05.09.2019

רופא/ה רוקח/ת נכבד/ה,
ברצוננו להודיעך על עדכון בעלון לרופא ועלון לצרכן של

Xtandi 40mg - soft capsules

חומר פעיל:

Enzalutamide 40 mg

להלן עדכונים בעלון לרופא (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן בצהוב משמעותו החמרה):

[…]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Xtandi 40 mg soft capsules
Each soft capsule contains 40 mg of enzalutamide.

[…]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Xtandi is indicated for:

- the treatment of adult men with high-risk non-metastatic castration-resistant prostate cancer (CRPC) (see section 5.1).
- the treatment of adult men with metastatic ~~castration-resistant prostate cancer (~~CRPC~~)~~ who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated (see section 5.1)
- the treatment of adult men with metastatic ~~castration-resistant prostate cancer (~~CRPC~~)~~ whose disease has progressed on or after docetaxel therapy.

4.2 Posology and method of administration

[…]

Posology
The recommended dose is 160 mg enzalutamide (four 40 mg *soft* capsules) as a single oral daily dose

[…]

Elderly
No dose adjustment is necessary for elderly (see sections 5.1 and 5.2).

Hepatic impairment
No dose adjustment is necessary for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively). An increased drug half-life has however been observed in patients with severe hepatic impairment. (see sections 4.4 and 5.2).

[…]

Paediatric population
There is no relevant use of enzalutamide in the paediatric population in the indication of treatment of adult men with ~~metastatic~~ CRPC.

[…]

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1.

Women who are or may become pregnant (see sections 4.6 and 6.6).

4.4 Special warnings and precautions for use

Risk of seizure
Use of enzalutamide has been associated with seizure (see section 4.8). ~~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 medicinal products that lower the seizure threshold.~~ The decision to continue treatment in patients who develop seizure should be taken case by case.

[…]

Hypersensitivity reactions
Hypersensitivity reactions manifested by symptoms including, but not limited to, rash, or face, tongue ~~oedema~~, lip, ~~oedema and~~or pharyngeal oedema, have been observed with enzalutamide (see section 4.8).

4.5 Interaction with other medicinal products and other forms of interaction

[…]

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)
- ~~Anticoagulants (e.g. acenocoumarol, warfarin)~~
- Antiepileptics (e.g. carbamazepine, clonazepam, phenytoin, primidone, valproic acid)
- Antipsychotics (e.g. haloperidol)
- Antithrombotics (e.g. acenocoumarol, 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)
- Immunosuppressant (e.g. tacrolimus)
- Proton pump inhibitor (e.g. omeprazole)
- Statins metabolized by CYP3A4 (e.g. atorvastatin, simvastatin)
- Thyroid agents (e.g. levothyroxine)

[…]

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
There are no human data on the use of Xtandi in pregnancy and this medicinal product is not for use in women of childbearing potential. This medicine may cause harm to the unborn child or potential loss of pregnancy if taken by women who are pregnant (see sections 4.3, 5.3, and 6.6).

[…]

Pregnancy
Enzalutamide is not for use in women. Enzalutamide is contraindicated in women who are or may become pregnant (see sections 4.3, ~~and~~ 5.3, and 6.6).

[…]

4.7 Effects on ability to drive and use machines

Xtandi has ~~Enzalutamide may have a~~ moderate influence on the ability to drive and use machines as psychiatric and neurologic events including seizure have been reported (see section 4.8). Patients ~~with a history of seizures or other predisposing factors (see section 4.4)~~ should be advised of the potential risk of experiencing a psychiatric or neurological event while driving or operating machines. No studies to evaluate ~~establish~~ the effects of enzalutamide on the ability to drive and use machines have been conducted.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions are asthenia/fatigue, hot flush, fractures~~headache~~, and hypertension. Other important adverse reactions include fall~~s~~, ~~nonpathologic fractures~~, cognitive disorder, and neutropenia.

Seizure occurred in 0.~~5~~4% of enzalutamide-treated patients, 0.1% of placebo-treated patients, and 0.3% in bicalutamide-treated patients.

[…]

Table 1: Adverse reactions identified in controlled clinical trials and post-marketing

MedDRA System organ class	Frequency
Blood and lymphatic system disorders	~~uncommon~~Uncommon: leucopenia, neutropenia ~~not~~ Not known*: thrombocytopenia
Immune system disorders	~~not~~ Not known*: face oedema, tongue oedema, lip oedema, pharyngeal oedema

Psychiatric disorders	~~common~~Common: anxiety ~~uncommon~~Uncommon: visual hallucinations
Nervous system disorders	~~very common: headache~~ ~~common~~Common: headache, memory impairment, amnesia, disturbance in attention, restless legs syndrome ~~uncommon~~Uncommon: cognitive disorder, seizure¥ ~~not~~ Not known*: posterior reversible encephalopathy syndrome
Cardiac disorders	Common: ischemic heart disease† ~~not~~ Not known*: QT-prolongation (see sections 4.4 and 4.5)
Vascular disorders	~~very~~ Very common: hot flush, hypertension
Gastrointestinal disorders	~~not~~ Not known*: nausea, vomiting, diarrhoea
Skin and subcutaneous tissue disorders	~~common~~Common: dry skin, pruritus ~~not~~ Not known*: rash
Musculoskeletal and connective tissue disorders	Very common: fractures‡~~**~~ ~~not~~ Not known*: myalgia, muscle spasms, muscular weakness, back pain
Reproductive system and breast disorder	~~common~~Common: gynaecomastia
General disorders and administration site conditions	~~very~~ Very common: asthenia~~/~~, fatigue
Injury, poisoning and procedural complications	~~common~~Common: fall~~s~~

* Spontaneous reports from post-marketing experience

¥ 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.

† As evaluated by narrow SMQs of 'Myocardial Infarction' and 'Other Ischemic Heart Disease' including the following preferred terms observed in at least two patients in randomized 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.

‡ Includes all preferred terms with the word 'fracture' in bones.

~~* Spontaneous reports from post-marketing experience~~

~~** Includes all fractures with the exception of pathological fractures~~

Description of selected adverse reactions

Seizure

In controlled clinical studies, ~~11~~ 13 patients (0.~~5~~1%) experienced a seizure out of ~~2051~~ 3179 patients treated with a daily dose of 160 mg enzalutamide, whereas one patient (~~<~~0.1%) receiving placebo and one patient (0.3%) receiving bicalutamide, experienced a seizure. Dose appears to be an important predictor of the risk of seizure, as reflected by preclinical data, and data from a dose-escalation study. In the controlled clinical studies, patients with prior seizure or risk factors for seizure were excluded.

~~In the AFFIRM trial, seven patients (0. 9%) experienced a seizure out of 800 post-chemotherapy patients treated with a daily dose of 160 mg enzalutamide, whereas no seizures occurred in patients receiving placebo. Potentially contributing factors were present in several of these patients that may have independently increased their risk of seizure. In the PREVAIL trial, one patient (0.1%) out of 871 chemotherapy-naive patients treated with a daily dose of 160 mg enzalutamide, and one patient (0.1%) receiving placebo experienced a seizure. In bicalutamide-controlled trials, 3 patients (0.8%) out of 380 chemotherapy-naïve patients treated with enzalutamide and 1 patient (0.3%) out of 387 receiving bicalutamide experienced a seizure.~~

In the 9785-CL-0403 (UPWARD) ~~a~~ single-arm trial to assess incidence of seizure in patients with predisposing factors for seizure (whereof 1.6% had a history of seizures), 8 of 366 (2.2%) patients treated with enzalutamide experienced a seizure. The median duration of treatment was 9.3 months.

The mechanism by which enzalutamide may lower the seizure threshold is not known, but could be related to data from *in vitro* studies showing that enzalutamide and its active metabolite bind to and can inhibit the activity of the GABA-gated chloride channel.

Ischemic Heart Disease
In randomized placebo-controlled clinical studies, ischemic heart disease occurred in 2.5% of patients treated with enzalutamide plus ADT compared to 1.3 % patients treated with placebo plus ADT.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
https://sideeffects.health.gov.il
~~http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il~~

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

[…]

Mechanism of action
Prostate cancer is known to be androgen sensitive and responds to inhibition of androgen receptor signalling. Despite low or even undetectable levels of serum androgen, androgen receptor signalling continues to promote disease progression. Stimulation of tumour cell growth via the androgen receptor requires nuclear localization and DNA binding. Enzalutamide is a potent androgen receptor signalling inhibitor that blocks several steps in the androgen receptor signalling pathway. Enzalutamide competitively inhibits androgen binding ~~of androgens~~ to androgen receptors, and consequently: inhibits nuclear translocation of activated receptors and inhibits the association of the activated androgen receptor with DNA even in the setting of androgen receptor overexpression and in prostate cancer cells resistant to anti-androgens. Enzalutamide treatment decreases the growth of prostate cancer cells and can induce cancer cell death and tumour regression. In preclinical studies enzalutamide lacks androgen receptor agonist activity.

[…]

In a single arm trial ~~study~~ (9785-CL-0410) of patients previously treated with at least 24 weeks of abiraterone (plus prednisone), 22.4% had a ≥ 50% decrease from baseline in PSA levels. According to prior chemotherapy history, the results proportion of patients with a ≥ 50% decrease in PSA levels were 22.1% and 23.2%, for the no prior chemotherapy and prior chemotherapy patient groups, respectively.

In the MDV3100-09 clinical trial (STRIVE) of non-metastatic and metastatic CRPC, patients receiving enzalutamide demonstrated a significantly higher total confirmed PSA response rate (defined as a ≥ 50% reduction from baseline) compared with patients receiving bicalutamide, 81.3% versus 31.3% (difference = 50.0%, p < 0.0001).

In the MDV3100-14 clinical trial (PROSPER) of non-metastatic CRPC, patients receiving enzalutamide demonstrated a significantly higher confirmed PSA response rate (defined as a ≥ 50% reduction from baseline), compared with patients receiving placebo, 76.3% versus 2.4% (difference = 73.9%, p < 0.0001).

Clinical efficacy and safety

Efficacy of enzalutamide was established in three ~~two~~ randomised ~~randomized~~ placebo-controlled multicentre phase 3 clinical studies [MDV3100-14 (PROSPER), CRPC2 (AFFIRM), MDV3100-03 (PREVAIL)] of patients with progressive ~~metastatic~~ prostate cancer who had failed androgen deprivation therapy [(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. All patients continued on a LHRH analogue or had prior bilateral orchiectomy. In the active treatment arm, Xtandi was administered orally at a dose of 160 mg daily. In the three ~~both~~ clinical trials, patients received placebo in the control arm and patients were allowed, but not required, to take prednisone (maximum daily dose allowed was 10 mg prednisone or equivalent).

Changes in PSA serum concentration independently do not always predict clinical benefit. Therefore, in the three ~~both~~ studies it was recommended that patients be maintained on their study treatments until discontinuation criteria were met as specified below for each study.

MDV3100-14 (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 2).

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 2: 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		
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).

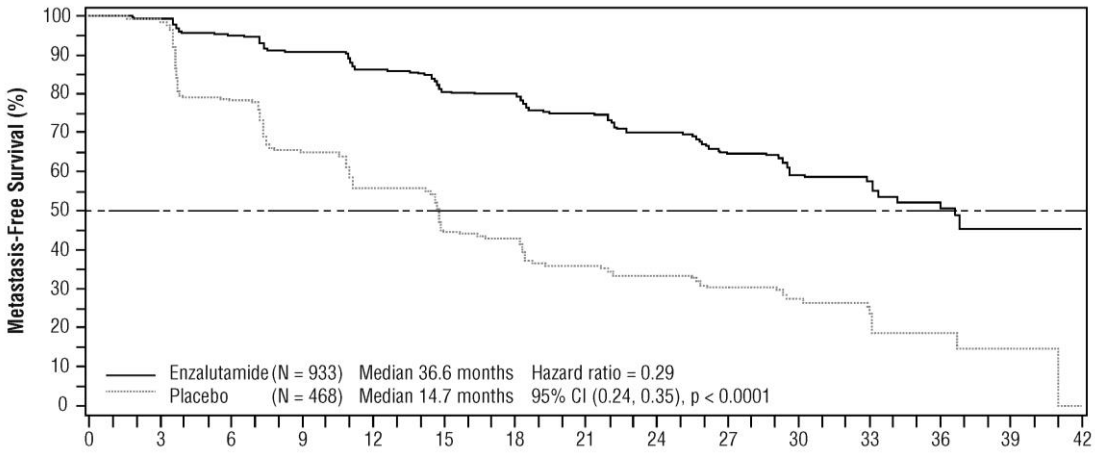


Figure 1: Kaplan-Meier Curves of metastasis-free survival in the PROSPER study (intent-to-treat analysis)

Overall survival was evaluated at two prespecified interim analyses to date; the first at the time of final MFS (n = 165) [HR = 0.80 (95% CI: 0.58, 1.09), p = 0.1519], and the second interim analysis (n = 288) [HR = 0.83 (95% CI: 0.65, 1.06), p = 0.1344]. The median was not reached in either treatment group and neither analysis showed a statistically significant difference between treatment arms.

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.

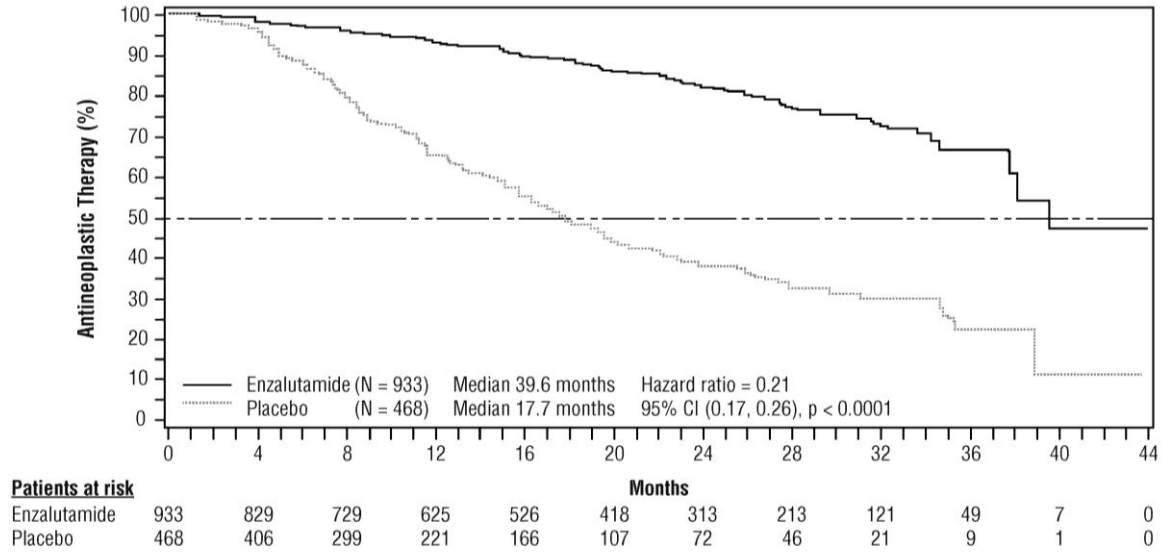


Figure 2: Kaplan-Meier curves of time to first use of new antineoplastic therapy in the PROSPER study (intent-to-treat analysis)

MDV3100-09 (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 radiographic progression, PSA 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 pre-specified patient subgroups. For the non-metastatic subgroup (N = 139) a total of 19 out of 70 (27.1%) patients treated with enzalutamide and 49 out of 69 (71.0%) patients treated with bicalutamide had PFS events (68 total events). The hazard ratio was 0.24 (95% CI: 0.14, 0.42) and the median time to a PFS event was not reached in the enzalutamide group versus 8.6 months in the bicalutamide group.

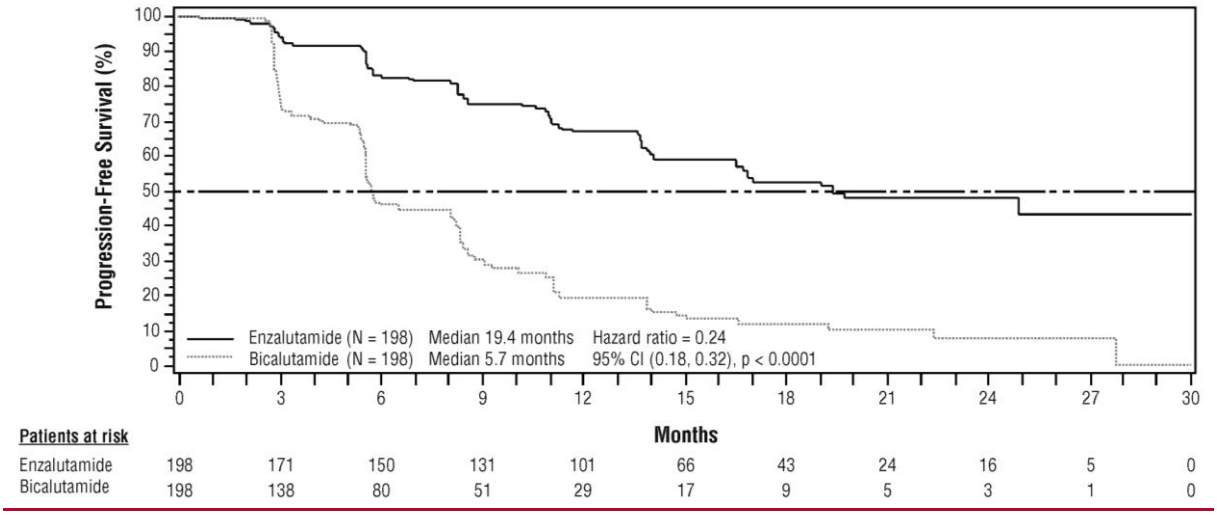


Figure 3: Kaplan-Meier Curves of progression-free survival in the STRIVE study (intent-to-treat analysis)

9785-CL-0222 (TERRAIN) study (chemotherapy-naïve patients with metastatic CRPC)

The TERRAIN study enrolled 375 chemo- and antiandrogen-therapy naïve patients with metastatic CRPC who were randomised to receive either enzalutamide at a dose of 160 mg once daily (N = 184) or bicalutamide at a dose of 50 mg once daily (N = 191). Median PFS was 15.7 months for patients on enzalutamide versus 5.8 months for patients on bicalutamide [HR = 0.44 (95% CI: 0.34, 0.57), p < 0.0001]. Progression-free survival 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.

MDV3100-03 (PREVAIL) study (chemotherapy-naïve patients with metastatic CRPC)

A total of 1717 asymptomatic or mildly symptomatic chemotherapy-naïve patients were randomized 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 medicinal products 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% 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 Tumors (RECIST v 1.1) criteria (for soft tissue lesions). Analysis of rPFS utilized 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 [~~Hazard Ratio~~ HR = 0.706~~,~~ (95% CI: 0.~~596~~60; 0.~~837~~84), p < 0.0001].. An updated survival analysis was conducted when 784 deaths were observed. Results from this analysis were consistent with those from the interim analysis (Table ~~2~~3, Figure ~~1~~4). At the updated analysis 52% of enzalutamide-treated and 81% of placebo-treated patients had received subsequent therapies for metastatic CRPC that may prolong overall survival.

Table ~~2~~3: 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%)
Median survival, months (95% CI)	32.4 (30.1, NR)	30.2 (28.0, NR)
P-value[1~~a~~]	p < 0.0001	
Hazard ratio (95% CI)[2~~b~~]	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~~a~~]	p = 0.0002	
Hazard ratio (95% CI)[2~~b~~]	0.77 (0.67, 0.88)	

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.

~~[a] P-value is derived from an unstratified log-rank test~~

~~[b] Hazard Ratio is derived from an unstratified proportional hazards model. Hazard ratio < 1 favours enzalutamide~~

~~NR, not reached.~~

~~**Figure 1: Kaplan-Meier overall survival curves based on updated survival analysis in the PREVAIL study (intent-to-treat analysis)**~~

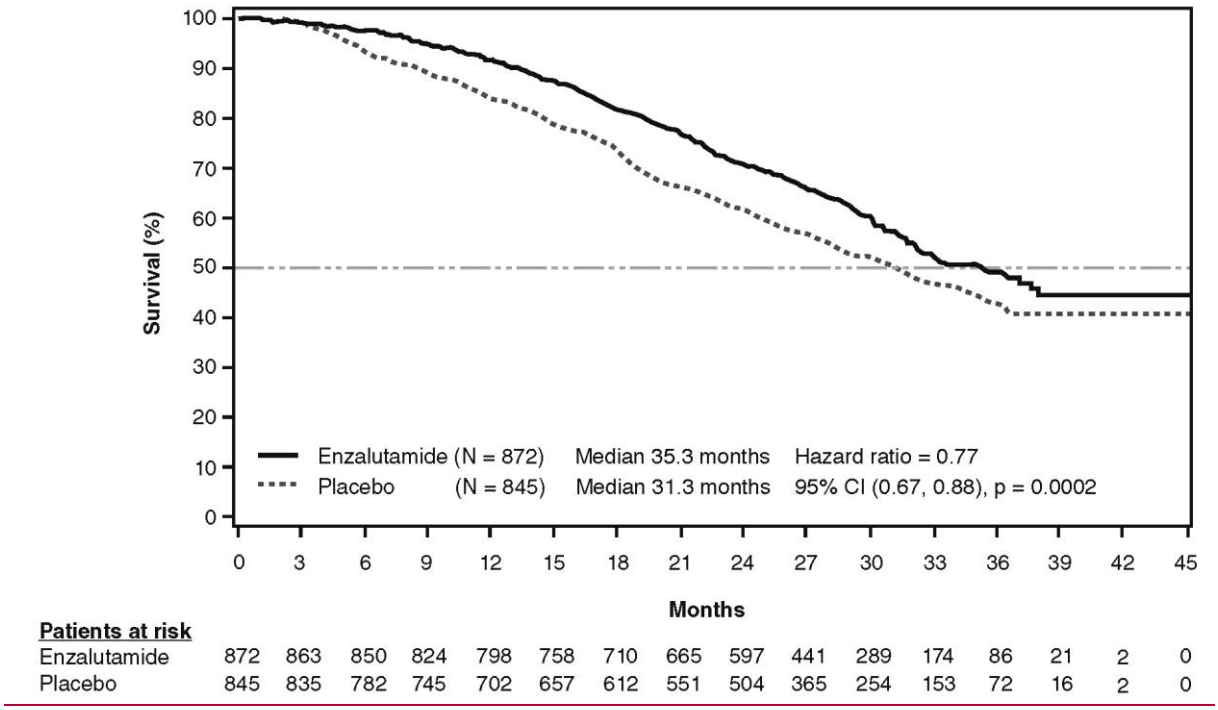


Figure 4: Kaplan-Meier curves of overall survival based on updated survival analysis in the PREVAIL study (intent-to-treat analysis)

~~**Figure 2: Updated overall survival analysis by subgroup: Hazard ratio and 95% confidence interval in the PREVAIL study (intent-to-treat analysis)**~~

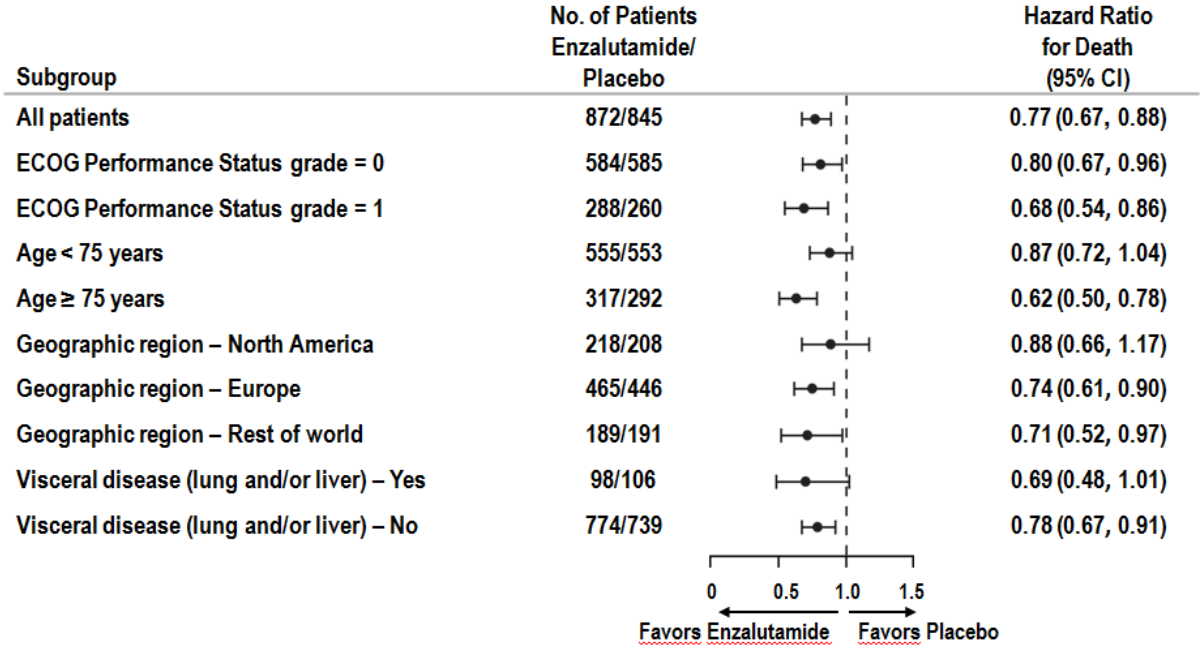
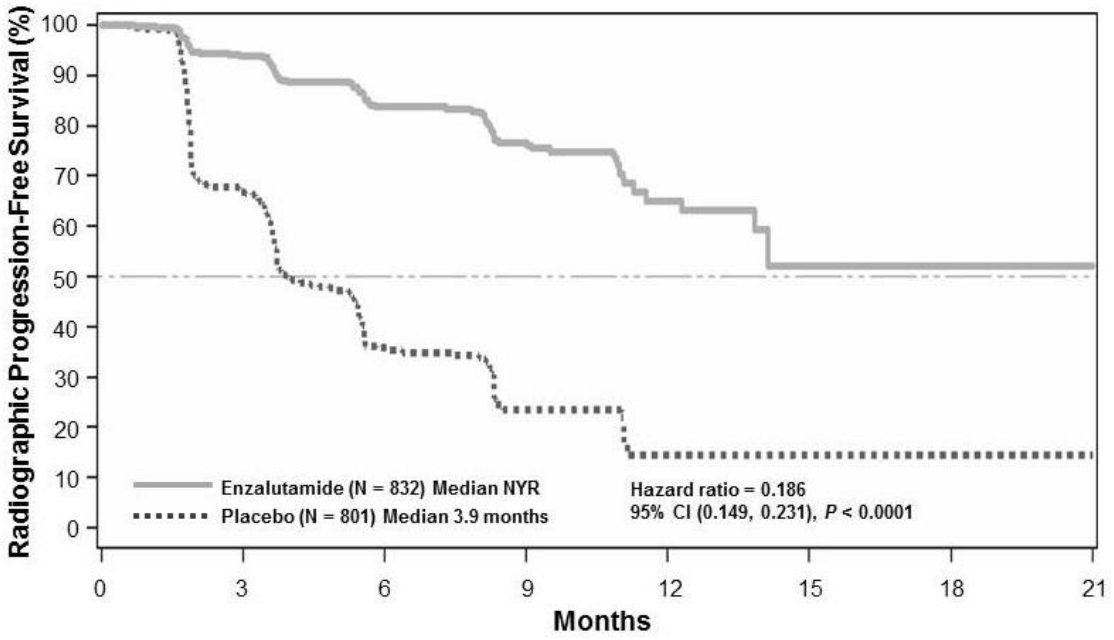


Figure 5: Updated overall survival analysis by subgroup: Hazard ratio and 95% confidence interval in the PREVAIL study (intent-to-treat analysis)

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.~~186~~19 (95% CI: 0.~~149~~15, 0.23~~1~~), 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 ~~3~~6). 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.~~307~~ 31 (95% CI: 0.~~267~~27, 0.35~~3~~), p < 0.0001]. The median rPFS was 19.7 months in the enzalutamide group and 5.4 months in the placebo group.

~~**Figure 3: Kaplan-Meier curves of radiographic progression-free survival in the PREVAIL study (intent-to-treat analysis)**~~



Patients at risk

Enzalutamide	832	514	256	128	34	5	1	0
Placebo	801	305	79	20	5	0	0	0

At the time of the primary analysis there were 1,633 patients randomised.

Figure 6: 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 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.~~169~~17, (95% CI: 0.~~147~~15, 0.~~195~~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.

[…]

CRPC2 (AFFIRM) study (patients with metastatic CRPC who previously received chemotherapy)

[…]

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~~randomization~~). Most (91%) patients had metastases in bone and 23% had visceral lung and/or liver involvement. At study entry, 41% of randomized 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 (see section 4.8) and medicinal products 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 enzalutamide compared to placebo (Table ~~3~~ 4 and Figures ~~4~~ 7 and ~~5~~8).

Table ~~3~~4: Overall survival of patients treated with either enzalutamide 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~~ P-value[1]~~[a]~~	p < 0.0001	
Hazard ratio (95% CI)[2]~~[b]~~	0.63~~1~~ (0.~~529~~53, 0.75~~2~~)	

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 enzalutamide.

~~[a] 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)~~

~~[b] Hazard Ratio is derived from a stratified proportional hazards model. Hazard ratio < 1 favours enzalutamide~~

~~NR, not reached.~~

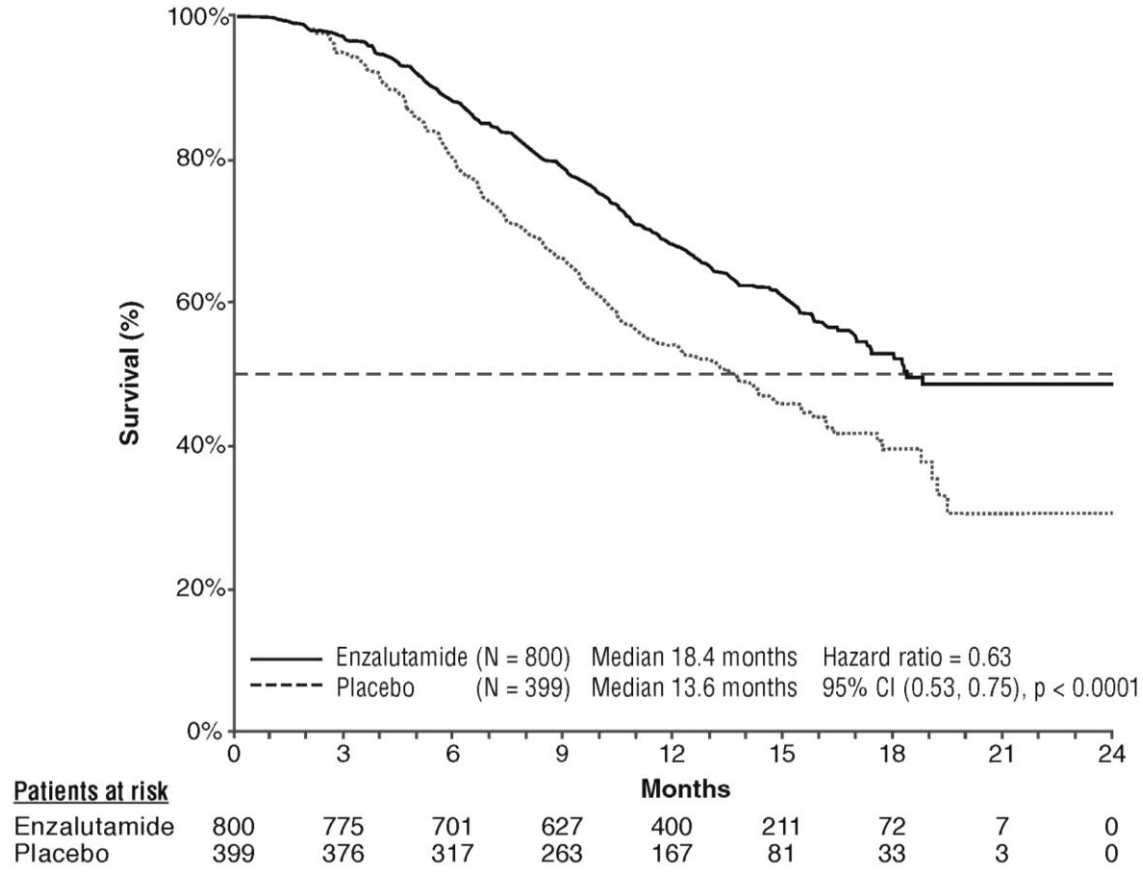
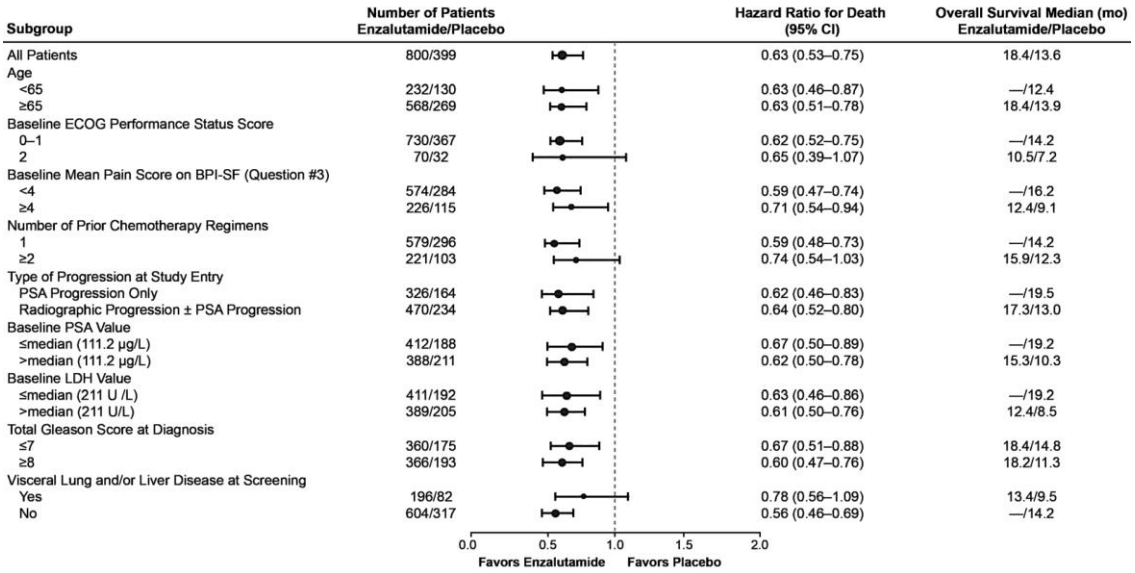


Figure 7: Kaplan-Meier curves of overall survival in the AFFIRM study (intent-to-treat analysis)

~~**Figure 5: Overall survival by subgroup in the AFFIRM study – Hazard ratio and 95% confidence interval**~~



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

Figure 8: 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 (PSA progression, radiographic progression-free survival, and time to first skeletal-related event) favoured enzalutamide and were statistically significant after adjusting for multiple testing.

Radiographic progression-free survival as assessed by the investigator using RECIST v 1.1 for soft tissue and appearance of 2 or more bone lesions in bone scan was 8.3 months for patients treated with enzalutamide and 2.9 months for patients who received placebo ~~(~~[HR = 0.404, (95% CI: ~~[~~0.350, 0.466~~47~~~~1;~~), 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.

Confirmed PSA decline of 50% or 90% were 54.0% and 24.8%, respectively, for patients treated with enzalutamide and 1.5% and 0.9%, respectively, for patients who received placebo (p < 0.0001). The median time to PSA progression was 8.3 months for patients treated with enzalutamide and 3.0 months for patients who received placebo ~~(~~[HR = 0.~~248~~25, (95% CI: ~~[~~0.204, 0.303~~];~~), p < 0.0001~~).~~].

The median time to first skeletal-related event was 16.7 months for patients treated with enzalutamide and 13.3 months for patients who received placebo ~~(~~[HR = 0.~~688~~69, (95% CI: ~~[~~0.~~566~~57, 0.~~835~~34~~];~~), 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 ~~145~~ 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 ~~69~~ 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~~Older people~~
Of the 3179~~1671~~ patients in the controlled clinical~~phase 3~~ trials who received enzalutamide, 2518~~1261~~ patients (~~75~~79%) were 65 years and over and ~~516~~ 1162 patients (~~31~~37%) 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

[…]

Race
Most patients in the controlled clinical trials (> 7484%) were Caucasian. Based on pharmacokinetic data from a studiesy in Japanese and Chinese patients with prostate cancer, there were no clinically relevant differences in exposure among the populationsbetween Japanese and Caucasians. There are insufficient data to evaluate potential differences in the pharmacokinetics of enzalutamide in other races.

[…]

5.3 Preclinical safety data

[…]

Enzalutamide was negative for genotoxicity in a standard battery of *in vitro* and *in vivo* tests.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. Long-term animal studies to evaluate the carcinogenic potential of enzalutamide have not been conducted. 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 per day (AUC_{24h} ~317 µg•h/mL), which resulted in plasma exposure levels similar to the clinical exposure (AUC_{24h} 322 µg•h/mL) in mCRPC patients receiving 160 mg, daily.

Daily dosing of rats for two years with enzalutamide at 10–100 mg/kg/day produced an increased incidence of several, mostly benign, tumour types. The most prominent of these were benign Leydig cell tumours, urothelium papilloma, and carcinoma of urinary bladder. Benign Leydig cell tumours are expected based on the pharmacological properties of this antiandrogen drug and not considered relevant to humans. Some urothelium papilloma and carcinoma of urinary bladder is expected in rats based on the horizontal structure of the rat urinary bladder, which can encounter concentrated urine and prolonged irritation from calculi. In the study, calculi and crystals were observed in rat urinary bladders. However, no obvious mechanistic rationale to explain specifically this malignancy can be established, and taking into account that exposure levels, based on AUC, achieved in the study, for enzalutamide plus its metabolites, were less than or similar to those in prostate cancer patients at the recommended dose of 160 mg/day, urinary bladder carcinogenicity potential of enzalutamide in humans cannot be excluded. Other tumours, which are also potentially related to the primary pharmacology include fibroadenoma of mammary glands and benign thymoma of thymus in males, benign granulosa cell tumours of ovaries in females, and adenoma of pituitary pars distalis in both sexes. The exposure levels achieved in this study in male rats at Week 26 at 100 mg/kg per day for enzalutamide plus its active metabolites M1 and M2 (AUC_{24}: enzalutamide ~457 µg•h/mL, M1 ~321 µg•h/mL, M2 ~35 µg•h/mL) were less than or similar to those in prostate cancer patients at the recommended dose (160 mg/day) of enzalutamide (AUC_{24}: enzalutamide ~322 µg•h/mL, M1 ~193 µg•h/mL, M2 ~278 µg•h/mL).

[…]

6.6 Special precautions for disposal and other handling

Xtandi should not be handled by persons other than the patient and his caregivers, and especially not by women who are or may become pregnant. The soft capsules should not be dissolved or opened.

להלן העדכונים בעלון לצרכן (טקסט מסומן ירוק משמעותו עדכון, טקסט מסומן בצהוב משמעותו החמרה):

[...]

1. למה מיועדת התרופה?

התרופה מיועדת לטיפול בגברים עם סרטן ערמונית אשר אינו מגיב עוד לטיפול הורמונלי להורדת רמת ההורמון הגברי, טסטוסטרון (androgen deprivation therapy).

[...]

2. לפני השימוש בתרופה

[...]

אזהרות מיוחדות הנוגעות לשימוש בתרופה
- פרכוסים:
פרכוסים דווחו ב- 4 מקרים לכל 1,000 מטופלים שנטלו את אקסטנדי, ובפחות מ- 1 מתוך 1,000 מטופלים שקיבלו פלצבו (ראה "אם אתה לוקח, או אם לקחת לאחרונה ,תרופות אחרות כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח" בהמשך סעיף זה וסעיף 4 "תופעות לוואי").

[...]

- לפני הטיפול באקסטנדי ספר לרופא אם:
  - הנך נוטל תרופות למניעת קרישי דם (כמו וורפרין, אצנוקומרול, קלופידוגרל).
  - הנך משתמש בכימותרפיה כגון דוסטאקסל.
  - הנך סובל מבעיות בתפקוד הכבד.
  - הנך סובל מבעיות בתפקוד הכליות.
  - אתה סובל מאחד המצבים הבאים: בעיה בלב או בכלי הדם, כולל בעיות בקצב הלב (אריתמיה), או באם הנך מטופל בתרופות למצבים האלה. עלולה להיות עליה בסיכון לבעיות בקצב הלב בזמן השימוש באקסטנדי.

רגישות (אלרגיה) לאנזלוטמיד עלולה לגרום לפריחה או להתנפחות של הפנים, הלשון, השפתיים או הגרון. אם אתה רגיש לאנזלוטמיד או לכל מרכיב אחר בתרופה זו - אל תיקח אקסטנדי.

[...]

- תרופות שיכולות להשפיע על יעילותה של אקסטנדי או שאקסטנדי יכולה להשפיע על יעילותן כמו:
  - תרופות להורדת כולסטרול (כמו גמפיברוזיל, אטורבסטאטין, סימבאסטאטין)
  - תרופות לטיפול בכאב (כמו פנטניל, טרמדול)
  - תרופות לטיפול בסרטן (כמו קאבאזיטאקסל)
  - תרופות לטיפול באפילפסיה (כמו קארבאמאזפין, קלונאזפאם, פניטואין, פרימידון, חומצה ולפרואית)
  - תרופות לטיפול בהפרעות פסיכיאטריות מסוימות כמו חרדה חמורה או סכיזופרניה (כמו דיאזפאם, מידזולם, האלופרידול)
  - תרופות לטיפול בהפרעות שינה (כמו זולפידם)
  - תרופות לטיפול בבעיות בלב או להורדת לחץ הדם (כמו ביסופרולול, דיגוקסין, דילטיאזם, פילודיפין, ניקרדיפין, ניפדיפין, פרופרנולול, וראפאמיל)
  - תרופות לטיפול במחלות חמורות הקשורות לדלקות (כמו דקסאמתאזון, פרדניזולון).
  - תרופות לטיפול ב-HIV (כמו אינדינאביר, ריטונאביר)
  - תרופות לטיפול בזיהומים חיידקיים (כמו קלאריתרומיצין, דוקסיציקלין)
  - תרופות לטיפול בהפרעות בבלוטת התריס (כמו לבותירוקסין)
  - תרופות לטיפול בשיגדון (כמו קולכיצין)
  - תרופות לטיפול בבעיות בקיבה (כמו אומפרזול)
  - תרופות למניעת מצבים לבבים או שבץ מוחי (כמו דביגטרן אטיקסילאט)
  - תרופות למניעה של דחיית שתל (כמו טקרולימוס)

[...]

הריון, הנקה ופוריות:

- **אקסטנדי אינה מיועדת לשימוש בנשים.** התרופה עלולה לגרום נזק לעובר או סיכון לאובדן ההריון אם היא נלקחת ע"י אישה בהריון. אין לקחת את התרופה ע"י נשים בהריון, נשים שמתכננות להיכנס להריון או נשים מניקות.
- התרופה עלולה להשפיע על פוריות הגבר.
- אם אתה מקיים יחסי מין עם אישה שיכולה להיכנס להריון, השתמש בקונדום ובאמצעי מניעה יעיל אחר במהלך הטיפול בתרופה ולמשך שלושת החודשים שלאחר סיום הטיפול בתרופה. אם אתה מקיים יחסי מין עם אישה בהריון השתמש בקונדום על מנת להגן על העובר.
- נשים שהן חלק מהצוות המטפל ראו סעיף 3 "כיצד תשתמש בתרופה" לאופן הטיפול והשימוש.

נהיגה ושימוש במכונות: לתרופה זו השפעה בינונית על היכולת שלך לנהוג או להשתמש בכלים או מכונות מכיוון שתופעות הלוואי של התרופה כוללות אירועים פסיכיאטריים ונוירולוגיים, כולל פרכוס. אם אתה בסיכון מוגבר לפרכוסים דבר עם הרופא שלך.

[...]

3. כיצד תשתמש בתרופה?

[...]

אופן השימוש:

- יש לבלוע את הכמוסה הרכה בשלמותה עם מים.
- אין ללעוס, להמיס או לפתוח את הכמוסה הרכה לפני הבליעה.
- ניתן לקחת את התרופה עם או בלי אוכל.
- אקסטנדי אסורה במגע לאנשים שאינם המטופלים או הצוות המטפל, ובמיוחד לנשים בהיריון או אשר עשויות להרות.

[...]

4. תופעות לוואי.

[...]

פרכוסים: דווחו ב- 4 מטופלים מתוך 1,000 שלקחו אקסטנדי ובפחות מ-1 מתוך 1,000 מטופלים שקיבלו פלצבו. הסיכון לפרכוסים מוגבר באם אתה נוטל מינון גבוה מהמינון המומלץ, אם אתה נוטל תרופות מסוימות נוספות או באם יש לך גורמי סיכון לפרכוסים.

[...]

תופעות לוואי נוספות:

- תופעות לוואי שכיחות מאוד (מופיעות ביותר מ-1 מתוך 10 מטופלים):
  - שברים בעצמות.
  - גלי חום.
  - עייפות.
  - לחץ דם גבוה.
- תופעות לוואי שכיחות (מופיעות ב-עד 1 מתוך 10 מטופלים):
  - כאבי ראש.
  - נפילות.
  - תחושת חרדה.
  - עור יבש.
  - גירוד.
  - קשיי זיכרון.
  - חסימה של העורקים בלב (מחלת לב איסכמית).

- הגדלת חזה בגברים (גינקומסטיה).
- סימפטומים של תסמונת רגל לא שקטה (דחף בלתי נשלט להזיז חלק מהגוף, בד"כ הרגל).
- ירידה בריכוז.
- שיכחה.

- תופעות לוואי לא שכיחות (מופיעות ב-עד 1 מתוך 100 מטופלים):
- הזיות.
- קושי לחשוב באופן צלול.
- ירידה בספירת כדוריות הדם הלבנות.

- תופעות לוואי בשכיחות לא ידועה:
- כאבי שרירים, התכווצויות שרירים, חולשת שרירים, כאבי גב.
- שינויים באק"ג (הארכת QT).
- כאבי בטן, כולל בחילות.
- פריחה.
- הקאות.
- התנפחות של הפנים, השפתיים, הלשון ו/או הגרון.
- ירידה בספירת טסיות דם (המעלה את הסיכון לדימום או חבלות).
- שלשול.

ניתן לדווח על תופעות לוואי למשרד הבריאות באמצעות לחיצה על הקישור "דיווח על תופעות לוואי עקב טיפול תרופתי" שנמצא בדף הבית של אתר משרד הבריאות (www.health.gov.il) המפנה לטופס המקוון לדיווח על תופעות לוואי, או ע"י כניסה לקישור:
https://sideeffects.health.gov.il

[...]

6. מידע נוסף

[...]

המרכיבים של מעטפת הכמוסה הרכה הם:

gelatin, sorbitol sorbitan solution, glycerol, titanium dioxide (E171), and purified water.

[...]

העלונים לרופא ולצרכן נשלחו למאגר התרופות שבאתר משרד הבריאות www.health.gov.il לצורך העלאתם לאתר וניתן לקבלם מודפסים על ידי פניה לבעל הרישום אסטלס פארמה אינטרנשונל בי.וי., ת.ד. 11458, ראש העין.

בברכה
גאי וגנר
רוקח ממונה