTANDI if the patient is engaged in sexual activity with a pregnant woman. If the patient engages in sexual intercourse with a woman of childbearing potential, a condom and another form of birth control must be used during and for 3 months after treatment. Studies in animals have shown reproductive toxicity (Refer to Section 4.6 – FERTILITY, PREGNANCY AND LACTATION).

Dysphagia related to product size

There have been reports of patients experiencing difficulty swallowing XTANDI, including reports of choking, due to product size. The swallowing difficulties were mostly reported with the capsule formulation. Advise patients to swallow the capsules whole with a sufficient amount of water.

Use in renal impairment

Caution is required in patients with severe renal impairment as XTANDI has not been studied in this patient population.

Use in the elderly

No overall differences in safety or effectiveness were observed between elderly patients and younger patients. No dose adjustment is required for the elderly.

Paediatric use

The safety and efficacy of XTANDI have not been established in children, and therefore it is not recommended for use in those < 18 years of age.

Effects on laboratory tests

Refer to Section 4.8 – ADVERSE EFFECTS - Laboratory abnormalities.

XTANDI as monotherapy in patients with nmHSPC with high-risk BCR

Results of the EMBARK study suggest that XTANDI as monotherapy and in combination with androgen deprivation therapy are not equivalent treatment options in patients with nmHSPC with high-risk BCR (see sections 4.8 and 5.1). XTANDI in combination with androgen deprivation therapy is considered the preferred treatment option except for cases in which the addition of androgen deprivation therapy may result in unacceptable toxicity or risk.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effects of other Medicines on XTANDI

CYP2C8 inhibitors

CYP2C8 plays an important role in the elimination of enzalutamide and in the formation of its active metabolite. Following oral administration of the strong CYP2C8 inhibitor gemfibrozil (600 mg twice daily) to healthy male subjects, the AUC of the sum of enzalutamide plus the active metabolite increased by 2.17-fold while C_{max} decreased by 18%. Strong inhibitors (e.g. gemfibrozil) of CYP2C8

are to be avoided or used with caution during enzalutamide treatment. If patients must be co-administered a strong CYP2C8 inhibitor, the dose of enzalutamide should be reduced to 80 mg once daily (Refer to Section 4.2 - DOSE AND METHOD OF ADMINISTRATION).

CYP3A4 inhibitors

CYP3A4 plays a minor role in the metabolism of enzalutamide. Following oral administration of the strong CYP3A4 inhibitor itraconazole (200 mg once daily) to healthy male subjects, the AUC of enzalutamide increased by 41% while C_{max} was unchanged. For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC increased by 27% while C_{max} was again unchanged. No dose adjustment is necessary when enzalutamide is co-administered with inhibitors of CYP3A4.

CYP2C8 and CYP3A4 inducers

In a drug-drug interaction trial in healthy volunteers, a single 160 mg oral dose of enzalutamide was administered alone or after multiple oral doses of rifampicin (moderate CYP2C8 and strong CYP3A4 inducer). Rifampicin decreased the AUC of enzalutamide plus N-desmethyl enzalutamide by 37% with no effect on C_{max}. No dose adjustment is necessary when enzalutamide is co-administered with inducers of CYP2C8 or CYP3A4.

Effects of XTANDI on other Medicines

Enzyme induction

Enzalutamide is a potent enzyme inducer and increases the synthesis of many enzymes and transporters; therefore, interaction with many common medicinal products that are substrates of enzymes or transporters is expected. The reduction in plasma concentrations can be substantial, and lead to lost or reduced clinical effect. There is also a risk of increased formation of active metabolites. Enzymes that may be induced include CYP3A in the liver and gut, CYP2B6, CYP2C9, CYP2C19 and uridine 5' diphospho glucuronosyltransferase (UGTs - glucuronide conjugating enzymes). Some transporters may also be induced, e.g. multidrug resistance-associated protein 2 (MRP2) and the organic anion transporting polypeptide 1B1 (OATP1B1).

In vivo studies have shown that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Co-administration of enzalutamide (160 mg once daily) with single oral doses of sensitive CYP substrates in prostate cancer patients resulted in an 86% decrease in the AUC of midazolam (CYP3A4 substrate), a 56% decrease in the AUC of S warfarin (CYP2C9 substrate), and a 70% decrease in the AUC of omeprazole (CYP2C19 substrate). UGT1A1 may have been induced as well. Enzalutamide did not have a clinically meaningful effect on plasma exposure to intravenously administered docetaxel (CYP3A4 substrate).

Interactions with certain medicinal products that are eliminated through metabolism or active transport are expected. If their therapeutic effect is of large importance to the patient, and dose adjustments are not easily performed based on monitoring of efficacy or plasma concentrations, these medicinal products are to be avoided or used with caution.

The risk for liver injury after paracetamol administration is suspected to be higher in patients concomitantly treated with enzyme inducers.

Groups of medicinal products that can be affected include, but are not limited to:

- Analgesics (e.g. fentanyl, tramadol)
- Antibiotics (e.g. clarithromycin, doxycycline)
- Anticancer agents (e.g. cabazitaxel)
- Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Antithrombotics (e.g. warfarin, clopidogrel)
- Betablockers (e.g. bisoprolol, propranolol)
- Calcium channel blockers (e.g. diltiazem, felodipine, nicardipine, nifedipine, verapamil)
- Cardiac glycosides (e.g. digoxin)
- Corticosteroids (e.g. dexamethasone, prednisolone)
- HIV antivirals (e.g. indinavir, ritonavir)
- Hypnotics (e.g. diazepam, midazolam, zolpidem)
- Immunosuppressants (e.g. cyclosporin, tacrolimus)
- Proton pump inhibitors (e.g. omeprazole)
- Statins metabolised by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

The full induction potential of enzalutamide may not occur until approximately 1 month after the start of treatment, when steady-state plasma concentrations of enzalutamide are reached, although some induction effects may be apparent earlier. Patients taking drugs that are substrates of CYP2B6, CYP3A4, CYP2C9, CYP2C19 or UGT1A1 should be evaluated for possible loss of pharmacological effects (or increase in effects in cases where active metabolites are formed) during the first month of XTANDI treatment and dose adjustment should be considered as appropriate. In consideration of the long half-life of enzalutamide (5.8 days, refer to Section 5.2 – PHARMACOKINETIC PROPERTIES), effects on enzymes may persist for one month or longer after stopping XTANDI. A gradual dose reduction of the concomitant medicinal product may be necessary when stopping XTANDI treatment.

Warfarin and coumarin-like anticoagulants

Co-administration with warfarin and coumarin-like anticoagulants should be avoided. If XTANDI is co-administered with an anticoagulant metabolised by CYP2C9 (such as warfarin), additional INR monitoring should be conducted.

CYP1A2, CYP2C8 and CYP2D6 substrates

Enzalutamide (160 mg once daily) did not cause a clinically relevant change in the AUC or C_{max} of caffeine (CYP1A2 substrate), pioglitazone (CYP2C8 substrate) or dextromethorphan (CYP2D6 substrate). The AUC of pioglitazone increased by 20% while C_{max} decreased by 18%. The AUC and

C_{max} of caffeine decreased by 11% and 4% respectively. No dose adjustment is indicated when a CYP1A2, CYP2C8 or CYP2D6 substrate is co-administered with XTANDI.

P-gp substrates

In vitro data indicate that enzalutamide is not a substrate for, but may be an inhibitor of the efflux transporter P-gp. A mild inhibitory effect of enzalutamide, at steady-state, on P-gp was observed in a study in patients with prostate cancer that received a single oral dose of the probe P-gp substrate digoxin before and concomitantly with enzalutamide (concomitant administration followed at least 55 days of once daily dosing of 160 mg enzalutamide). The plasma levels of digoxin were measured using a validated liquid chromatography-tandem mass spectrometry assay.
The AUC and C_{max} of digoxin increased by 33% and 17%, respectively. Medicinal products with a narrow therapeutic range that are substrates for P-gp (e.g. colchicine, dabigatran etexilate, digoxin) should be used with caution when administered concomitantly with XTANDI and may require dose adjustment to maintain optimal plasma concentrations.

Laboratory Test Interference

Enzalutamide has been shown to interfere with the Chemiluminescent Microparticle Immunoassay (CMIA), resulting in falsely elevated digoxin plasma level results. Therefore, results from the CMIA method should be interpreted cautiously in patients receiving XTANDI and should be confirmed by other assay methods. In patients taking XTANDI and digoxin, monitoring of digoxin levels should be done with tests that do not use the CMIA method.

BCRP substrates

At steady-state, enzalutamide did not cause a clinically meaningful change in exposure to the probe breast cancer resistance protein (BCRP) substrate rosuvastatin in patients with prostate cancer that received a single oral dose of rosuvastatin before and concomitantly with enzalutamide (concomitant administration followed at least 55 days of once daily dosing of 160 mg enzalutamide). The AUC of rosuvastatin decreased by 14% while C_{max} increased by 6%. No dose adjustment is necessary when a BCRP substrate is co-administered with XTANDI.

MRP2, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 substrates

Based on *in vitro* data, inhibition of MRP2 (in the intestine), as well as organic anion transporter 3 (OAT3), OATP1B1, and OCT1 (systemically) cannot be excluded. Theoretically, induction of OAT3, OATP1B1, OCT1 and MRP2 is also possible, and the net effect is presently unknown. The effects of enzalutamide on these transporters have not been evaluated *in vivo. In vitro* data indicate that enzalutamide and its major metabolites do not inhibit the following transporters at clinically relevant concentrations: OAT1, OATP1B3, or OCT2.

Effect of Food on XTANDI Exposure

Food has no clinically significant effect on the extent of exposure to XTANDI. In clinical trials, XTANDI was administered without regard to food.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Based on its pharmacology and findings in animal studies, male fertility may be impaired by treatment with enzalutamide. Findings in the male reproductive tract of mice, rats and/or dogs treated with enzalutamide included atrophy of the prostate gland, epididymis and seminal vesicles, testicular hypospermia and seminiferous tubule degeneration. These effects were observed at doses below the clinical exposure (based on AUC) and reversed or partially resolved after an 8-week recovery period (Refer to Section 4.4 – Special warnings and precautions for use, Contraception in Males and Females).

Use in pregnancy – Category X

XTANDI is not indicated for use in women. XTANDI has not been shown to be safe for use in women. XTANDI is contraindicated in women who are or may become pregnant (Refer to Section 4.3 - Contraindications). There are no human data on the use of XTANDI in pregnancy.

Teratogenicity (cleft palate, cervical rib and decreased anogenital distance) and embryofetal lethality were seen in mouse embryofetal development studies at greater than or equal to 10 mg/kg/day (below the AUC at the maximum recommended human dose). This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant.

Studies in pregnant rats have shown that enzalutamide and/or its metabolites are transferred to foetuses. After oral administration of radiolabelled ^{14}C-enzalutamide to rats on Day 14 of pregnancy at a dose of 30 mg/kg, the maximum radioactivity in the foetus was reached 4 hours after administration and was lower than that in the maternal plasma with tissue/plasma ratio of 0.27. Radioactivity in the foetus decreased to 0.08 times the maximum concentration at 72 hours after administration.

Use in lactation

XTANDI is not indicated for use in females. There is no information available on the presence of XTANDI human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. XTANDI and/or its metabolites are secreted in rat milk. After oral administration of radiolabelled ^{14}C-enzalutamide to lactating rats at a dose of 30 mg/kg, the maximum radioactivity in the milk was reached 4 hours after administration and was up to 3.54-fold higher than that in the maternal plasma. Study results have also shown that enzalutamide and/or its metabolites are transferred to infant rat tissues via milk and subsequently eliminated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No formal studies of the effects of XTANDI on the ability to drive or use machines have been conducted. Neurological and psychiatric events (such as seizure, amnesia, fatigue, memory impairment, cognitive disorder, and disturbance in attention) associated with XTANDI may affect some patients' ability to drive or operate machinery (Refer to Section 4.8 – ADVERSE EFFECTS). Patients with a history of seizures or other predisposing factors should be advised of the risk of driving or operating machines (Refer to Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE – Risk of seizure).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trial Experience:

Six randomised, controlled clinical studies enrolled patients with castration-resistant prostate cancer that had progressed on androgen deprivation therapy (LHRH therapy or bilateral orchiectomy). Four studies were placebo-controlled and two studies were bicalutamide-controlled. In the AFFIRM, PREVAIL, Asian PREVAIL, and PROSPER studies, patients received XTANDI 160 mg or placebo orally once daily. In the TERRAIN and STRIVE studies, patients received XTANDI 160 mg or bicalutamide 50 mg orally once daily. A randomised, placebo-controlled clinical study was also conducted in patients with metastatic hormone-sensitive prostate cancer (mHSPC) on androgen deprivation therapy (ARCHES). Patients in the ARCHES study received XTANDI 160 mg or placebo orally once daily. All patients continued androgen deprivation therapy.

A randomised, controlled clinical study was also conducted in patients with high-risk BCR who had received prior definitive therapy with radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent (EMBARK). Patients in the EMBARK study received either XTANDI 160 mg orally once daily in combination with androgen deprivation therapy (LHRH analogue), XTANDI 160 mg orally once daily as open-label monotherapy, or placebo orally once daily in combination with androgen deprivation therapy (LHRH analogue). At week 37, treatment was suspended for patients whose PSA values were undetectable (<0.2 ng/mL) at week 36. Treatment was reinitiated when PSA values increased to ≥2.0 ng/mL for patients with prior prostatectomy or ≥5.0 ng/mL for patients without prior prostatectomy. For patients whose PSA values were detectable (≥2.0 ng/mL) at week 36, treatment continued without suspension until permanent treatment discontinuation criteria were met.

The most common adverse reactions (≥ 10%) seen in XTANDI-treated patients in clinical studies, in decreasing order of frequency are fatigue, hot flush, nausea, decreased appetite, hypertension, diarrhoea, fall, fracture, and asthenia. Other important adverse reactions include ischaemic heart disease and seizure.

AFFIRM study: Metastatic Castration-Resistant Prostate Cancer Following Chemotherapy

AFFIRM enrolled 1199 patients with metastatic castration-resistant prostate cancer (CRPC) who had previously received docetaxel. The median duration of treatment was 8.3 months with XTANDI and 3.0 months with placebo. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids. Grade 3 and higher adverse reactions were reported among 47% of XTANDI-treated patients and 53% of placebo-treated patients. Discontinuations due to adverse events were reported for 16% of XTANDI-treated patients and 18% of placebo-treated patients. The most common adverse reaction leading to treatment discontinuation was seizure, which occurred in 0.9% of the XTANDI-treated patients compared to none (0%) of the placebo-treated patients. Table 1 shows adverse reactions reported in AFFIRM that occurred at a ≥ 2% absolute increase in frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in AFFIRM

	XTANDI (N = 800)		Placebo (N = 399)	
	Grade 1 – 4[1] (%)	Grade 3 – 4 (%)	Grade 1 – 4 (%)	Grade 3 – 4 (%)
General Disorders				
Asthenic Conditions[2]	50.6	9.0	44.4	9.3
Peripheral Oedema	15.4	1.0	13.3	0.8
Musculoskeletal and Connective Tissue Disorders				
Back Pain	26.4	5.3	24.3	4.0
Arthralgia	20.5	2.5	17.3	1.8
Musculoskeletal Pain	15.0	1.3	11.5	0.3
Muscular Weakness	9.8	1.5	6.8	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0.0
Gastrointestinal Disorders				
Diarrhoea	21.8	1.1	17.5	0.3
Vascular Disorders				
Hot Flush	20.3	0.0	10.3	0.0
Hypertension	6.4	2.1	2.8	1.3
Nervous System Disorders				
Headache	12.1	0.9	5.5	0.0
Dizziness[3]	9.5	0.5	7.5	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7.4	6.6	4.5	3.8
Paraesthesia	6.6	0.0	4.5	0.0
Mental Impairment Disorders[4]	4.3	0.3	1.8	0.0
Hypoesthesia	4.0	0.3	1.8	0.0
Infections and Infestations				
Upper Respiratory Tract Infection[5]	10.9	0.0	6.5	0.3
Lower Respiratory Tract and Lung Infection[6]	8.5	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	8.8	0.0	6.0	0.5
Anxiety	6.5	0.3	4.0	0.0
Renal and Urinary Disorders				
Haematuria	6.9	1.8	4.5	1.0
Pollakiuria	4.8	0.0	2.5	0.0
Injury, Poisoning and Procedural Complications				
Fall	4.6	0.3	1.3	0.0
Non-pathologic Fractures	4.0	1.4	0.8	0.3
Skin and Subcutaneous Tissue Disorders				
Pruritus	3.8	0.0	1.3	0.0
Dry Skin	3.5	0.0	1.3	0.0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.9

1. CTCAE v 4
2. Includes asthenia and fatigue
3. Includes dizziness and vertigo
4. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention
5. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis
6. Includes pneumonia, lower respiratory tract infection, bronchitis, and lung infection

PREVAIL study: Chemotherapy-naïve Metastatic Prostate Cancer that Progressed on Androgen Deprivation Therapy

PREVAIL enrolled 1717 patients with metastatic prostate cancer that progressed on an LHRH analogue or after bilateral orchiectomy and had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 16.6 months with XTANDI and 4.6 months with placebo. The most common adverse reaction leading to treatment discontinuation was fatigue, which occurred in 0.2% of the XTANDI-treated patients compared to 0.9% of placebo-treated patients.

Table 2 includes adverse reactions reported in Study 2 that occurred at a ≥ 2% absolute increase in frequency in the XTANDI arm compared to the placebo arm.

Table 2. Adverse Reactions in PREVAIL

	XTANDI (N = 872)		**Placebo (N = 845)**	
	Grade 1 – 4[1] (%)	**Grade 3 – 4 (%)**	**Grade 1 – 4 (%)**	**Grade 3 – 4 (%)**
General Disorders				
Asthenic Conditions[2]	46.9	3.4	33.0	2.8
Peripheral Oedema	11.5	0.2	8.2	0.4
Musculoskeletal and Connective Tissue Disorders				
Back Pain	28.6	2.5	22.4	3.0
Arthralgia	21.4	1.6	16.1	1.1
Gastrointestinal Disorders				
Constipation	23.2	0.7	17.3	0.4
Diarrhoea	16.8	0.3	14.3	0.4
Vascular Disorders				
Hot Flush	18.0	0.1	7.8	0.0
Hypertension	14.2	7.2	4.1	2.3
Nervous System Disorders				
Headache	11.0	0.2	7.0	0.4
Dizziness[3]	11.3	0.3	7.1	0.0
Dysgeusia	7.6	0.1	3.7	0.0
Mental Impairment Disorders[4]	5.7	0.0	1.3	0.1
Restless Legs Syndrome	2.1	0.1	0.4	0.0
Respiratory Disorders				
Dyspnea[5]	11.0	0.6	8.5	0.6
Infections and Infestations				
Upper Respiratory Tract Infection[6]	16.4	0.0	10.5	0.0
Lower Respiratory Tract and Lung Infection[7]	7.9	1.5	4.7	1.1
Psychiatric Disorders				
Insomnia	8.2	0.1	5.7	0.0
Renal and Urinary Disorders				
Haematuria	8.8	1.3	5.8	1.3
Injury, Poisoning and Procedural Complications				
Fall	12.7	1.6	5.3	0.7
Non-pathologic Fractures	8.8	2.1	3.0	1.1
Metabolism and Nutrition Disorders				
Decreased Appetite	18.9	0.3	16.4	0.7
Investigations				
Weight Decreased	12.4	0.8	8.5	0.2

	XTANDI (N = 872)		Placebo (N = 845)	
	Grade 1 – 4[1] (%)	Grade 3 – 4 (%)	Grade 1 – 4 (%)	Grade 3 – 4 (%)
Reproductive System and Breast Disorders				
Gynaecomastia	3.4	0.0	1.4	0.0

Data cut-off date: 16-Sep-2013

1. CTCAE v 4
2. Includes asthenia and fatigue
3. Includes dizziness and vertigo
4. Includes amnesia, memory impairment, cognitive disorder and disturbance in attention
5. Includes dyspnea, exertional dyspnea and dyspnea at rest
6. Includes nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis and laryngitis
7. Includes pneumonia, lower respiratory tract infection, bronchitis and lung infection

TERRAIN Study: XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

TERRAIN enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTANDI and 5.8 months with bicalutamide. Discontinuations with an adverse event as the primary reason were reported for 7.6% of XTANDI-treated patients and 6.3% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation were back pain and pathological fracture, which occurred in 3.8% of XTANDI-treated patients for each event and in 2.1% and 1.6% of bicalutamide-treated patients, respectively. Table 3 shows overall and common adverse reactions (≥ 10%) in XTANDI-treated patients.

Table 3. Adverse Reactions in TERRAIN

	XTANDI (N = 183)		Bicalutamide (N = 189)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Overall	94	39	94	38
General Disorders				
Asthenic Conditions[2]	32	1.6	23	1.1
Musculoskeletal And Connective Tissue Disorders				
Back Pain	19	2.7	18	1.6
Musculoskeletal Pain[3]	16	1.1	14	0.5
Vascular Disorders				
Hot Flush	15	0	11	0
Hypertension	14	7.1	7.4	4.2
Gastrointestinal Disorders				
Nausea	14	0	18	0
Constipation	13	1.1	13	0.5
Diarrhoea	12	0	9.0	1.1
Infections And Infestations				
Upper Respiratory Tract Infection[4]	12	0	6.3	0.5
Investigational				
Weight Loss	11	0.5	7.9	0.5

1. CTCAE v 4
2. Including asthenia and fatigue
3. Including musculoskeletal pain and pain in extremity
4. Including nasopharyngitis, upper respiratory tract infection, sinusitis, rhinitis, pharyngitis, and laryngitis

PROSPER Study: XTANDI versus Placebo in Non-metastatic CRPC Patients

PROSPER enrolled 1401 patients with non-metastatic CRPC, of whom 1395 received at least one dose of study drug. Patients were randomised 2:1 and received either XTANDI at a dose of 160 mg once daily (N = 930) or placebo (N = 465). The median duration of treatment at the time of analysis was 18.4 months (range: 0.0 to 42 months) with XTANDI and 11.1 months (range: 0.0 to 43 months) with placebo.

Overall, 32 patients (3.4%) receiving XTANDI died from adverse events. The reasons for death with ≥ 2 patients included coronary artery disorders (n = 7), sudden death (n = 2), cardiac arrhythmias (n = 2), general physical health deterioration (n = 2), stroke (n = 2), and secondary malignancy (n = 5; one each of acute myeloid leukemia, brain neoplasm, mesothelioma, small cell lung cancer, and malignant neoplasm of unknown primary site). Three patients (0.6%) receiving placebo died from adverse events of cardiac arrest (n = 1), left ventricular failure (n = 1), and pancreatic carcinoma (n = 1). Grade 3 or higher adverse reactions were reported among 31% of XTANDI-treated patients and 23% of placebo-treated patients. Discontinuations with an adverse event as the primary reason were reported for 9.4% of XTANDI-treated patients and 6.0% of placebo-treated patients. Of these, the most common adverse event leading to treatment discontinuation was fatigue, which occurred in 1.6% of the XTANDI-treated patients compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 4. Adverse Reactions in PROSPER

	XTANDI (N = 930)		**Placebo (N = 465)**	
	Grade 1-4[1] (%)	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Metabolism and Nutrition Disorders				
Decreased Appetite	9.6	0.2	3.9	0.2
Nervous System Disorders				
Dizziness[2]	12	0.5	5.2	0
Headache	9.1	0.2	4.5	0
Cognitive and Attention Disorders[3]	4.6	0.1	1.5	0
Vascular Disorders				
Hot Flush	13	0.1	7.7	0
Hypertension	12	4.6	5.2	2.2
Gastrointestinal Disorders				
Nausea	11	0.3	8.6	0
Constipation	9.1	0.2	6.9	0.4
General Disorders and Administration Site Conditions				
Asthenic Conditions[4]	40	4.0	20	0.9

	XTANDI (N = 930)		Placebo (N = 465)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Investigations				
Weight Decreased	5.9	0.2	1.5	0
Injury, Poisoning and Procedural Complications				
Fractures[5]	9.8	2.0	4.9	1.7
Fall	11	1.3	4.1	0.6
Psychiatric Disorders				
Anxiety	2.8	0.2	0.4	0

Data cut-off date: 28-Jun-2017

1. CTCAE v 4
2. Includes dizziness and vertigo
3. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention
4. Includes asthenia and fatigue
5. Includes all osseous fractures from all sites

ARCHES Study: XTANDI versus Placebo in Metastatic HSPC Patients

ARCHES randomised 1150 patients with mHSPC, of whom 1146 received at least one dose of study drug. Patients received either XTANDI at a dose of 160 mg once daily (N = 572) or placebo (N = 574). At the time of analysis, the median duration of treatment was 12.8 months (range: 0.2 to 26.6 months) with XTANDI and 11.6 months (range: 0.2 to 24.6 months) with placebo. Seventy-six percent (76%) of patients remained on treatment with XTANDI and 58% of patients remained on placebo at the time of analysis.

Grade 3 or higher adverse events were reported in 24% of patients treated with XTANDI and 26% of patients treated with placebo. The primary reason for study drug discontinuation in both treatment groups was disease progression. Disease progression was approximately 3-fold lower in patients in the XTANDI group (11.3%) compared to the placebo group (29.7%). Discontinuation due to adverse events as the primary reason were reported in 4.9% of XTANDI-treated patients and 3.6% of placebo-treated patients. The most common adverse events for the XTANDI group (0.9% each) that were the primary reason leading to study drug discontinuation were anemia (0.5% in the placebo group), decreased appetite (0.7% in the placebo group), diarrhoea (0.3% in the placebo group) and fatigue (0.7% in the placebo group).

Table 5 shows adverse reactions reported in ARCHES that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Table 5. Adverse Reactions in ARCHES

	XTANDI (N = 572)		Placebo (N = 574)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Metabolism and Nutrition Disorders				
Decreased Appetite	4.9	0.2	2.6	0

	XTANDI (N = 572)		Placebo (N = 574)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Nervous System Disorders				
Restless Legs Syndrome	2.4	0	0.3	0
Vascular Disorders				
Hot Flush	27.1	0.3	22.3	0
Hypertension	8.0	3.3	5.6	1.7
General Disorders and Administration Site Conditions				
Asthenic conditions[2]	24.1	1.7	19.5	1.6
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	6.3	0.2	4.0	0.2
Injury, Poisoning and Procedural Complications				
Fractures[3]	6.5	1.0	4.2	1.0

Data cut-off date: 14 Oct 2018

1. CTCAE v 4.03
2. Includes asthenia and fatigue
3. Defined by MedDRA v21.0 high level group term of "fractures"

ENZAMET Study: XTANDI versus Non-Steroidal Anti-Androgen in Metastatic HSPC Patients

ENZAMET randomised 1125 patients with mHSPC, of whom 1121 received at least one dose of study drug. Patients received either XTANDI at a dose of 160 mg once daily (N = 563) or NSAA (non-steroidal anti-androgen bicalutamide, nilutamide, or flutamide) (N = 558). Patients were allowed up to 6 cycles of concomitant docetaxel (at the start of study with up to 2 cycles prior to study). At the time of analysis, the median duration of treatment was 29.5 months (range: 0.1 to 58.4 months) with XTANDI and 22.1 months (range: 0.0 to 58.6 months) with NSAA. Sixty-four percent (64%) of patients remained on treatment with XTANDI and 36% of patients remained on treatment with NSAA at the time of analysis.

Grade 3 or 4 adverse events were reported in a higher percentage of patients who received docetaxel in each arm; in the XTANDI arm, 60% of patients treated with docetaxel vs 55% without docetaxel, and in the NSAA arm, 52% of patients treated with docetaxel vs 35% without docetaxel. Discontinuations due to serious adverse events were reported in 11% of XTANDI-treated patients and 9% of NSAA-treated patients. The most common serious adverse event leading to study drug discontinuation was seizure which occurred in 0.9% of the XTANDI-treated patients compared to none in the NSAA-treated patients.

Table 6 shows Grade 3 and Grade 4 adverse reactions reported in ENZAMET that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the NSAA arm.

Table 6. Grade 3 and Grade 4 Adverse Reactions in ENZAMET[1]

	XTANDI			NSAA		
	With Docetaxel N = 243 (%)	Without Docetaxel N = 320 (%)	Total N = 563 (%)	With Docetaxel N = 235 (%)	Without Docetaxel N = 323 (%)	Total N = 558 (%)
Vascular Disorders						
Hypertension	7.4	7.8	7.6	4.7	4.3	4.5
Blood and Lymphatic System Disorders						
Neutrophil count decreased	12.3	0.3	5.5	6.4	0.3	2.9
General Disorders and Administration Site Conditions						
Fatigue	5.8	5.3	5.5	0.9	0.6	0.7
Nervous System Disorders						
Syncope	4.1	3.4	3.7	1.7	0.6	1.1

Data cut-off date: 28 Feb 2019

1. CTCAE v 4.03

EMBARK: XTANDI versus Placebo in Non-metastatic HSPC Patients with High-Risk BCR

EMBARK enrolled 1068 patients with high-risk BCR. A total of 1061 patients received at least one dose of study drug. Patients received XTANDI at a dose of 160 mg once daily concurrently with a LHRH analogue (N = 353), XTANDI at a dose of 160 mg once daily as open label monotherapy (N = 354), or placebo concurrently with a LHRH analogue (N = 354).

Table 7 shows the total duration of treatment (inclusive of time receiving drug treatment plus any time during which drug treatment was suspended because of undetectable PSA levels), the duration of time receiving drug treatment, the duration of treatment suspension, and the number of patients who had treatment suspended at week 37, for the three treatment arms.

Table 7. Drug Treatment and Suspension in EMBARK

	XTANDI + LHRH Analogue (N = 353)	Placebo + LHRH Analogue (N = 354)	XTANDI Monotherapy (N = 354)
Total Duration of Treatment[1]			
Median, months	60.6	55.6	60.4
Range, months	0.1 - 90.4	0.7 - 94.1	0.4 – 95.0
Duration Receiving Drug Treatment			
Median, months	32.4	35.4	45.9
Range, months	0.1 – 83.4	0.7 – 85.7	0.4 – 88.9
Duration of Suspension from Drug Treatment			
Median, months	20.2	16.8	11.1
Range, months	5.7 – 87.9	3.4 – 83.0	2.3 – 84.9
Patients who had Drug Treatment Suspended at Week 37			
Number of Patients (%)	321 (90.9)	240 (67.8)	304 (85.9)

1. Inclusive of time receiving drug treatment plus any time during which drug treatment was suspended because of undetectable PSA levels.

Overall, deaths from adverse reactions during the total duration of treatment occurred in 6 patients (1.7%) receiving XTANDI plus a LHRH analogue, 8 patients (2.3%) receiving XTANDI as monotherapy, and 3 patients (0.8%) receiving placebo plus a LHRH analogue. The reason for death in ≥ 2 patients receiving XTANDI plus a LHRH analogue was infection (n = 2), and the reason for death in ≥ 2 patients receiving XTANDI as monotherapy was arterial thromboembolism (n=2). Patients receiving placebo plus a LHRH analogue died from sepsis (n = 1), acute myeloid leukemia (n = 1), and myocardial ischaemia (n = 1).

Grade 3 or higher adverse events were reported in 46.5% of patients treated with XTANDI plus a LHRH analogue, 50% of patients receiving XTANDI as monotherapy, and 42.7% of patients receiving placebo plus a LHRH analogue. Permanent treatment discontinuation due to adverse events as the primary reason was reported in 20.7% of patients treated with XTANDI plus a LHRH analogue, 17.8% of patients receiving XTANDI as monotherapy, and 10.2% of patients receiving placebo plus a LHRH analogue. The most common adverse events resulting in permanent discontinuation included fatigue (3.4% of patients treated with XTANDI plus a LHRH analogue, 2.3% of patients receiving XTANDI as monotherapy, and 1.1% of patients receiving placebo plus a LHRH analogue), hot flush (2% of patients treated with XTANDI plus a LHRH analogue, 0% of patients receiving XTANDI as monotherapy, and 1.1% of patients receiving placebo plus a LHRH analogue), nausea (1.1% of patients treated with XTANDI plus a LHRH analogue, 0.6% of patients receiving XTANDI as monotherapy, and 0.3% of patients receiving placebo plus a LHRH analogue), and asthenia (0% of patients treated with XTANDI plus a LHRH analogue, 1.4% of patients receiving XTANDI as monotherapy, and 0.3% of patients receiving placebo plus a LHRH analogue).

Dose reductions due to an adverse reaction occurred in 7% of patients who received XTANDI plus a LHRH analogue, 16% of patients who received XTANDI as monotherapy, and 4.5% of patients who received placebo plus a LHRH analogue. Fatigue was the most frequent adverse reaction requiring dose reduction in 3.1% of patients treated with XTANDI plus a LHRH analogue, 10% of patients receiving XTANDI as monotherapy, and 1.7% of patients receiving placebo plus a LHRH analogue.

Table 8 shows adverse reactions reported in EMBARK that occurred at a ≥ 2% higher frequency in either of the XTANDI arms than in the placebo arm.

Table 8. Adverse Reactions in EMBARK

	XTANDI + LHRH Analogue (N = 353)		**Placebo + LHRH Analogue (N = 354)**		**XTANDI Monotherapy (N = 354)**	
	Grade 1-4[1] (%)	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Metabolism and Nutrition Disorders						
Decreased Appetite	7.6	0.6	4.2	0	9.0	0.3
Nervous System Disorders						
Headache	11	0.8	9.0	0	12	0.3
Memory Impairment	7.4	0	3.4	0.6	5.9	0
Amnesia	4.8	0	2.3	0	4.5	0
Paresthesia	4.8	0	2.5	0	3.4	0
Restless Legs Syndrome	3.7	0	2.0	0	4.2	0

	XTANDI + LHRH Analogue (N = 353)		Placebo + LHRH Analogue (N = 354)		XTANDI Monotherapy (N = 354)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Syncope	4.8	4.2	2.3	1.7	2.5	2.0
Dysgeusia	2.3	0	0.3	0	3.7	0
Disturbance in Attention	2.3	0	0.6	0	3.1	0
Hyperesthesia	0.6	0	0.3	0	3.1	0
Cognitive Disorder	0.6	0	0.3	0	2.3	0
Vascular Disorders						
Hot Flush	69	0.6	57	0.8	22	0.3
Hypertension	23	6.8	20	5.1	19	5.4
Gastrointestinal Disorders						
Diarrhoea	14	0.6	8.8	0.3	13	0.3
Nausea	12	0.3	8.2	0.3	15	0.6
Constipation	13	0.3	8.8	0	9.6	0.3
Vomiting	4.5	0.3	2.5	0	3.1	0.3
Dyspepsia	2.0	0	2.5	0	5.6	0
Rectal Haemorrhage	2.5	0.3	0.8	0	2.8	0.3
Infections and Infestations						
COVID-19	7.6	0.6	10	1.1	12	0.6
Urinary Tract Infection	7.6	0.3	7.3	0.6	11	2.0
Nasopharyngitis	7.1	0	6.2	0	8.8	0
Bronchitis	5.4	0.6	3.4	0	2.8	0
Investigations						
Weight Decreased	6.8	0.3	3.4	0	11	0.3
Blood Creatinine Increased	4.2	0.6	2.0	0	2.5	0
General Disorders and Administration Site Conditions						
Fatigue	43	3.4	33	1.4	47	4.0
Asthenia	11	0.6	5.9	0.3	11	0.8
Pain	3.7	0.3	1.1	0	2.5	0
Non-cardiac Chest Pain	0.6	0	0.8	0	2.8	0.3
Musculoskeletal and Connective Tissue Disorders						
Arthralgia	28	2.0	21	0.3	23	0.6
Back Pain	17	0.8	15	0.3	18	0.8
Osteoarthritis	5.9	2.8	4.2	0.6	5.4	0.6
Arthritis	4.8	1.1	3.7	0.3	6.5	0.8
Osteoporosis	4.8	0	0.8	0	0.6	0
Psychiatric Disorders						
Anxiety	5.4	0.3	3.1	0.0	5.1	0
Renal and Urinary Disorders						
Urinary Incontinence	9.6	1.1	7.9	0.8	10	1.7
Nocturia	7.4	0	4.5	0	2.5	0
Micturition Urgency	4.0	0	1.7	0	2.5	0
Injury, Poisoning and Procedural Complications						
Fall	21	1.1	14	1.1	16	2.0
Limb Injury	3.4	0	0.6	0	1.1	0
Reproductive System and Breast Disorders						
Gynaecomastia	8.2	0	9.0	0	45	0.8
Nipple Pain	3.1	0	1.1	0	15	0

	XTANDI + LHRH Analogue (N = 353)		Placebo + LHRH Analogue (N = 354)		XTANDI Monotherapy (N = 354)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Breast Tenderness	1.4	0	1.1	0	14	0
Breast Pain	1.1	0	0.8	0	7.1	0
Breast Enlargement	0.6	0	0.8	0	3.4	0
Skin and Subcutaneous Tissue Disorders						
Dry Skin	6.2	0	2.8	0	4.8	0
Alopecia	5.4	0	1.1	0	3.7	0
Hyperhidrosis	4.0	0.3	1.4	0	1.7	0
Respiratory, Thoracic and Mediastinal Disorders						
Epistaxis	5.4	0	0.6	0	5.1	0
Dysphonia	0.6	0	0.3	0	2.8	0
Blood and Lymphatic System Disorders						
Anaemia	7.1	1.4	3.4	0.8	4.8	0.8
Cardiac Disorders						
Ischemic Heart Disease[2]	5.4	4.0	5.6	3.1	9.0	5.9

Data cut-off date: 31 Jan 2023

1. CTCAE v 4.03
2. Includes multiple terms

Summary of adverse reactions

Adverse reactions observed during clinical studies are listed below by frequency category in each system organ class. Frequency categories are defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); and not known (cannot be estimated from the available data).

Table 9. Adverse Reactions Summary

MedDRA System Organ Class[1]	Adverse Reaction (Preferred Term)	Frequency Category
Blood and lymphatic system disorders	Neutropenia	uncommon
	Leukopenia	uncommon
Cardiac disorders	Ischaemic Heart Disease[2]	common
Gastrointestinal disorders	Nausea	not known[10]
	Diarrhoea	not known[10]
	Vomiting	not known[10]
	Dysphagia[3]	not known[10]
General disorders and administration site conditions	Fatigue	very common
	Asthenia	very common
Immune system disorders	Face oedema[4] Tongue oedema[5] Lip oedema[6] Pharyngeal oedema	not known[10]

MedDRA System Organ Class[1]	Adverse Reaction (Preferred Term)	Frequency Category
Injury, poisoning and procedural complications	Fracture[7]	very common
	Fall	very common
Metabolism and nutrition disorders	Decreased appetite	not known[10]
Nervous system disorders	Headache	common
	Cognitive Disorders[8]	common
	Dysgeusia	common
	Restless Legs Syndrome	common
	Seizure[9]	uncommon
	Posterior Reversible Encephalopathy Syndrome	not known[10]
Psychiatric disorders	Anxiety	common
	Visual Hallucination	uncommon
Reproductive system and breast disorders	Gynaecomastia	common
Skin and subcutaneous tissue disorders	Pruritus	common
	Dry Skin	common
	Rash	not known[10]
Vascular disorders	Hot Flush	very common
	Hypertension	very common

1. MedDRA v. 21.1
2. As evaluated by narrow SMQs of 'Myocardial Infarction' and 'Other Ischaemic Heart Disease' including the following preferred terms observed in at least two patients in randomised placebo-controlled phase 3 studies: angina pectoris, coronary artery disease, myocardial infarctions, acute myocardial infarction, acute coronary syndrome, angina unstable, myocardial ischaemia, and arteriosclerosis coronary artery
3. Dysphagia has been reported due to XTANDI product size (see section 4.4)
4. Includes events of face oedema and swelling face
5. Includes events of swollen tongue and tongue oedema
6. Includes events of lip swelling and lip oedema
7. Includes all preferred terms with the word 'fracture' in bones
8. Includes amnesia, memory impairment, cognitive disorder, and disturbance in attention
9. As evaluated by narrow SMQs of 'Convulsions' including convulsion, grand mal convulsion, complex partial seizures, partial seizures, and status epilepticus. This includes rare cases of seizure with complications leading to death
10. Adverse reactions of an unknown frequency have been identified during post approval use of XTANDI. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure

Post Marketing Experience

The following adverse events, which are not listed above, have been reported in association with enzalutamide use during worldwide post-marketing experience:

Musculoskeletal and connective tissue disorders: myalgia, muscle spasms, muscular weakness, back pain.

Skin and connective tissue disorders: acute generalized exanthematous pustulosis, dermatitis bullous, dermatitis exfoliative generalized, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, exfoliative rash, Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and toxic skin eruption.

Description of Selected Adverse Reactions

Seizures
In controlled clinical studies, 31 patients (0.6%) experienced a seizure out of 5110 patients treated with a daily dose of 160 mg XTANDI, whereas four patients (0.1%) receiving placebo and one patient (0.3%) receiving bicalutamide experienced a seizure. In the patients who experienced seizure when treated with XTANDI, there was one case of seizure where the patient experienced complications resulting in death. In the controlled clinical studies, patients with prior seizures or other risk factors for seizures were excluded (Refer to Section 4.4 – SPECIAL WARNINGS AND PRECAUTIONS FOR USE - Risk of seizure).

Patients who are taking concomitant medicines (strong CYP2C8 inhibitors) that increase the blood levels of enzalutamide may be at increased risk of seizure (Refer to Section 4.2 - DOSE AND METHOD OF ADMINISTRATION; and Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

In the single-arm UPWARD study to assess incidence of seizure in patients with predisposing factors for seizure (whereof 1.7% had a history of seizures), and 8 of 366 (2.2%) patients treated with XTANDI experienced a seizure. The median duration of treatment was 9.3 months.

Laboratory abnormalities
Table 10 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled Phase 3 placebo-controlled studies.

Table 10. Laboratory Abnormalities

	XTANDI (N = 3526)		**Placebo (N = 2636)**	
	Grade 1-4 (%)	**Grade 3-4 (%)**	**Grade 1-4 (%)**	**Grade 3-4 (%)**
Hematology				
Haemoglobin decreased	49.7	1.8	46.8	1.5
Neutrophil count decreased	20.3	1.0	17.0	0.5
White blood cell decreased	18.0	0.5	11.3	0.2
Chemistry				
Hyponatremia	13.7	1.6	9.3	1.4
Hyperglycaemia	85.7	3.7	78.2	4.3
Hypermagnesemia	16.8	0.1	13.7	0.3
Hypercalcemia	7.8	0.1	5.0	0.1
Hypophosphatemia	9.6	1.4	7.0	0.8

Infections
In the AFFIRM trial, 1% of patients treated with XTANDI compared to 0.3% of patients on placebo died from infections or sepsis. In the PREVAIL trial, 1 patient in each treatment group (0.1%) had an infection resulting in death.

Hallucinations
In the AFFIRM trial, 1.6% of patients treated with XTANDI were reported to have Grade 1 or 2 hallucinations compared to 0.3% of patients on placebo. In the PREVAIL trial, 1 patient in each treatment group (0.1%) reported an event of Grade 1 hallucination. Of the patients with hallucinations, the majority were on opioid-containing medications at the time of the event. Hallucinations were visual, tactile, or undefined.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no antidote for XTANDI. In the event of an overdose, treatment with XTANDI should be stopped and general supportive measures initiated taking into consideration the half-life of 5.8 days. Patients may be at increased risk of seizures following an overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Enzalutamide is an androgen receptor signalling inhibitor that blocks the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding to androgen receptors, and consequently, inhibits nuclear translocation of these receptors and inhibits the binding of androgen receptor to DNA. *In vitro*, enzalutamide treatment decreased proliferation and induced prostate cancer cell death. Decreased tumour growth was seen in a mouse prostate cancer xenograft model. In preclinical studies enzalutamide lacked androgen receptor agonist activity against several prostate cancer cell lines. The active metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide in the inhibition of testosterone binding to the androgen receptor.

Pharmacodynamics

In the EMBARK study, mean baseline serum testosterone levels were comparable across the three treatment arms (XTANDI plus ADT: 329.3 ng/dL; placebo plus ADT: 329.7 ng/dL; XTANDI as open-label monotherapy: 316.7 ng/dL) (ADT defined as LHRH analogue). During therapy, the treatment arms receiving ADT showed a decrease in mean testosterone serum levels by week 37,

whereas the treatment arm that received XTANDI as open-label monotherapy showed an increase in mean serum testosterone levels (XTANDI plus ADT: 44.5 ng/dL; placebo plus ADT: 38.8 ng/dL; XTANDI as monotherapy: 564.5 ng/dL). Following treatment suspension, mean serum testosterone levels increased in the ADT arms (229.6 ng/dL for the XTANDI plus ADT arm, and 218.2 ng/dL for the placebo plus ADT arm, by week 85). In contrast, mean serum testosterone levels decreased following the suspension of XTANDI monotherapy (407.2 ng/dL by week 61). With continued follow up and an increasing number of patients undergoing treatment reinitiation, mean serum testosterone levels were consistently suppressed in the ADT arms, and consistently elevated in the XTANDI as monotherapy arm, when compared to the respective mean baseline levels. See Figure 1.

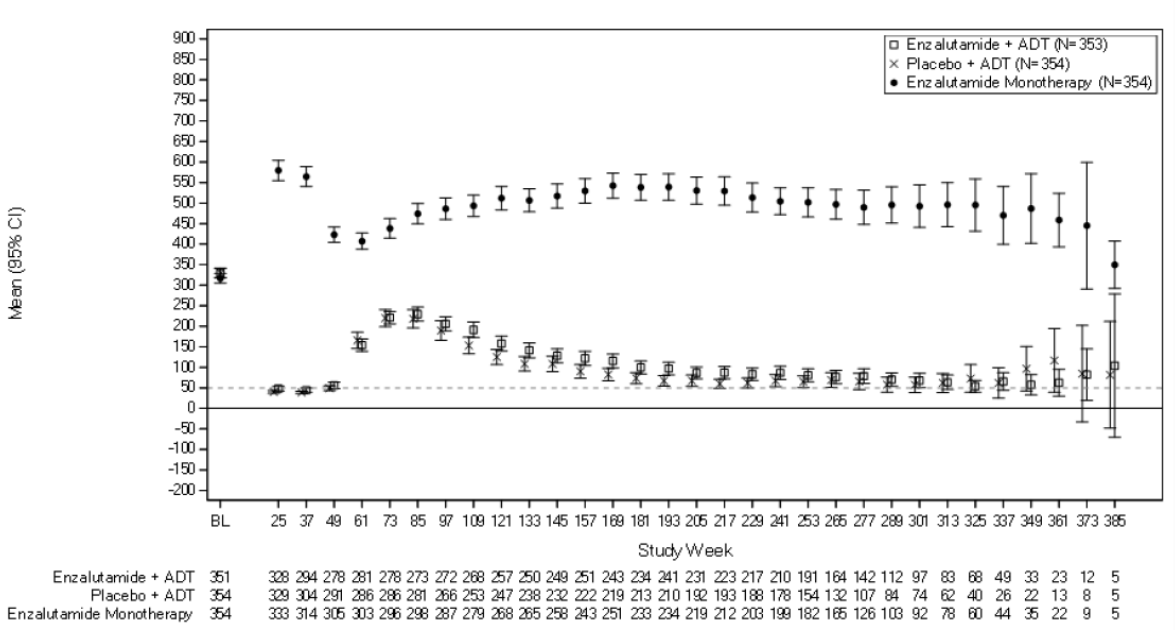


Figure 1. Mean Testosterone (ng/dL) Levels in Patients by Visit in EMBARK Study (Safety Population)

Clinical trials

Efficacy of enzalutamide was established in three randomised placebo-controlled multicentre phase 3 clinical studies [MDV3100-14 (PROSPER), CRPC2 (AFFIRM), MDV3100-03 (PREVAIL)] of patients with progressive prostate cancer who had disease progression on androgen deprivation therapy [luteinising hormone-releasing hormone (LHRH) analogue or after bilateral orchiectomy]. The PREVAIL study enrolled metastatic CRPC chemotherapy-naïve patients; whereas the AFFIRM study enrolled metastatic CRPC patients who had received prior docetaxel; and the PROSPER study enrolled patients with non-metastatic CRPC. Additionally, efficacy in patients with mHSPC was also established in one randomised, placebo-controlled multicentre phase 3 clinical study (ARCHES). Another randomised, placebo-controlled multicentre phase 3 clinical study [MDV3100-13 (EMBARK)] established efficacy in patients with nmHSPC with high-risk BCR. All patients continued on a LHRH analogue or had bilateral orchiectomy, unless otherwise indicated.

In the active treatment arm, XTANDI was administered orally at a dose of 160 mg daily. In the five clinical studies (EMBARK, ARCHES, PROSPER, AFFIRM and PREVAIL), patients received placebo in the control arm and patients were not required to take prednisone.

Changes in prostate specific antigen (PSA) serum concentration independently do not always predict clinical benefit. Therefore, in the five studies, it was recommended that patients be maintained on their study treatments until suspension or discontinuation criteria were met as specified below for each study.

EMBARK study (patients with non-metastatic HSPC with high-risk BCR)

The EMBARK study enrolled 1068 patients with nmHSPC with high-risk BCR who were randomised 1:1:1 to receive treatment with XTANDI orally at a dose of 160 mg once daily concurrently with ADT (N = 355), XTANDI orally at a dose of 160 mg once daily as open-label monotherapy (N = 355), or placebo orally once daily concurrently with ADT (N = 358) (ADT defined as LHRH analogue). All patients had prior definitive therapy with radical prostatectomy or radiotherapy (including brachytherapy) or both, with curative intent. Patients were not candidates for salvage radiotherapy at the time of enrolment. Patients were required to have confirmation of non-metastatic disease by BICR, high-risk BCR (defined by a PSA doubling time ≤ 9 months), and PSA values ≥1 ng/mL if they had prior radical prostatectomy (with or without radiotherapy) as the primary treatment for prostate cancer or PSA values at least 2 ng/mL above the nadir if they had prior radiotherapy only.

Patients were stratified by screening PSA (≤10 ng/mL vs. >10 ng/mL), PSA doubling time (≤3 months versus >3 months to ≤ 9 months), and prior hormonal therapy (prior hormonal therapy vs. no prior hormonal therapy). For patients whose PSA values were undetectable (<0.2 ng/mL) at week 36, treatment was suspended at week 37 and then reinitiated when PSA values increased to ≥2.0 ng/mL for patients with prior prostatectomy or ≥5.0 ng/mL for patients without prior prostatectomy. For patients whose PSA values were detectable (≥2.0 ng/mL) at week 36, treatment continued without suspension until permanent treatment discontinuation criteria were met.

The demographic and baseline characteristics were well balanced between the three treatment groups. The median age at randomisation was 69 years in both the XTANDI plus ADT and the XTANDI monotherapy treatment groups. The median age at randomisation was 70 years in the placebo plus ADT treatment group. Most patients in the total population were Caucasian (83.2%), 7.3% were Asian, and 4.4% were Black. The median PSA doubling time was 4.9 months. Seventy-four percent (74%) of patients had prior definitive therapy with radical prostatectomy, 75% of patients had prior therapy with radiotherapy (including brachytherapy), and 49% of patients had prior therapy with both. Thirty-two percent (32%) of patients had a Gleason score of ≥ 8. The ECOG PS score was 0 for 92.2% of patients and 1 for 7.6% of patients at study entry.

Metastasis-free survival (MFS) in patients randomised to receive XTANDI plus ADT compared to patients randomised to receive placebo plus ADT was the primary endpoint. Metastasis-free survival was defined as the time from randomisation to radiographic progression or death on study, whichever occurred first.

Key secondary endpoints were time to PSA progression, time to first use of antineoplastic therapy, and overall survival. Another key secondary endpoint was MFS in patients randomised to receive XTANDI as monotherapy compared to patients randomised to receive placebo plus ADT.

XTANDI plus ADT demonstrated a statistically significant 58% reduction in the risk of developing an MFS event as compared to placebo plus ADT [HR = 0.42 (95% CI: 0.30, 0.61) $p < 0.0001$]. The median time to an MFS event was not reached in either treatment arm.

Table 11. Summary of Efficacy in patients treated with either XTANDI plus ADT, placebo plus ADT, or XTANDI as monotherapy, in the EMBARK study (Intent-to-Treat Analysis)

	XTANDI plus ADT (N = 355)	Placebo plus ADT (N = 358)	XTANDI as Monotherapy (N = 355)
Metastasis-free Survival			
Number of events (%)[1]	45 (12.7)	92 (25.7)	63 (17.7)
Median, months (95% CI)[2]	NR (NR, NR)	NR (85.1, NR)	NR (NR, NR)
Hazard ratio relative to Placebo plus ADT (95% CI)[3]	0.42 (0.30, 0.61)	--	0.63 (0.46, 0.87)
P-value for comparison to Placebo plus ADT[4]	p < 0.0001	--	p = 0.0049

NR = Not reached

1. Based on the earliest contributing event (radiographic progression or death)
2. Based on Kaplan-Meier estimates
3. Hazard Ratio is based on a Cox regression model stratified by screening PSA, PSA doubling time, and prior hormonal therapy
4. Two-sided P-value is based on a stratified log-rank test by screening PSA, PSA doubling time, and prior hormonal therapy

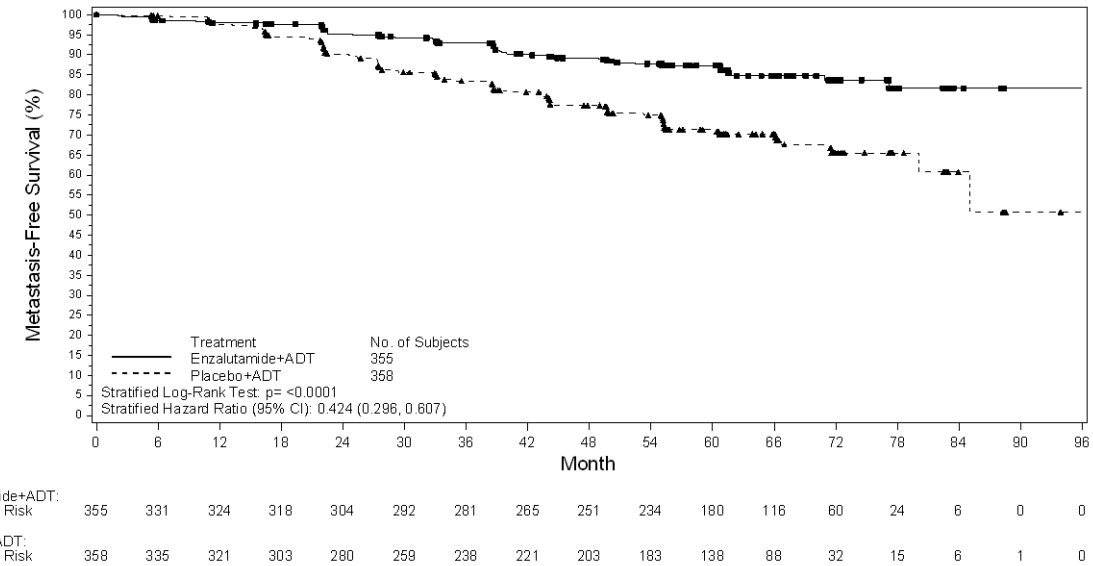


Figure 2. Kaplan-Meier Curves of MFS in the XTANDI plus ADT vs. Placebo plus ADT treatment arms of the EMBARK study (Intent-to-Treat Analysis)

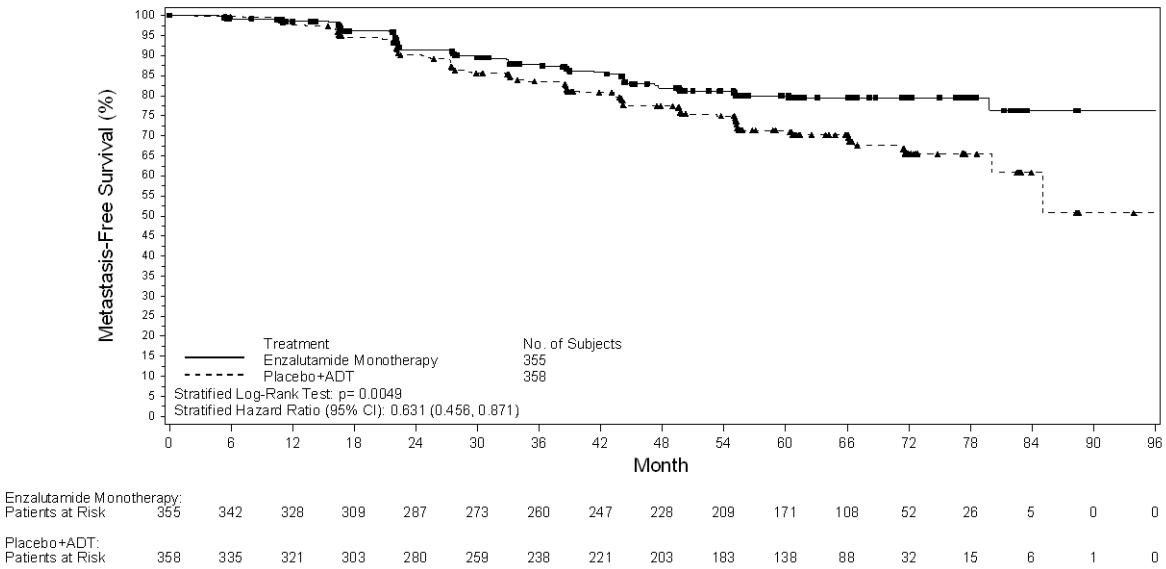


Figure 3. Kaplan-Meier Curves of MFS in the XTANDI as Monotherapy vs. Placebo plus ADT treatment arms of the EMBARK study (Intent-to-Treat Analysis)

XTANDI as monotherapy also demonstrated a statistically significant 37% reduction in the risk of developing an MFS event as compared to placebo plus ADT [HR = 0.63 (95% CI: 0.46, 0.87) p = 0.0049]. The median time to an MFS event was not reached in either treatment arm).

XTANDI plus ADT demonstrated a statistically significant 93% reduction in the risk of PSA progression compared to placebo plus ADT [HR = 0.07 (95% CI: 0.03, 0.14) p < 0.0001]. XTANDI as monotherapy also demonstrated a statistically significant 67% reduction in the risk of PSA progression compared to placebo plus ADT [HR = 0.33 (95% CI: 0.23, 0.49) p < 0.0001]. The median time to PSA progression was not reached in any of the treatment arms.

XTANDI plus ADT demonstrated a statistically significant 64% reduction in risk of new antineoplastic therapy compared to placebo plus ADT [HR = 0.36 (95% CI: 0.26, 0.49), p < 0.0001]. XTANDI as monotherapy also demonstrated a statistically significant 46% reduction in risk of new antineoplastic therapy compared to placebo plus ADT [HR = 0.54 (95% CI: 0.41, 0.71), p < 0.0001]. The median time to first use of new antineoplastic therapy was not reached in the XTANDI plus ADT arm or in the XTANDI as monotherapy arm, and was 76.2 months (95% CI: 71.3, NR) in the placebo plus ADT arm.

A pre-specified interim analysis for overall survival was planned at the time of the MFS analysis. At the time of the interim analysis, overall survival data were not mature and did not show a statistically significant difference in patients treated with XTANDI plus ADT compared to placebo plus ADT [HR = 0.59 (95% CI: 0.38, 0.91) p = 0.0153] or in patients treated with XTANDI as monotherapy compared to placebo plus ADT [HR = 0.78 (95% CI: 0.52, 1.17) p = 0.2304]. The median overall survival was not reached in any of the treatment arms.

ARCHES study (patients with metastatic HSPC)

The ARCHES study enrolled 1150 patients with mHSPC randomised 1:1 to receive treatment orally once daily with XTANDI 160 mg (N = 574) or placebo (N = 576). All patients in the trial received a LHRH analog or had a prior bilateral orchiectomy. Patients were stratified by volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (no prior docetaxel, 1-5 cycles, or 6 prior

cycles). Treatment with concurrent docetaxel was not allowed. Patients were required to have confirmation of metastatic prostate cancer by positive bone scan or metastatic lesions on CT or MRI scan. Patients continued treatment until radiographic disease progression, initiation of new treatment, unacceptable toxicity, or withdrawal.

The following patient demographics and baseline characteristics were balanced between the two treatment arms. The median age at randomisation was 70 years in both treatment groups. Most patients in the total population were Caucasian (80.5%), 13.5% were Asian and 1.4% were Black. Sixty-seven percent (67%) of patients treated with XTANDI and 65% of patients who received placebo had a Gleason score of ≥ 8. Thirty-seven percent (37%) of patients had a low volume of disease and 63% of patients had a high volume of disease. High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Eighty-two percent (82%) of patients had no prior docetaxel treatment; 2% of patients had 1 to 5 cycles of docetaxel and 16% of patients had 6 prior cycles of docetaxel treatment. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) score was 0 for 78% of patients and 1 for 22% of patients at study entry.

Radiographic progression-free survival (rPFS), based on independent central review, was the primary endpoint defined as the time from randomisation to the first objective evidence of radiographic disease progression or death (due to any cause from the time of randomisation through 24 weeks after study drug discontinuation), whichever occurred first. XTANDI demonstrated a statistically significant 61% reduction in the risk of an rPFS event compared to placebo. Consistent rPFS results were also observed in patients with high or low volume of disease, and patients with and without prior docetaxel therapy. At the pre-specified final analysis for overall survival (OS), conducted when 356 deaths were observed, a statistically significant 34% reduction in the risk of death was demonstrated in the group randomised to receive enzalutamide compared with the group randomised to receive placebo [HR = 0.66, (95% CI: 0.53; 0.81), p < 0.0001]. The median time for overall survival was not reached in either treatment group. The estimated median follow-up time for all patients was 44.6 months. Efficacy results for rPFS and OS from ARCHES are summarized in Table 12, Figure 4 and Figure 5.

Table 12. Summary of Efficacy Results in ARCHES (Intent-to-Treat Analysis)

	XTANDI (N = 574)	**Placebo (N = 576)**
Radiographic Progression-free Survival		
Number of events (%)	91 (15.9)	201 (34.9)
Median, months (95% CI)[1]	NR (NR, NR)	19.0 (16.6, 22.2)
Hazard ratio (95% CI)[2]	0.39 (0.30, 0.50)	
P-value[3]	p < 0.0001	

	XTANDI (N = 574)	Placebo (N = 576)
Overall Survival[4]		
Number of events (%)	154 (26.8)	202 (35.1)
Median, months (95% CI)[1]	NR (NR, NR)	NR (49.7, NR)
Hazard ratio (95% CI)[2]	0.66 (0.53, 0.81)	
P-value[3]	p < 0.0001	

NR = Not reached

1. Based on Kaplan-Meier estimates
2. Hazard Ratio is based on a Cox regression model stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no)
3. P-value is based on a stratified log-rank test by volume of disease (low vs high) and prior docetaxel use (yes or no)
4. Based upon a pre-specified final analysis with data cutoff date of 28 May 2021

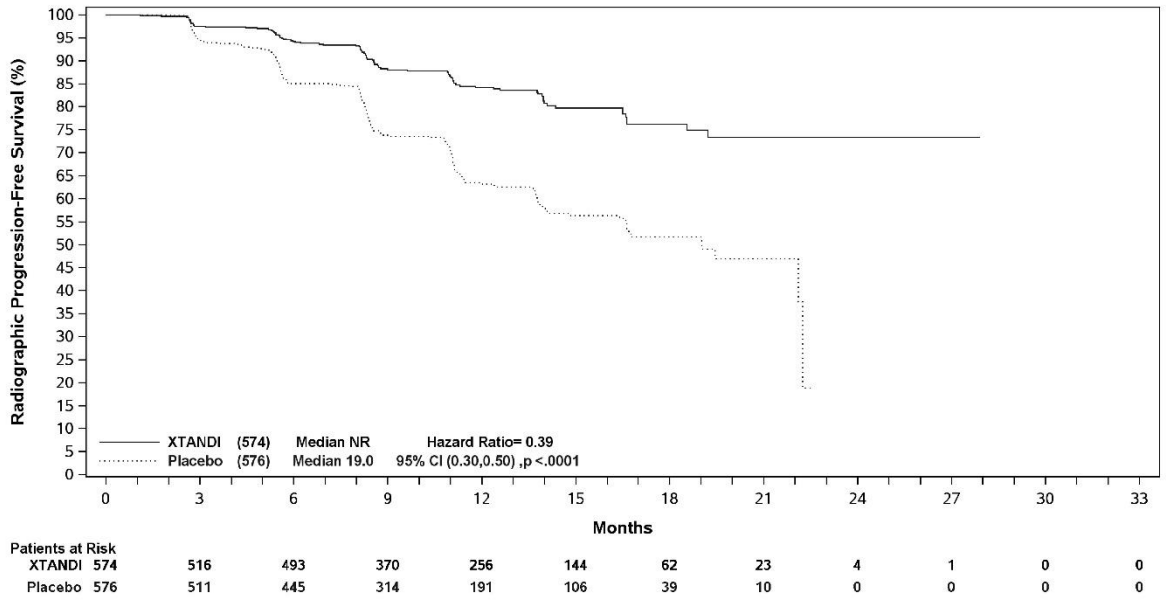


Figure 4. Kaplan-Meier Curves of rPFS in ARCHES (Intent-to-Treat Analysis)

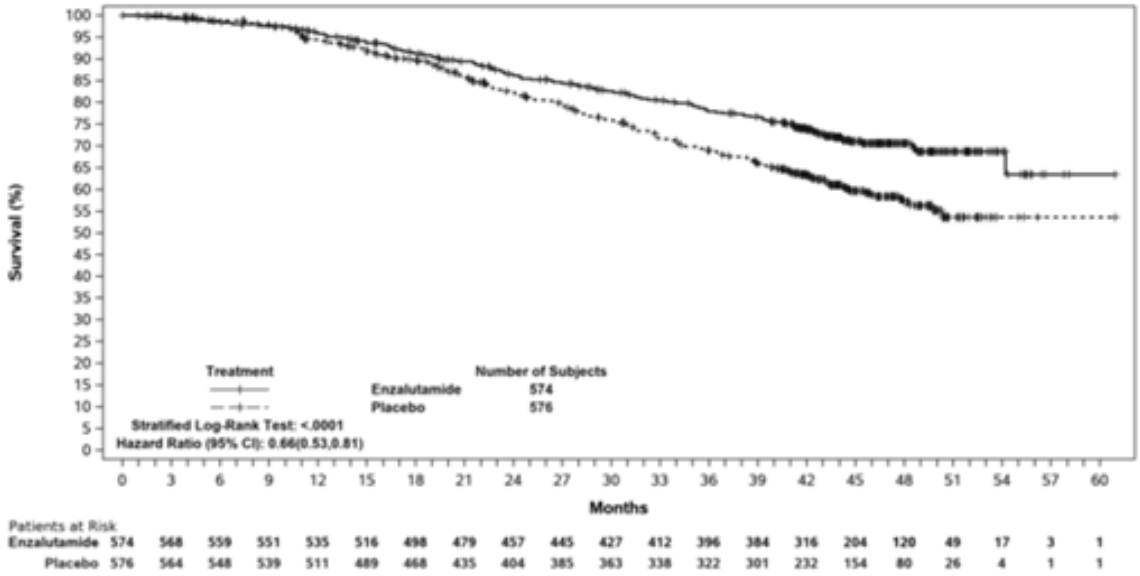


Figure 5. Kaplan-Meier Curves of overall survival in the ARCHES study (intent-to-treat analysis)

The major efficacy outcome was supported by multiple secondary endpoints. A statistically significant 72% reduction in risk of initiation of a new antineoplastic therapy was demonstrated for patients in the XTANDI arm compared to patients in the placebo arm (HR = 0.28 [95% CI: 0.20, 0.40], $p < 0.0001$). A statistically significant improvement of 19.3% in objective response rate (percentage of patients with complete or partial response in their soft tissue disease) was demonstrated with an Objective Response Rate (OSS) (calculated as percentage of patients with measurable disease at baseline who achieved a complete or partial response in their soft tissue disease) of 83.1% for patients in the XTANDI arm compared to 63.7% for patients in the placebo arm (95% CI: 10.4, 28.2; $p < 0.0001$). Time to First Symptomatic Skeletal Event (SSE) (time from randomization to the occurrence of the first symptomatic skeletal event) was associated with a 48% reduction in the risk of a patient experiencing an SSE compared with patients in the placebo arm [HR = 0.52, 95% CI: 0.33, 0.80; nominal p = 0.0026].

ENZAMET study (patients with metastatic HSPC)

The ENZAMET study enrolled 1125 patients with mHSPC randomised 1:1 to receive treatment orally once daily with XTANDI 160 mg (N = 563) or NSAA (N = 562). All patients in the trial received a LHRH analog or had a prior bilateral orchiectomy. Patients were stratified by volume of disease (low vs high), concomitant antiresorptive therapy (yes vs no), comorbidities (ACE-27: 0 to 1 vs 2 to 3) and planned use of a total of 6 cycles of docetaxel, of which 0-2 cycles were allowed before randomisation (yes vs no). Patients were required to have confirmation of metastatic prostate cancer by positive bone scan or metastatic lesions on CT or MRI scan. Patients continued treatment until evidence of clinical progression via CT, MRI or whole body bone scan.

The following patient demographics and baseline characteristics were balanced between the two treatment arms. The median age at randomisation was 69 years in the XTANDI group and 68 years in the NSAA group (treated with bicalutamide, nilutamide, or flutamide). The majority of patients had an ECOG performance status score of 0 (72%) and a Gleason score of ≥ 8 (58%). Forty-eight percent (48%) of patients had a low volume of disease and 52% of patients had a high volume of disease.

High volume of disease is defined as metastases involving the viscera or, in the absence of visceral lesions, there must be 4 or more bone lesions, at least 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. Ten percent (10%) of patients had concomitant antiresorptive therapy; 75% had no or mild comorbidities (ACE-27 score of 0 to 1) and 45% had a total of 6 cycles of docetaxel, of which 0-2 cycles were allowed before randomisation.

At the time of primary analysis, the median follow-up for OS was 33.8 months. The analysis demonstrated a statistically significant 33% reduction in the risk of death for patients treated with XTANDI compared to conventional NSAA treatment [HR of 0.67 (95% CI: 0.52, 0.86); p = 0.0018].

At the time of final analysis, the median follow-up for OS was 68.2 months. The analysis demonstrated a statistically significant 30% reduction in the risk of death for patients treated with XTANDI compared to conventional NSAA treatment [HR of 0.70 (95% CI: 0.58, 0.83); p < 0.0001].

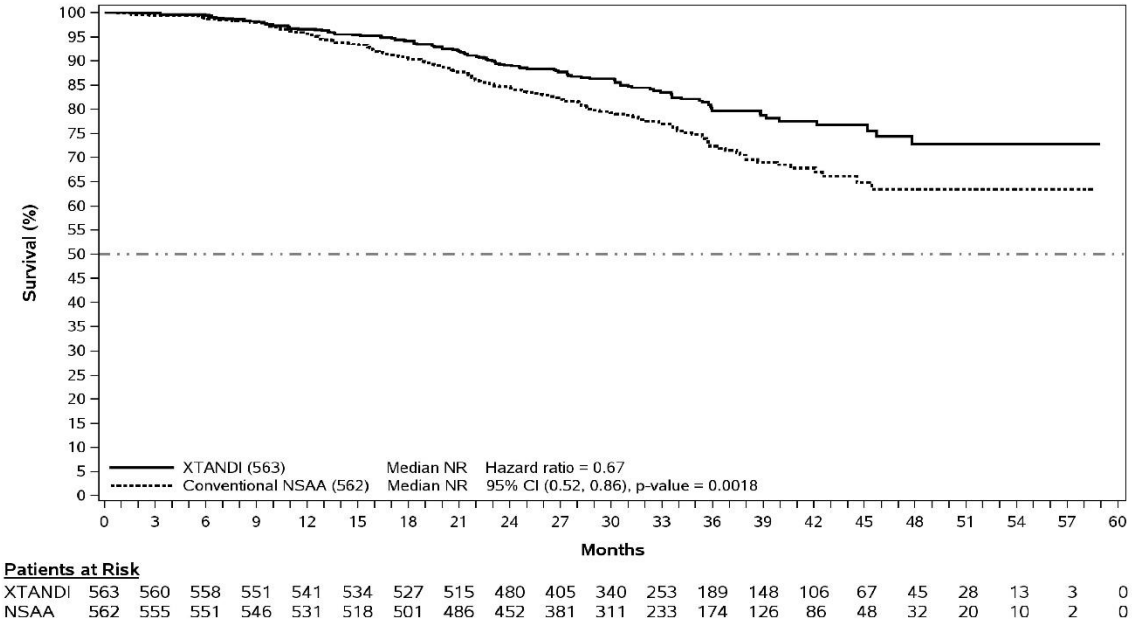


Figure 6. Kaplan-Meier Curves of Interim Overall Survival in ENZAMET (intent-to-treat analysis)

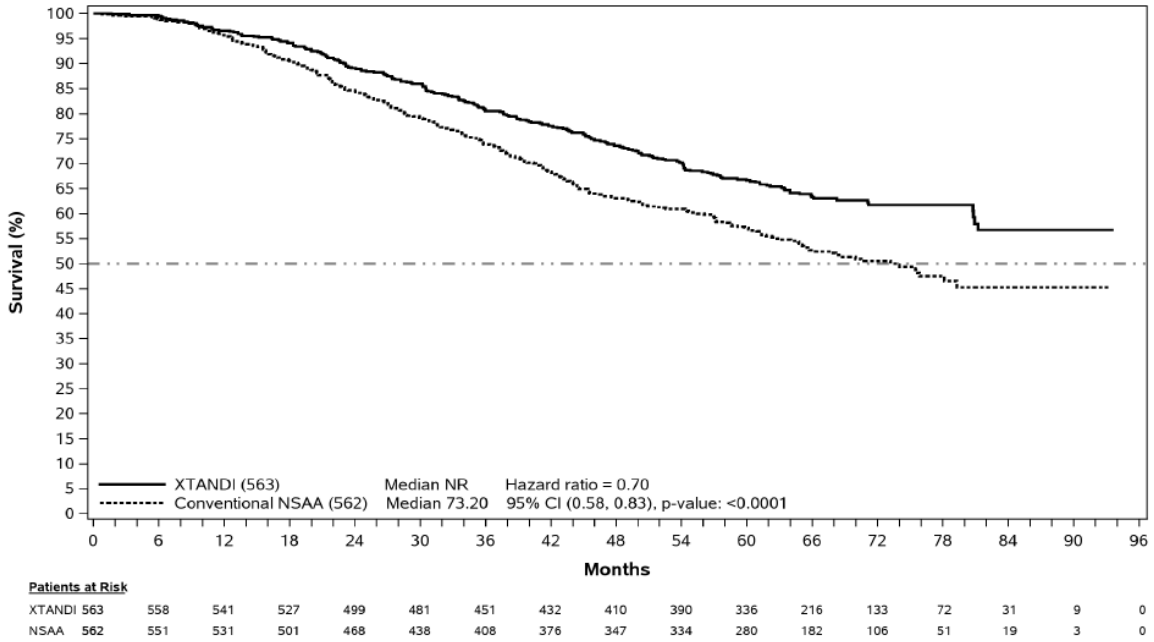


Figure 7. Kaplan-Meier Curves of Final Overall Survival in ENZAMET (intent-to-treat analysis)

PROSPER study (patients with non-metastatic CRPC)

The PROSPER study enrolled 1401 patients with asymptomatic, high-risk non-metastatic CRPC who continued on androgen deprivation therapy (ADT; defined as LHRH analogue or prior bilateral orchiectomy). Patients were required to have a PSA doubling time ≤ 10 months, PSA ≥ 2 ng/mL, and confirmation of non-metastatic disease by blinded independent central review (BICR).

Patients with a history of mild to moderate heart failure (NYHA Class I or II), and patients taking medicinal products associated with lowering the seizure threshold were allowed. Patients were excluded with a previous history of seizure, a condition that might predispose them to seizure, or certain prior treatments for prostate cancer (i.e., chemotherapy, ketoconazole, abiraterone acetate, aminoglutethimide and/or enzalutamide).

Patients were randomised 2:1 to receive either enzalutamide at a dose of 160 mg once daily (N = 933) or placebo (N = 468). Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time (PSADT) (< 6 months or ≥ 6 months) and the use of bone-targeting agents (yes or no).

The demographic and baseline characteristics were well-balanced between the two treatment arms. The median age at randomisation was 74 years in the enzalutamide arm and 73 years in the placebo arm. Most patients (approximately 71%) in the study were Caucasian; 16% were Asian and 2% were Black. Eighty-one percent (81%) of patients had an ECOG performance status score of 0 and 19% patients had an ECOG performance status of 1.

Metastasis-free survival (MFS) was the primary endpoint defined as the time from randomisation to radiographic progression or death within 112 days of treatment discontinuation without evidence of radiographic progression, whichever occurred first. Key secondary endpoints assessed in the study

were time to PSA progression, time to first use of new antineoplastic therapy (TTA), overall survival (OS). Additional secondary endpoints included time to first use of cytotoxic chemotherapy and chemotherapy-free survival. See results below (Table 13).

Enzalutamide demonstrated a statistically significant 71% reduction in the relative risk of radiographic progression or death compared to placebo [HR = 0.29 (95% CI: 0.24, 0.35), p < 0.0001]. Median MFS was 36.6 months (95% CI: 33.1, NR) on the enzalutamide arm versus 14.7 months (95% CI: 14.2, 15.0) on the placebo arm. Consistent MFS results were also observed in all pre-specified patient sub-groups including PSADT (< 6 months or ≥ 6 months), demographic region (North America, Europe, rest of world), age (< 75 or ≥ 75), use of a prior bone-targeting agent (yes or no).

Table 13. Summary of efficacy results in the PROSPER study (intent-to-treat analysis)

	Enzalutamide N = 933	**Placebo N = 468**
Primary Endpoint		
Metastasis-free survival		
Number of Events (%)	219 (23.5)	228 (48.7)
Median, months (95% CI)[1]	36.6 (33.1, NR)	14.7 (14.2, 15.0)
Hazard Ratio (95% CI)[2]	0.29 (0.24, 0.35)	
P-value[3]	p < 0.0001	
Key Secondary Efficacy Endpoints		
Overall Survival[4]		
Number of Events (%)	288 (30.9)	178 (38.0)
Median, months (95% CI)[1]	67.0 (64.0, NR)	56.3 (54.4, 63.0)
Hazard Ratio (95% CI)[2]	0.734 (0.608, 0.885)	
P-value[3]	p = 0.0011	
Time to PSA progression		
Number of Events (%)	208 (22.3)	324 (69.2)
Median, months (95% CI)[1]	37.2 (33.1, NR)	3.9 (3.8, 4.0)
Hazard Ratio (95% CI)[2]	0.07 (0.05, 0.08)	
P-value[3]	p < 0.0001	
Time to first use of new antineoplastic therapy		
Number of Events (%)	142 (15.2)	226 (48.3)
Median, months (95% CI)[1]	39.6 (37.7, NR)	17.7 (16.2, 19.7)
Hazard Ratio (95% CI)[2]	0.21 (0.17, 0.26)	
P-value[3]	p < 0.0001	

NR = Not reached

1. Based on Kaplan-Meier estimates

2. HR is based on a Cox regression model (with treatment as the only covariate) stratified by PSA doubling time and prior or concurrent use of a bone targeting agent. The HR is relative to placebo with < 1 favouring enzalutamide
3. P-value is based on a stratified log-rank test by PSA doubling time (< 6 months, ≥ 6 months) and prior or concurrent use of a bone targeting agent (yes, no)
4. Based upon a prespecified interim analysis with data cut-off date of 15 Oct 2019

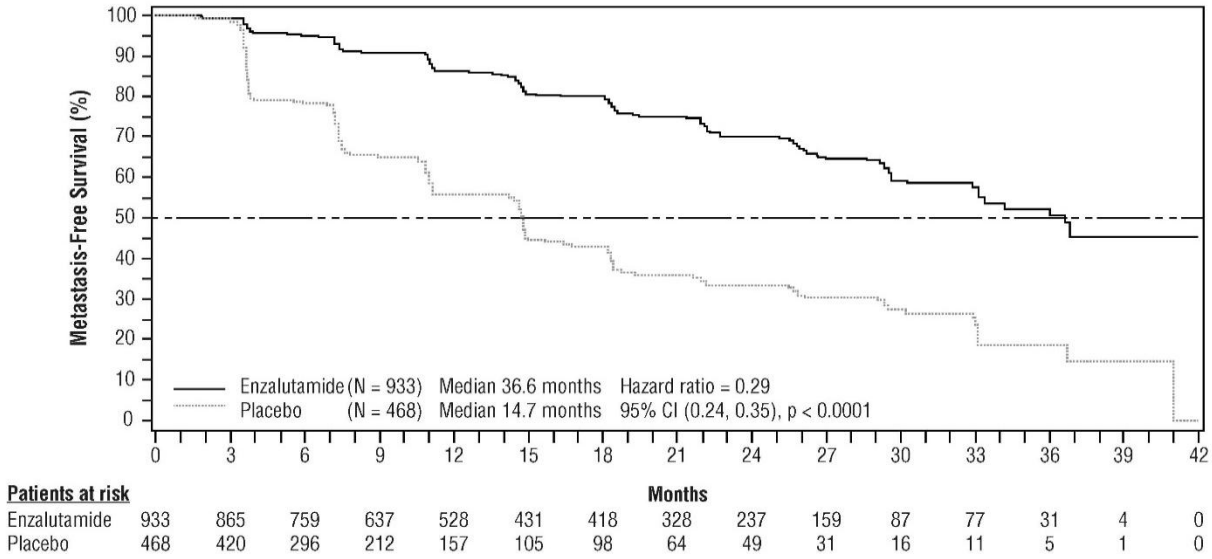


Figure 8. Kaplan-Meier Curves of metastasis-free survival in the PROSPER study (intent-to-treat analysis)

At the final analysis for overall survival, conducted when 466 deaths were observed, a statistically significant improvement in overall survival was demonstrated in patients randomised to receive enzalutamide compared with patients randomised to receive placebo with a 26.6% reduction in risk of death [hazard ratio (HR) = 0.734, (95% CI: 0.608; 0.885), p = 0.0011]. The median follow-up time was 48.6 and 47.2 months for the enzalutamide and placebo groups, respectively. Thirty-three percent of enzalutamide-treated and 65% of placebo-treated patients received at least one subsequent antineoplastic therapy that may prolong overall survival.

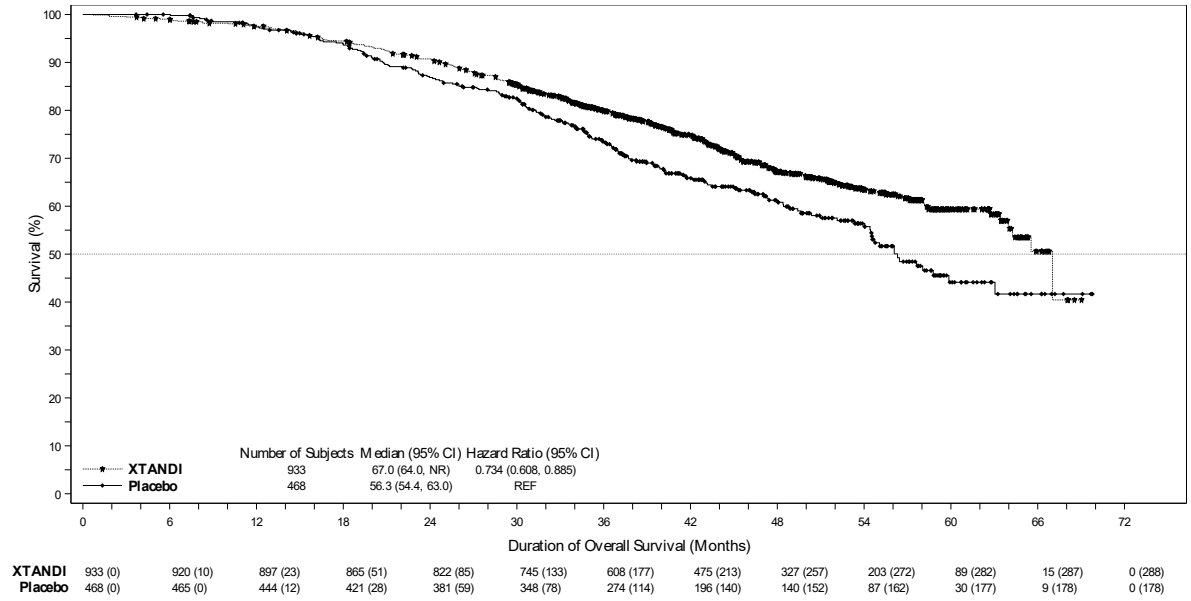


Figure 9. Kaplan-Meier Curves of overall survival in the PROSPER study (intent-to-treat analysis)

Enzalutamide demonstrated a statistically significant 93% reduction in the relative risk of PSA progression compared to placebo [HR = 0.07 (95% CI: 0.05, 0.08), p < 0.0001]. Median time to PSA progression was 37.2 months (95% CI: 33.1, NR) on the enzalutamide arm versus 3.9 months (95% CI: 3.8, 4.0) on the placebo arm.

Enzalutamide demonstrated a statistically significant delay in the time to first use of new antineoplastic therapy compared to placebo [HR = 0.21 (95% CI: 0.17, 0.26), p < 0.0001]. Median time to first use of new antineoplastic therapy was 39.6 months (95% CI: 37.7, NR) on the enzalutamide arm versus 17.7 months (95% CI: 16.2, 19.7) on the placebo arm.

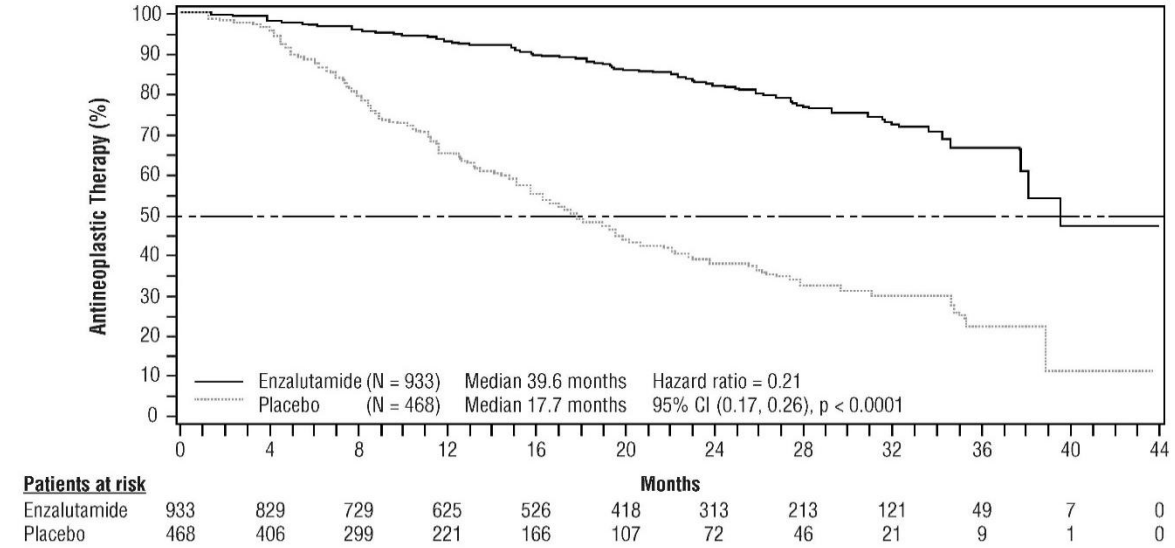


Figure 10. Kaplan-Meier curves of time to first use of new antineoplastic therapy in the PROSPER study (intent-to-treat analysis)

STRIVE study (chemotherapy-naïve patients with non-metastatic/metastatic CRPC)

The STRIVE study enrolled 396 non-metastatic or metastatic CRPC patients who had serologic or radiographic disease progression despite primary androgen deprivation therapy who were randomised to receive either enzalutamide at a dose of 160 mg once daily (N = 198) or bicalutamide at a dose of 50 mg once daily (N = 198). PFS was the primary endpoint defined as the time from randomisation to the earliest objective evidence of PSA progression, radiographic progression, or death on study. Median PFS was 19.4 months (95% CI: 16.5, not reached) in the enzalutamide group versus 5.7 months (95% CI: 5.6, 8.1) in the bicalutamide group [HR = 0.24 (95% CI: 0.18, 0.32), p < 0.0001]. Consistent benefit of enzalutamide over bicalutamide on PFS was observed in all prespecified patient subgroups.

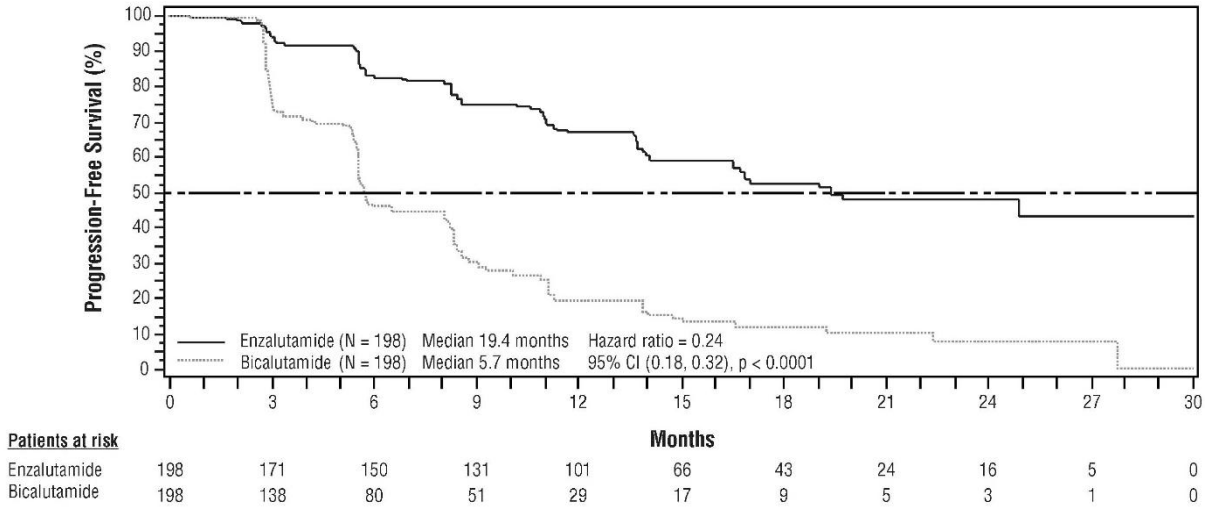


Figure 11. Kaplan-Meier Curves of progression-free survival in the STRIVE study (intent-to-treat analysis)

TERRAIN Study (chemotherapy-naïve patients)

TERRAIN enrolled 375 chemotherapy- and anti-androgen-therapy naïve patients who were randomised to receive either enzalutamide orally at a dose of 160 mg once daily (N = 184) or bicalutamide orally at a dose of 50 mg once daily (N = 191). Median progression-free survival (PFS) was 15.7 months for patients on enzalutamide vs. 5.8 months for patients on bicalutamide [HR = 0.44 (95% CI: 0.34, 0.57), p < 0.0001] (Figure 12). PFS was defined as objective evidence of radiographic disease progression by independent central review, skeletal-related events, initiation of new antineoplastic therapy or death by any cause, whichever occurred first. Consistent PFS benefit was observed across all pre-specified patient subgroups.

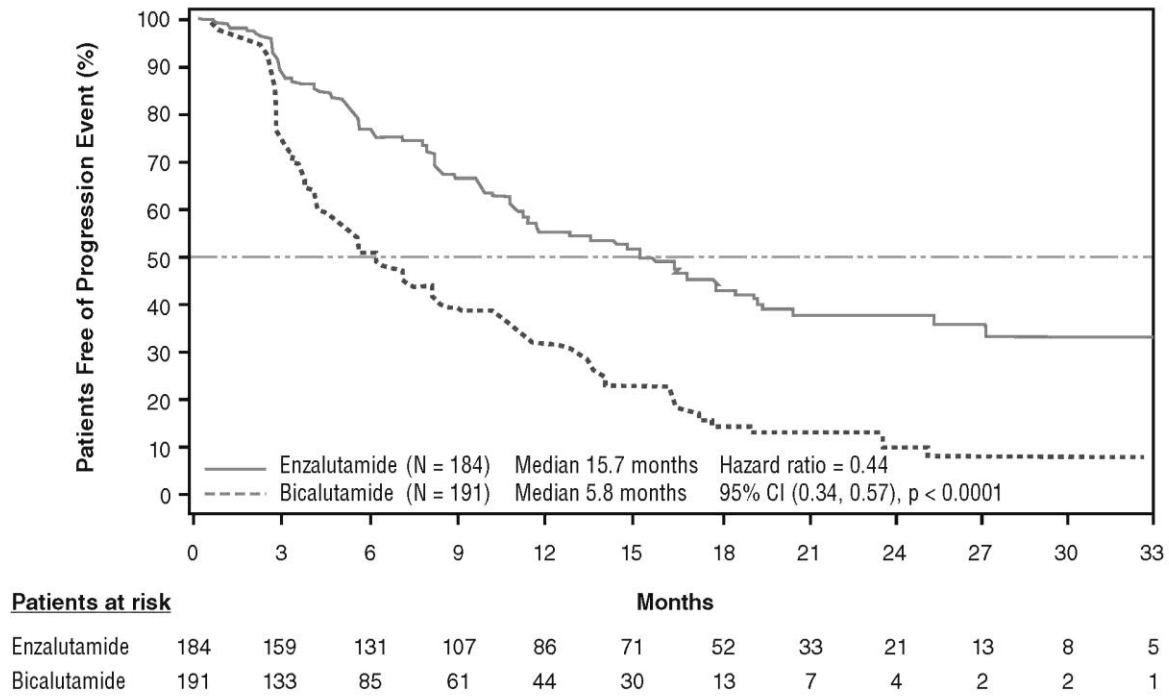


Figure 12. Kaplan-Meier Curves of Progression-Free Survival in the TERRAIN Study (Full Analysis Set)

PREVAIL Study (chemotherapy-naïve patients with metastatic CRPC)

A total of 1717 asymptomatic or mildly symptomatic chemotherapy-naïve patients were randomised 1:1 to receive either enzalutamide orally at a dose of 160 mg once daily (N = 872) or placebo orally once daily (N = 845). Patients with visceral disease, patients with a history of mild to moderate heart failure (NYHA Class I or II), and patients taking medications associated with lowering the seizure threshold were allowed. Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate or severe pain from prostate cancer were excluded. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal related event, or clinical progression) and the initiation of either a cytotoxic chemotherapy or an investigational agent, or until unacceptable toxicity.

Patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 71 years (range 42 – 93) and the racial distribution was 77% Caucasian, 10% Asian, 2% Black and 11% other or unknown races. Sixty-eight percent (68%) of patients had an ECOG performance status score of 0 and 32% of patients had an ECOG performance status of 1. Baseline pain assessment was 0 – 1 (asymptomatic) in 67% of patients and 2 – 3 (mildly symptomatic) in 32% of patients as defined by the Brief Pain Inventory Short Form (worst pain over past 24 hours on a scale of 0 to 10). Approximately 45% of patients had measurable soft tissue disease at study entry, and 12% of patients had visceral (lung and/or liver) metastases.

Co-primary efficacy endpoints were overall survival and radiographic progression-free survival (rPFS). In addition to the co-primary endpoints, benefit was also assessed using time to initiation of cytotoxic chemotherapy, best overall soft tissue response, time to first skeletal-related event, PSA

response (≥ 50% decrease from baseline), time to PSA progression, and time to FACT-P total score degradation.

Radiographic progression was assessed with the use of sequential imaging studies as defined by Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria (for bone lesions) and/or Response Evaluation Criteria in Solid Tumours (RECIST v 1.1) criteria (for soft tissue lesions). Analysis of rPFS utilised centrally-reviewed radiographic assessment of progression.

At the pre-specified interim analysis for overall survival, when 540 deaths were observed, treatment with enzalutamide demonstrated a statistically significant improvement in overall survival compared to treatment with placebo with a 29.4% reduction in risk of death [HR = 0.71 (95% CI: 0.60; 0.84), p < 0.0001] (Table 14). Of note, 40.4% of enzalutamide-treated patients and 70.5% of placebo-treated patients received subsequent therapies with a demonstrated survival benefit.

An updated overall survival analysis was conducted when 784 deaths were observed. Results from this analysis were consistent with those from the pre-specified interim analysis (Table 14). At the updated analysis, 52% of enzalutamide-treated and 81% of placebo-treated patients had received subsequent therapies for metastatic castration resistant prostate cancer which may prolong overall survival.

A final analysis of 5-year PREVAIL data showed a statistically significant increase in overall survival was maintained in patients treated with enzalutamide compared to placebo [HR = 0.835, (95% CI: 0.75, 0.93); p-value = 0.0008] despite 28% of patients on placebo crossing over to enzalutamide. (Table 14 and Figures 13 and 14). The 5-year OS rate was 26% for the enzalutamide arm compared to 21% for the placebo arm.

Table 14. Overall Survival of Patients Treated with Either Enzalutamide or Placebo in the PREVAIL Study (Intent-to-Treat Analysis)

	Enzalutamide (N = 872)	**Placebo (N = 845)**
Pre-specified interim analysis		
Number of deaths (%)	241 (27.6%)	299 (35.4%)
Estimated median, months (95% CI)	32.4 (30.1, NR)	30.2 (28.0, NR)
P-value[1]	p < 0.0001	
Hazard ratio (95% CI)[2]	0.71 (0.60, 0.84)	
Updated survival analysis		
Number of deaths (%)	368 (42.2%)	416 (49.2%)
Median survival, months (95% CI)	35.3 (32.2, NR)	31.3 (28.8, 34.2)
P-value[1]	p = 0.0002	
Hazard ratio (95% CI)[2]	0.77 (0.67, 0.88)	
5-year survival analysis		
Number of deaths (%)	689 (79)	693 (82)
Median survival, months (95% CI)	35.5 (33.5, 38.0)	31.4 (28.9, 33.8)
P-value[1]	p = 0.0008	
Number of deaths (%)	0.835 (0.75, 0.93)	

NR = Not reached

1. P-value is derived from an unstratified log-rank test
2. Hazard ratio is derived from an unstratified proportional hazards model. Hazard ratio < 1 favours enzalutamide

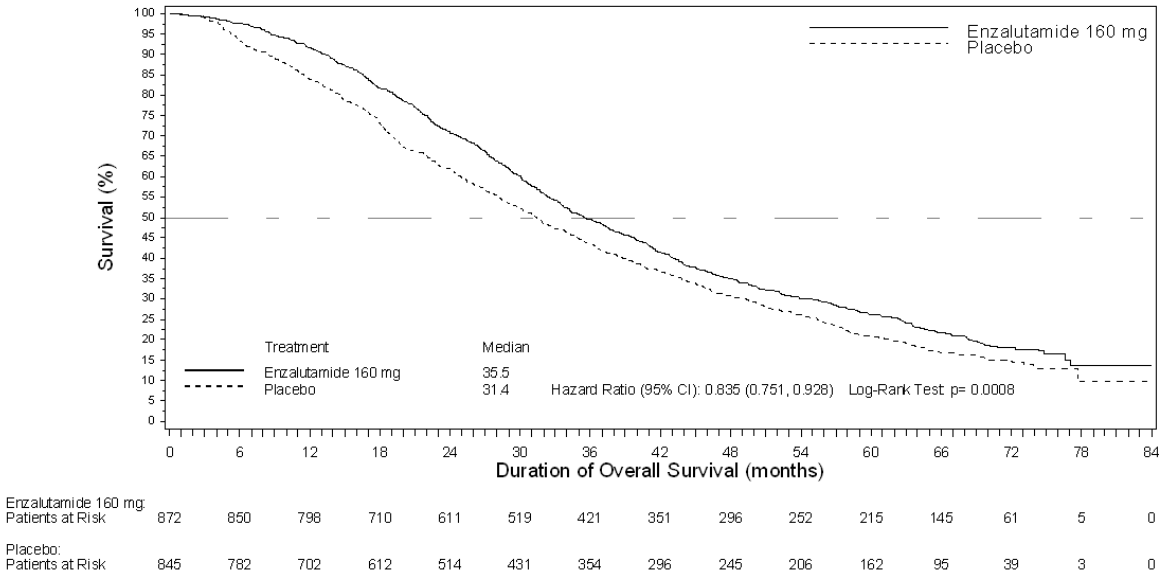


Figure 13. Kaplan-Meier curves of overall survival based on 5-year survival analysis in the PREVAIL study (intent-to-treat analysis)

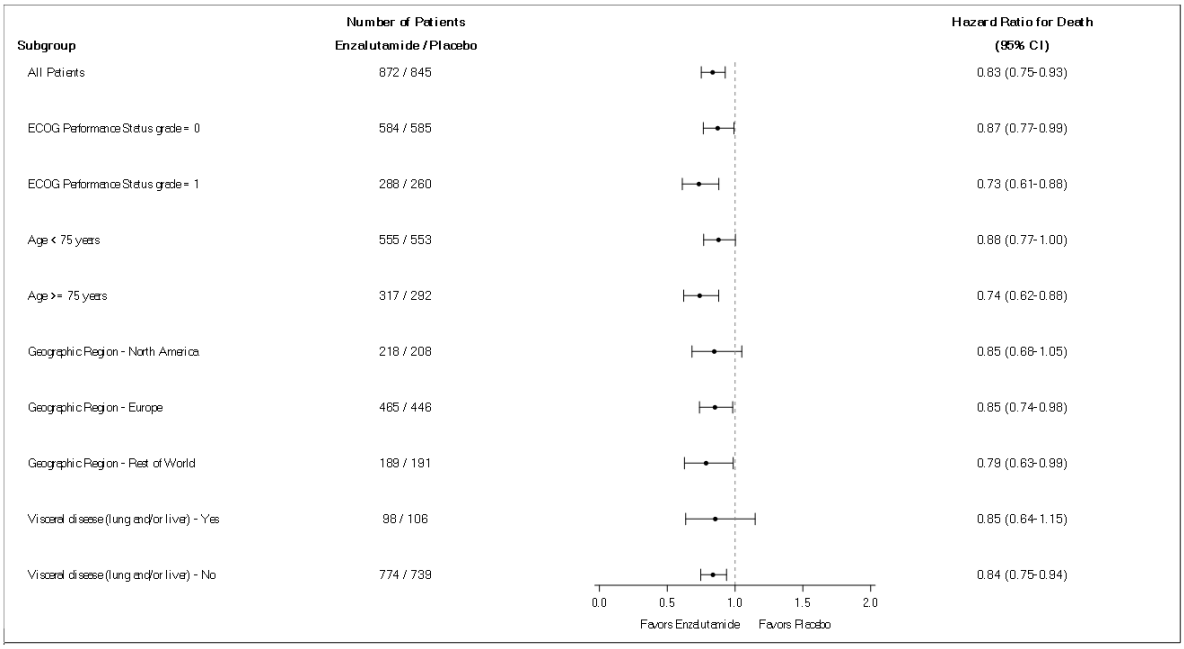
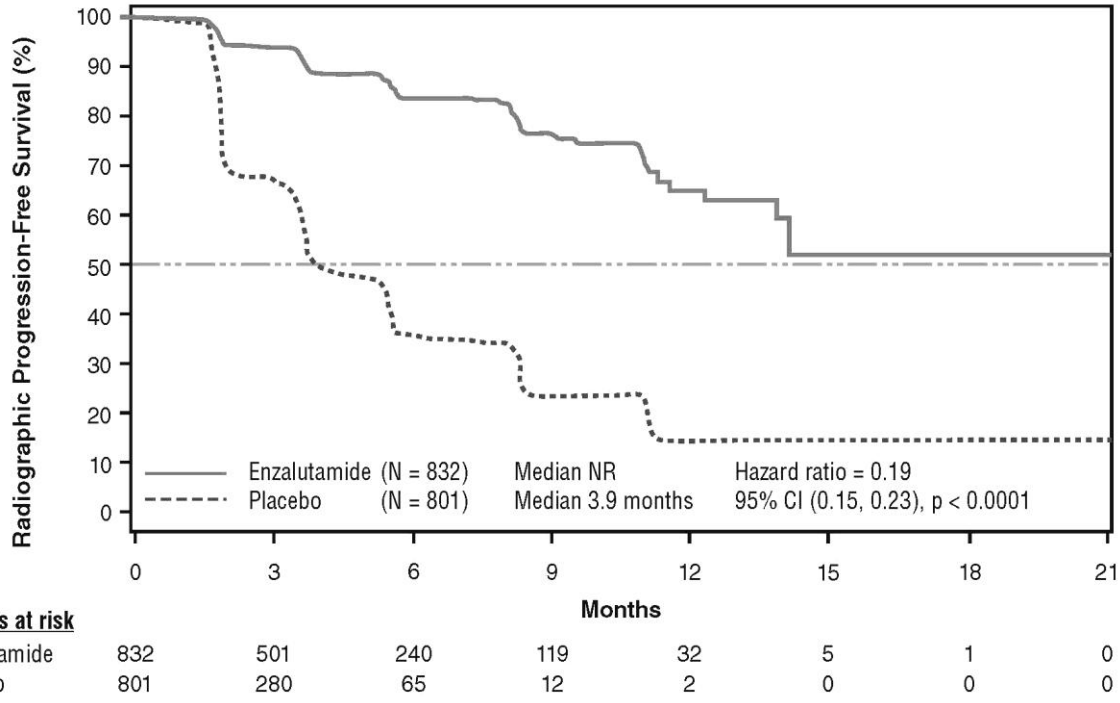


Figure 14. 5-year overall survival analysis by subgroup: Hazard ratio and 95% confidence interval in the PREVAIL study (intent-to-treat analysis)

At the pre-specified rPFS analysis, a statistically significant improvement was demonstrated between the treatment groups with an 81.4% reduction in risk of radiographic progression or death [HR = 0.19 (95% CI: 0.15, 0.23), p < 0.0001]. One hundred and eighteen (14%) enzalutamide-treated

patients and 321 (40%) of placebo-treated patients had an event. The median rPFS was not reached (95% CI: 13.8, not reached) in the enzalutamide-treated group and was 3.9 months (95% CI: 3.7, 5.4) in the placebo-treated group (Figure 15). Consistent rPFS benefit was observed across all pre-specified patient subgroups (e.g., age, baseline ECOG performance, baseline PSA and LDH, Gleason score at diagnosis, and visceral disease at screening). A pre-specified follow-up rPFS analysis based on the investigator assessment of radiographic progression demonstrated a statistically significant improvement between the treatment groups with a 69.3% reduction in risk of radiographic progression or death [HR = 0.31 (95% CI: 0.27, 0.35), p < 0.0001]. The median rPFS was 19.7 months in the enzalutamide group and 5.4 months in the placebo group.



At the time of the primary analysis there were 1633 patients randomised.

Figure 15. Kaplan-Meier curves of radiographic progression-free survival in the PREVAIL study (intent-to-treat analysis)

In addition to the co-primary efficacy endpoints, statistically significant improvements were also demonstrated in the following prospectively defined endpoints.

The median time to initiation of cytotoxic chemotherapy was 28.0 months for patients receiving enzalutamide and 10.8 months for patients receiving placebo (HR = 0.35, 95% CI: [0.30, 0.40], p < 0.0001).

The proportion of enzalutamide-treated patients with measurable disease at baseline who had an objective soft tissue response was 58.8% (95% CI: 53.8, 63.7) compared with 5.0% (95% CI: 3.0, 7.7) of patients receiving placebo. The absolute difference in objective soft tissue response between enzalutamide and placebo arms was [53.9% (95% CI: 48.5, 59.1, p < 0.0001)]. Complete responses were reported in 19.7% of enzalutamide-treated patients compared with 1.0% of placebo-treated patients, and partial responses were reported in 39.1% of enzalutamide-treated patients versus 3.9% of placebo-treated patients.

Enzalutamide significantly decreased the risk of the first skeletal-related event by 27% [HR = 0.526, (95% CI: 0.421, 0.656), p < 0.0001], 21.6% of enzalutamide-treated patients reported a skeletal-related event versus 18.5% of placebo-treated patients, an absolute difference of 3.1% events. A skeletal-related event was defined as radiation therapy or surgery to bone for prostate cancer, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain.

The median time to PSA progression per PCWG2 criteria was 11.2 months for patients treated with enzalutamide and 2.8 months for patients who received placebo [HR = 0.17, (95% CI: 0.15, 0.20), p < 0.0001].

Treatment with enzalutamide decreased the risk of FACT-P degradation by 37.5% compared with placebo (p < 0.0001). The median time to degradation in FACT-P was 11.3 months in the enzalutamide group and 5.6 months in the placebo group.

AFFIRM Study (patients with metastatic CRPC who previously received chemotherapy)

The efficacy and safety of XTANDI in patients with metastatic castration-resistant prostate cancer who had received docetaxel and were using a LHRH analogue or had undergone orchiectomy were assessed in a randomised, placebo-controlled, multicentre phase 3 clinical trial (AFFIRM). A total of 1199 patients were randomised 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 800) or placebo once daily (N = 399). Patients were allowed but not required to take prednisone (maximum daily dose allowed was 10 mg prednisone or equivalent). Patients randomised to either arm were to continue treatment until disease progression (defined as confirmed radiographic progression or the occurrence of a skeletal-related event) and initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal. Following progression, 41% of study drug arm and 61.7% of placebo arm received ≥ 1 further systemic treatment; therefore, the observed survival data and Kaplan-Meier curve reflect a median duration of treatment of 8 months of enzalutamide vs. 3 months of placebo followed by additional treatments.

The following patient demographics and baseline disease characteristics were balanced between the treatment arms. The median age was 69 years (range 41 – 92) and the racial distribution was 93% Caucasian, 4% Black, 1% Asian and 2% Other. The ECOG performance score was 0 – 1 in 91.5% of patients and 2 in 8.5% of patients; 28% had a mean Brief Pain Inventory score of ≥ 4 (mean of patient's reported worst pain over the previous 24 hours calculated for seven days prior to randomisation). Most (91%) patients had metastases in bone and 23% had visceral lung and/or liver involvement. At study entry, 41% of randomised patients had PSA progression only, whereas 59% of patients had radiographic progression. Fifty-one percent (51%) of patients were on bisphosphonates at baseline.

The AFFIRM study excluded patients with medical conditions that may predispose them to seizures and medications known to decrease the seizure threshold, as well as clinically significant cardiovascular disease such as uncontrolled hypertension, recent history of myocardial infarction or unstable angina, New York Heart Association class III or IV heart failure (unless ejection fraction was ≥ 45%), clinically significant ventricular arrhythmias or AV block (without permanent pacemaker).

The protocol pre-specified interim analysis after 520 deaths showed a statistically significant superiority in overall survival in patients treated with XTANDI compared to placebo (Table 15 and Figures 16 and 17).

Table 15. Overall Survival of Patients treated with either XTANDI or Placebo in the AFFIRM Study (Intent-to-Treat analysis)

	Enzalutamide (N = 800)	**Placebo (N = 399)**
Deaths (%)	308 (38.5%)	212 (53.1%)
Median survival (months) (95% CI)	18.4 (17.3, NR)	13.6 (11.3, 15.8)
P-value[1]	p < 0.0001	
Hazard ratio (95% CI)[2]	0.63 (0.53, 0.75)	

NR = Not reached

1. P-value is derived from a log rank test stratified by ECOG performance status score (0 – 1 vs. 2) and mean pain score (< 4 vs. ≥ 4)
2. Hazard ratio is derived from a stratified proportional hazards model. Hazard ratio < 1 favours XTANDI

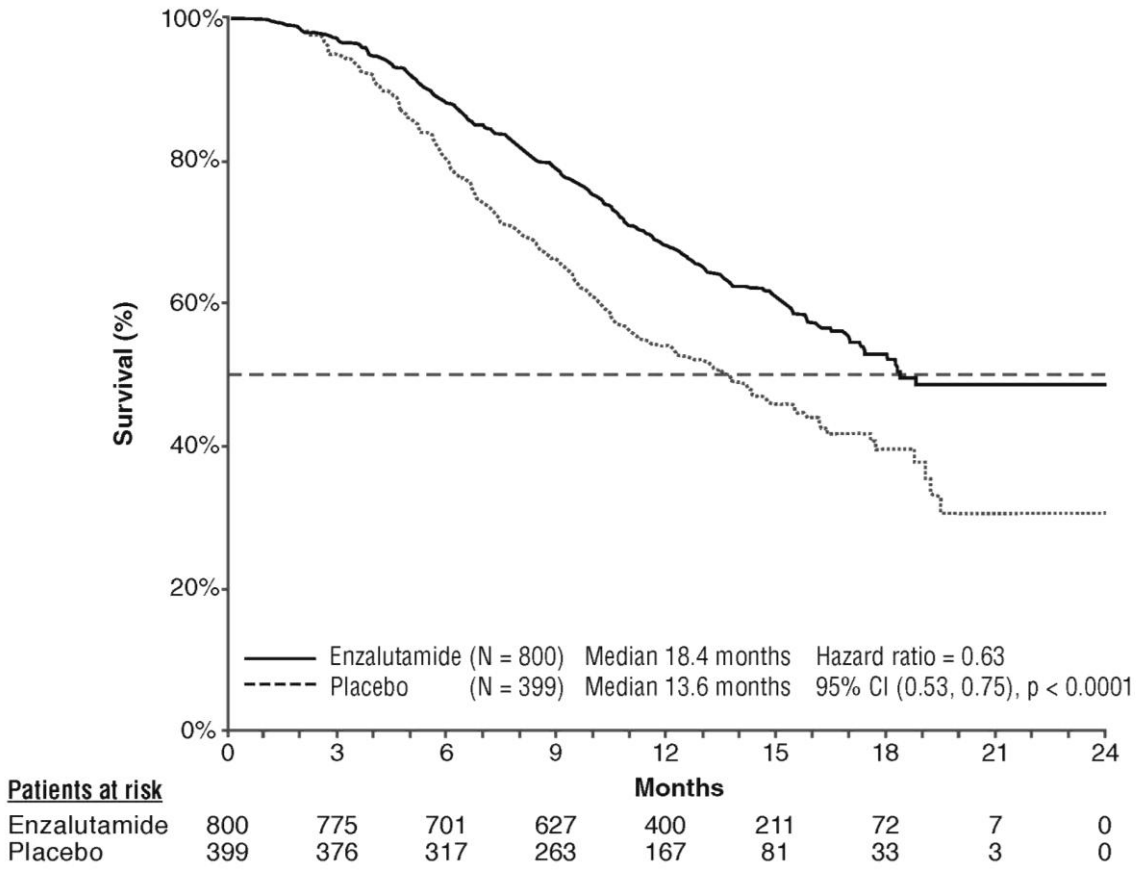
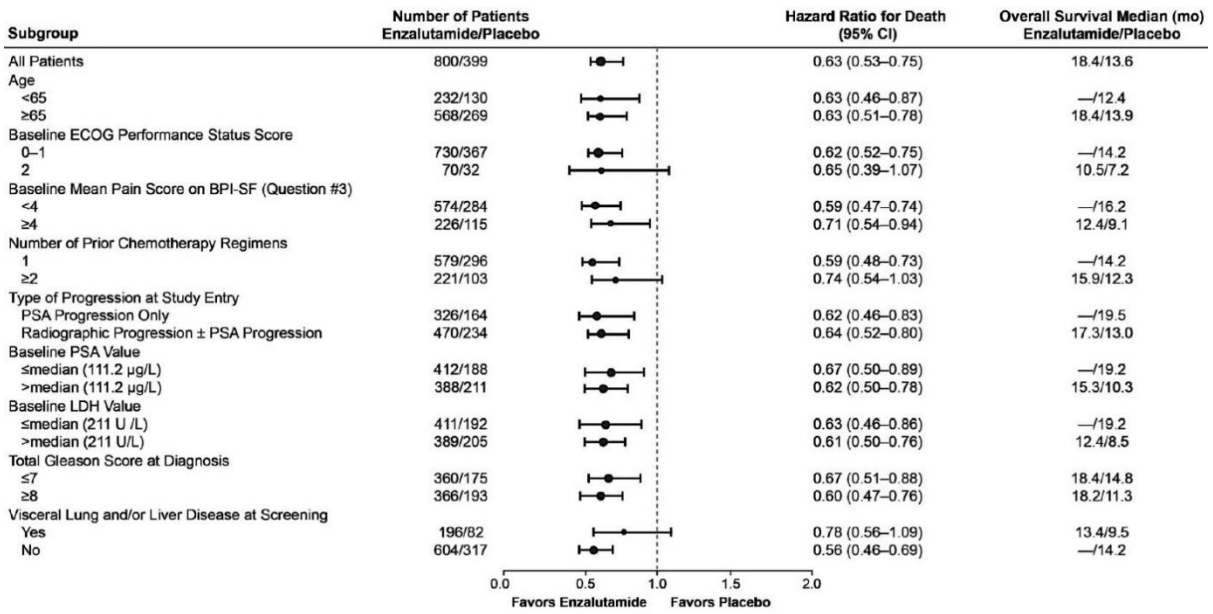


Figure 16. Kaplan-Meier curves of overall survival in the AFFIRM study (intent-to-treat analysis)



ECOG: Eastern Cooperative Oncology Group; BPI-SF: Brief Pain Inventory-Short Form; PSA: Prostate Specific Antigen

Figure 17. Overall Survival by Subgroup in the AFFIRM Study – Hazard Ratio and 95% Confidence Interval

In addition to the observed improvement in overall survival, key secondary endpoints (radiographic progression-free survival, and time to first skeletal-related event) favoured XTANDI and were statistically significant after adjusting for multiple testing.

Radiographic progression-free survival as assessed by the investigator using RECIST v1.1 for soft tissue and appearance of 2 or more bone lesions in bone scan was 8.3 months for patients treated with XTANDI and 2.9 months for patients who received placebo [HR = 0.40 (95% CI: 0.35, 0.47), $p < 0.0001$]. The analysis involved 216 deaths without documented progression and 645 documented progression events, of which 303 (47%) were due to soft tissue progression, 268 (42%) were due to bone lesion progression and 74 (11%) were due to both soft tissue and bone lesions.

The median time to first skeletal-related event was 16.7 months for patients treated with XTANDI and 13.3 months for patients who received placebo [HR = 0.69, (95% CI: 0.57, 0.84), $p < 0.0001$)]. A skeletal-related event was defined as radiation therapy or surgery to bone, pathologic bone fracture, spinal cord compression, or change of antineoplastic therapy to treat bone pain. The analysis involved 448 skeletal-related events, of which 277 events (62%) were radiation to bone, 95 events (21%) were spinal cord compression, 47 events (10%) were pathologic bone fracture, 36 events (8%) were change in antineoplastic therapy to treat bone pain and 7 events (2%) were surgery to bone.

9785-CL-0410 study (enzalutamide post abiraterone in patients with metastatic CRPC)

The study was a single-arm study in 214 patients with progressing metastatic CRPC who received enzalutamide (160 mg once daily) after at least 24 weeks of treatment with abiraterone acetate plus prednisone. Median rPFS (radiologic progression free survival, the study´s primary endpoint) was 8.1 months (95% CI: 6.1, 8.3). Median OS was not reached. PSA Response (defined as ≥ 50% decrease from baseline) was 22.4% (95% CI: 17.0, 28.6).

For the 69 patients who previously received chemotherapy, median rPFS was 7.9 months (95% CI: 5.5, 10.8). PSA Response was 23.2% (95% CI: 13.9, 34.9).

For the 145 patients who had no previous chemotherapy, median rPFS was 8.1 months (95% CI: 5.7, 8.3). PSA Response was 22.1% (95% CI: 15.6, 29.7).

Although there was a limited response in some patients from treatment with enzalutamide after abiraterone, the reason for this finding is currently unknown. The study design could neither identify the patients who are likely to benefit, nor the order in which enzalutamide and abiraterone should be optimally sequenced.

Elderly

Of the 5110 patients in the controlled clinical trials who received enzalutamide, 3988 patients (78%) were 65 years and over and 1703 patients (33%) were 75 years and over. No overall differences in safety or effectiveness were observed between these older patients and younger patients.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of enzalutamide have been evaluated in prostate cancer patients and in healthy male subjects. The mean terminal half-life ($t_{1/2}$) for enzalutamide in patients after a single oral dose is 5.8 days (range 2.8 to 10.2 days), and steady state is achieved in approximately one month. With daily oral administration, enzalutamide accumulates approximately 8.3-fold relative to a single dose. Daily fluctuations in plasma concentrations are low (peak-to-trough ratio of 1.25). Clearance of enzalutamide is primarily via hepatic metabolism, producing an active metabolite that circulates at approximately the same plasma concentration as enzalutamide.

Absorption

Maximum plasma concentrations (C_{max}) of enzalutamide in patients are observed 1 to 2 hours after administration. Based on a mass balance study in humans, oral absorption of enzalutamide is estimated to be at least 84.2%. Enzalutamide is not a substrate of the efflux transporters P-gp or BCRP. At steady state, the mean C_{max} values for enzalutamide and its active metabolite are 16.6 µg/mL (23% coefficient of variation [CV]) and 12.7 µg/mL (30% CV), respectively.

Food has no clinically significant effect on the extent of absorption. In clinical trials, XTANDI was administered without regard to food.

Distribution

The mean apparent volume of distribution (V/F) of enzalutamide in patients after a single oral dose is 110 L (29% CV). The volume of distribution of enzalutamide is greater than the volume of total body water, indicative of extensive extravascular distribution. Studies in rodents indicate that enzalutamide and its active metabolite can cross the blood brain barrier.

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. The active metabolite is 95% bound to plasma proteins. There was no protein binding displacement between enzalutamide and other highly bound medicinal products (warfarin, ibuprofen and salicylic acid) *in vitro*.

Metabolism

Enzalutamide is extensively metabolised. There are two major metabolites in human plasma: N-desmethyl enzalutamide (active) and a carboxylic acid derivative (inactive). Enzalutamide is metabolised by CYP2C8 and to a lesser extent by CYP3A4/5 (Refer to Section 4.5 - Interactions with other medicines and other forms of interactions), both of which play a role in the formation of the active metabolite. N-desmethyl enzalutamide was not metabolised by CYPs *in vitro*.

Under conditions of clinical use, enzalutamide is a strong inducer of CYP3A4, a moderate inducer of CYP2C9 and CYP2C19, and has no clinically relevant effect on CYP2C8 (Refer to Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS).

In vitro, small amounts of N-desmethyl enzalutamide are metabolised to the carboxylic acid metabolite by carboxylesterase 1 which also plays a minor role in the metabolism of enzalutamide to the inactive carboxylic acid metabolite. Carboxylesterase 2 does not appear to play a role in the metabolism of either enzalutamide or N-desmethyl enzalutamide.

Excretion

The mean apparent clearance (CL/F) of enzalutamide in patients ranges from 0.520 and 0.564 L/h.

Following oral administration of ^{14}C-enzalutamide, 84.6% of the radioactivity is recovered by 77 days post dose: 71.0% is recovered in urine (primarily as the inactive metabolite, with trace amounts of enzalutamide and the active metabolite), and 13.6% is recovered in faeces (0.39% of dose as unchanged enzalutamide).

Linearity

No major deviations from dose proportionality are observed over the dose range 40 to 160 mg. The steady state C_{min} values of enzalutamide and the active metabolite in individual patients remained constant during more than one year of chronic therapy, demonstrating time linear pharmacokinetics once steady state is achieved.

Pharmacokinetic Characteristics in Special Populations

Patients with hepatic impairment: The pharmacokinetics of enzalutamide were examined in subjects with baseline mild (N = 6), moderate (N = 8) or severe (N = 8) hepatic impairment (Child Pugh Class A, B and C respectively) and in 22 matched control subjects with normal hepatic function.

Following a single oral 160 mg dose of enzalutamide, the AUC and C_{max} for enzalutamide in subjects with mild impairment increased by 5% and 24%, respectively, the AUC and C_{max} of enzalutamide in subjects with moderate impairment increased by 29% and decreased by 11%, respectively and the AUC and C_{max} of enzalutamide in subjects with severe impairment increased by 5% and decreased by 41%, respectively, compared to healthy control subjects.

For the sum of unbound enzalutamide plus the unbound active metabolite, the AUC and C_{max} in subjects with mild impairment increased by 14% and 19%, respectively, the AUC and C_{max} in subjects with moderate impairment increased by 14% and decreased by 17%, respectively, and the AUC and C_{max} of enzalutamide in subjects with severe hepatic impairment increased by 34% and decreased by 27%, respectively, compared to healthy control subjects.

Patients with renal impairment: No formal renal impairment study for enzalutamide has been completed. Patients with serum creatinine > 177 µmol/L (2 mg/dL) were excluded from clinical studies. Based on a population pharmacokinetic analysis, no dose adjustment is necessary for patients with calculated creatinine clearance (CrCL) values ≥ 30 mL/min (estimated by the Cockcroft and Gault formula). Enzalutamide has not been evaluated in patients with severe renal impairment (CrCL < 30 mL/min) or end-stage renal disease, and caution is advised when treating these patients. It is unlikely that enzalutamide will be significantly removed by intermittent haemodialysis or continuous ambulatory peritoneal dialysis.

Elderly: No clinically relevant effect of age on enzalutamide pharmacokinetics was seen in the elderly population pharmacokinetic analysis.

Paediatric use: The pharmacokinetics of enzalutamide in paediatric patients have not been established.

Gender and race: The effect of gender on the pharmacokinetics of enzalutamide has not been evaluated. Most patients in the randomised clinical studies (> 75%) were Caucasian. Based on pharmacokinetic data from studies in Japanese and Chinese patients with prostate cancer, there were no clinically relevant differences in exposure among the populations. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Enzalutamide did not induce mutations in the microbial mutagenesis (Ames) assay and was not clastogenic in either the *in vitro* cytogenetic assay with mouse lymphoma cells or the *in vivo* mouse micronucleus assay.

Carcinogenicity

In a 6-month study in transgenic rasH2 mice, enzalutamide did not show carcinogenic potential (absence of neoplastic findings) at doses up to 20 mg/kg/day, which resulted in combined exposure levels (based on AUC), for enzalutamide plus its active metabolite M2, approximately half the clinical exposure in metastatic CRPC patients receiving 160 mg daily.

Daily oral dosing of rats for two years with enzalutamide at 10–100 mg/kg/day produced an increased incidence of neoplastic findings (compared to control) that were considered related to the primary pharmacology of enzalutamide. These included benign thymoma, fibroadenoma in the mammary glands, and benign Leydig cell tumours in the testes in males; benign granulosa cell tumour in the of ovaries in females; and adenoma in the pars distalis of the pituitary in both sexes.

Benign Leydig cell tumours are generally not considered relevant to humans based on experience with other anti-androgens. The human relevance of thymoma, pituitary adenoma and fibroadenoma in rats is unclear, but a potential relevance cannot be ruled out.

The urothelial papilloma and carcinoma of the urinary bladder observed at the 100 mg/kg/day dose in male rats are considered secondary to the continuous irritation caused by the increased accumulation of urinary crystal/calculi in the rat urinary bladder possibly due to its horizontal structure. The finding is not expected to occur in humans due to the upright positioning of the

bladder. Prolonged irritation by urinary crystalluria or calculi may dispose rats to urothelial hyperplasia and/or tumour formation, however the incidence of bladder calculi reported in the clinical trials of enzalutamide was comparable between enzalutamide and the placebo groups.

The combined exposure levels (based on AUC) achieved in this study, for enzalutamide and its active metabolite M2 in rats were less than or similar to those in prostate cancer patients receiving 160 mg daily.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

XTANDI contains the following inactive ingredients: caprylocaproyl macrogolglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerol, purified water, titanium dioxide. The soft capsules also contain OPACODE WB monogramming ink NSP-78-17827 BLACK.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

See also Section 4.5 - INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

XTANDI 40 mg capsules are supplied in a cardboard wallet incorporating a PVC/PCTFE/aluminium blister of 28 soft capsules. Each carton contains 4 wallets (112 soft capsules).

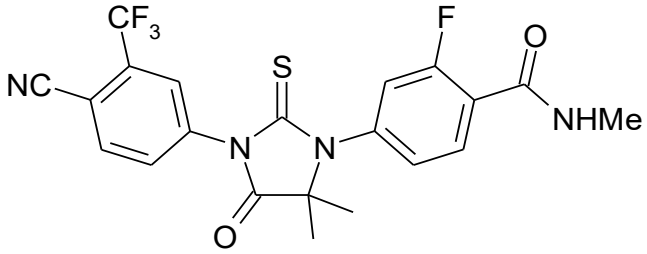
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Enzalutamide is a white crystalline non-hygroscopic solid. It is practically insoluble in water.

Chemical structure



Chemical name: 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-thioxoimidazolidin-1-yl}-2-fluoro-N-methylbenzamide.

Molecular formula: $C_{21}H_{16}F_4N_4O_2S$

CAS number

915087-33-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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Suite 2.01, 2 Banfield Road Macquarie Park NSW 2113

Tel: 1800 751 755 (Medical Information)
Email: aaumedinfo@astellas.com (Medical Information)
Website: www.astellas.com/au

9 DATE OF FIRST APPROVAL

1 July 2014

10 DATE OF REVISION

25 September 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.5	Information regarding the interaction between enzalutamide and the CMIA laboratory test, which results in falsely elevated digoxin plasma levels, has been added. Clarification regarding the assay used to evaluate the plasma levels of digoxin in the study related to the effect of enzalutamide on P-gp substrates has been added.