HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XTANDI safely and effectively. See full prescribing information for XTANDI.

XTANDI® (enzalutamide) capsules, for oral use
XTANDI® (enzalutamide) tablets, for oral use
Initial U.S. Approval: 2012

RECENT MAJOR CHANGES

Dosage and Administration (2.1)	1/2025
Warnings and Precautions (5.7)	1/2025

INDICATIONS AND USAGE

XTANDI is an androgen receptor inhibitor indicated for the treatment of patients with:

- castration-resistant prostate cancer. (1)
- metastatic castration-sensitive prostate cancer. (1)
- non-metastatic castration-sensitive prostate cancer with biochemical recurrence at high risk for metastasis. (1)

DOSAGE AND ADMINISTRATION

- Take XTANDI 160 mg administered orally once daily with or without food. (2.1)
- Advise patients to take each capsule or tablet whole with a sufficient amount of water to ensure that all medication is successfully swallowed. (2.1, 5.7)
- Patients receiving XTANDI for castration-resistant prostate cancer, or metastatic castration sensitive prostate cancer should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy. (2.1)
- Patients with non-metastatic castration-sensitive prostate cancer with biochemical recurrence at high risk for metastasis may be treated with or without a GnRH analog. (2.1)

DOSAGE FORMS AND STRENGTHS

- Capsules: 40 mg (3)
- Tablets: 40 mg, 80 mg (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Seizure occurred in 0.6% of patients receiving XTANDI. In patients with predisposing factors, seizures were reported in 2.2% of patients. Permanently discontinue XTANDI in patients who develop a seizure during treatment. (5.1)
- Posterior reversible encephalopathy syndrome (PRES): Discontinue XTANDI. (5.2)
- Hypersensitivity: Discontinue XTANDI. (5.3)
- Ischemic Heart Disease: Optimize management of cardiovascular risk factors. Discontinue XTANDI for Grade 3-4 adverse reactions (5.4)
- Falls and Fractures: Evaluate patients for fracture and fall risk, and treat patients with bone-targeted agents according to established guidelines. (5.5)
- Embryo-Fetal Toxicity: XTANDI can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception. (5.6, 8.1, 8.3)
- Severe Dysphagia or Choking Related to Product Size: Consider using smaller XTANDI tablet(s) in patients who have difficulty swallowing. Discontinue XTANDI for patients who cannot swallow capsules or tablets. (2.1, 5.7)

ADVERSE REACTIONS

The most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients are musculoskeletal pain, fatigue, hot flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture, and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP2C8 Inhibitors: Avoid strong CYP2C8 inhibitors. If coadministration cannot be avoided, reduce the dosage of XTANDI. (2.3, 7.1)
- Strong CYP3A4 Inducers: Avoid strong CYP3A4 inducers. If coadministration cannot be avoided, increase the dosage of XTANDI. (2.3, 7.1)
- Avoid coadministration with certain CYP3A4, CYP2C9, or CYP2C19 substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate. In cases where active metabolites are formed, there may be increased exposure to the active metabolites. (7.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 3/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XTANDI® is indicated for the treatment of patients with:

- castration-resistant prostate cancer (CRPC)
- metastatic castration-sensitive prostate cancer (mCSPC)
- non-metastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR)

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosage of XTANDI is 160 mg administered orally once daily with or without food *[see Clinical Pharmacology (12.3)]* until disease progression or unacceptable toxicity.

Advise patients to take each capsule or tablet whole with a sufficient amount of water to ensure that all medication is successfully swallowed. Do NOT chew, dissolve, or open the capsules. Do NOT cut, crush, or chew the tablets.

Patients with CRPC or mCSPC receiving XTANDI should also receive a gonadotropic-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

Patients with nmCSPC with high-risk BCR may be treated with XTANDI with or without a GnRH analog. For patients who receive XTANDI with or without a GnRH analog, treatment can be suspended if PSA is undetectable (< 0.2 ng/mL) after 36 weeks of therapy. Reinitiate treatment 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 *[see Clinical Studies (14)]*.

2.2 Dosage Modifications for Adverse Reactions

If a patient experiences a ≥ Grade 3 or an intolerable adverse reaction, withhold XTANDI 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 *[see Warnings and Precautions (5.1, 5.2)]*.

2.3 Dosage Modifications for Drug Interactions

Strong CYP2C8 Inhibitors

Avoid the coadministration of strong CYP2C8 inhibitors. If the coadministration of a strong CYP2C8 inhibitor cannot be avoided, reduce the XTANDI dosage to 80 mg once daily. If the coadministration of the strong inhibitor is discontinued, increase the XTANDI dosage to the dosage used prior to initiation of the strong CYP2C8 inhibitor *[see Clinical Pharmacology (12.3)]*.

Strong CYP3A4 Inducers

Avoid the coadministration of strong CYP3A4 inducers. If the coadministration of a strong CYP3A4 inducer cannot be avoided, increase the XTANDI dosage from 160 mg to 240 mg orally once daily. If the coadministration of the strong CYP3A4 inducer is discontinued, decrease the XTANDI dosage to the dosage used prior to initiation of the strong CYP3A4 inducer *[see Clinical Pharmacology (12.3)]*.

3 DOSAGE FORMS AND STRENGTHS

XTANDI 40 mg capsules are white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ.

XTANDI 40 mg tablets are yellow, round, film-coated and debossed with E 40.

XTANDI 80 mg tablets are yellow, oval, film-coated and debossed with E 80.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Seizure

Seizure occurred in 0.6% of patients receiving XTANDI in eight randomized clinical trials. In these trials, patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 2250 days after initiation of XTANDI. Patients experiencing seizure were permanently discontinued from therapy, and all seizure events resolved.

In a single-arm trial designed to assess the risk of seizure in patients with pre-disposing factors for seizure, 8 of 366 (2.2%) XTANDI-treated patients experienced a seizure. Three of the 8 patients experienced a second seizure during continued treatment with XTANDI after their first seizure resolved. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following pre-disposing factors: the use of medications that may lower the seizure threshold (~ 54%), history of traumatic brain or head injury (~ 28%), history of cerebrovascular accident or transient ischemic attack (~ 24%), and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, past history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection (all < 5%). Approximately 17% of patients had more than one risk factor.

Advise patients of the risk of developing a seizure while receiving XTANDI and of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others.

Permanently discontinue XTANDI in patients who develop a seizure during treatment.

5.2 Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI *[see Adverse Reactions (6.2)]*. PRES is a neurological disorder which can present with rapidly evolving symptoms including seizure, headache, lethargy, 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). Discontinue XTANDI in patients who develop PRES.

5.3 Hypersensitivity

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with enzalutamide in eight randomized clinical trials. Pharyngeal edema has been reported in post-marketing cases. Advise patients who experience any symptoms of hypersensitivity to temporarily discontinue XTANDI and promptly seek medical care. Permanently discontinue XTANDI for serious hypersensitivity reactions.

5.4 Ischemic Heart Disease

In the combined data of five randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (3.5% vs 2%). Grade 3-4 ischemic events occurred in 1.8% of patients on the XTANDI arm compared to 1.1% on the placebo arm. Ischemic events led to death in 0.4% of patients on the XTANDI arm compared to 0.1% on the placebo arm.

Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Discontinue XTANDI for Grade 3-4 ischemic heart disease.

5.5 Falls and Fractures

Falls and fractures occurred in patients receiving XTANDI. Evaluate patients for fracture and fall risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

In the combined data of five randomized, placebo-controlled clinical studies, falls occurred in 12% of patients treated with XTANDI compared to 6% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 13% of patients treated with XTANDI and in 6% of patients treated with placebo. Grade 3-4 fractures occurred in 3.4% of patients treated with XTANDI and in 1.9% of patients treated with placebo. The median time to onset of fracture was 420 days (range: 1 to 2348 days) for patients treated with XTANDI. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the studies.

5.6 Embryo-Fetal Toxicity

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI *[see Use in Specific Populations (8.1, 8.3)]*.

5.7 Dysphagia or Choking

Severe dysphagia or choking, including events that could be life-threatening requiring medical intervention or fatal, can occur due to XTANDI product size. Advise patients to take each capsule or tablet whole with a sufficient amount of water to ensure that all medication is successfully swallowed. Consider use of a smaller tablet size of XTANDI in patients who have difficulty swallowing. Discontinue XTANDI for patients who cannot swallow capsules or tablets.

6 ADVERSE REACTIONS

The following is discussed in more detail in other sections of the labeling:

- Seizure *[see Warnings and Precautions (5.1)]*
- Posterior Reversible Encephalopathy Syndrome (PRES) *[see Warnings and Precautions (5.2)]*
- Hypersensitivity *[see Warnings and Precautions (5.3)]*
- Ischemic Heart Disease *[see Warnings and Precautions (5.4)]*
- Falls and Fractures *[see Warnings and Precautions (5.5)]*
- Dysphagia or Choking *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in WARNINGS and PRECAUTIONS reflect eight randomized, controlled trials [AFFIRM, PREVAIL, TERRAIN, PROSPER, ARCHES, EMBARK, Asian PREVAIL (NCT02294461), and STRIVE (NCT01664923)] that were pooled to conduct safety analyses in patients with CRPC (N = 3651), mCSPC (N = 752), or nmCSPC with high-risk BCR (N = 707) treated with XTANDI. Patients received XTANDI 160 mg (N = 5110) or placebo orally once daily (N = 2829) or bicalutamide 50 mg orally once daily (N = 387). In these eight trials, the median duration of treatment was 22.1 months (range: < 0.1 to 95.0) in patients that received XTANDI.

In five placebo-controlled trials (AFFIRM, PROSPER, PREVAIL, ARCHES, and EMBARK), the median duration of treatment was 19.4 months (range: < 0.1 to 90.4) in the XTANDI group *[see Clinical Studies (14)]*. In these five trials, the most common adverse reactions (≥ 10%) that occurred more frequently (≥ 2% over placebo) in the XTANDI-treated patients were musculoskeletal pain, fatigue, hot flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture and headache.

AFFIRM: XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy

AFFIRM enrolled 1199 patients with metastatic 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. Discontinuations due to adverse reactions were reported for 16% of XTANDI-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% higher 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]	51	9	44	9
Peripheral Edema	15	1	13	0.8
Musculoskeletal and Connective Tissue Disorders				
Back Pain	26	5	24	4
Arthralgia	21	2.5	17	1.8
Musculoskeletal Pain	15	1.3	12	0.3
Muscular Weakness	10	1.5	7	1.8
Musculoskeletal Stiffness	2.6	0.3	0.3	0
Gastrointestinal Disorders				
Diarrhea	22	1.1	18	0.3
Vascular Disorders				
Hot Flush	20	0	10	0
Hypertension	6	2.1	2.8	1.3

	XTANDI (N = 800)		Placebo (N = 399)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Nervous System Disorders				
Headache	12	0.9	5	0
Dizziness[3]	9	0.5	7	0.5
Spinal Cord Compression and Cauda Equina Syndrome	7	7	4.5	3.8
Paresthesia	7	0	4.5	0
Mental Impairment Disorders[4]	4.3	0.3	1.8	0
Hypoesthesia	4	0.3	1.8	0
Infections and Infestations				
Upper Respiratory Tract Infection[5]	11	0	6	0.3
Lower Respiratory Tract And Lung Infection[6]	8	2.4	4.8	1.3
Psychiatric Disorders				
Insomnia	9	0	6	0.5
Anxiety	6	0.3	4	0
Renal and Urinary Disorders				
Hematuria	7	1.8	4.5	1
Pollakiuria	4.8	0	2.5	0
Injury, Poisoning and Procedural Complications				
Fall	4.6	0.3	1.3	0
Non-pathologic Fractures	4	1.4	0.8	0.3
Skin and Subcutaneous Tissue Disorders				
Pruritus	3.8	0	1.3	0
Dry Skin	3.5	0	1.3	0
Respiratory Disorders				
Epistaxis	3.3	0.1	1.3	0.3

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: XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

PREVAIL enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse reactions were reported for 6% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in PREVAIL that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 2. Adverse Reactions in PREVAIL

	XTANDI (N = 871)		Placebo (N = 844)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
General Disorders				
Asthenic Conditions[2]	47	3.4	33	2.8
Peripheral Edema	12	0.2	8	0.4
Musculoskeletal and Connective Tissue Disorders				
Back Pain	29	2	22	3
Arthralgia	21	1.6	16	1.1
Gastrointestinal Disorders				
Constipation	23	0.7	17	0.4
Diarrhea	17	0.3	14	0.4
Vascular Disorders				
Hot Flush	18	0.1	8	0
Hypertension	14	7	4.1	2.3
Nervous System Disorders				
Dizziness[3]	11	0.3	7	0
Headache	11	0.2	7	0.4
Dysgeusia	8	0.1	3.7	0
Mental Impairment Disorders[4]	6	0	1.3	0.1
Restless Legs Syndrome	2.1	0.1	0.4	0
Respiratory Disorders				
Dyspnea[5]	11	0.6	8	0.6
Infections and Infestations				
Upper Respiratory Tract Infection[6]	16	0	11	0
Lower Respiratory Tract And Lung Infection[7]	8	1.5	4.7	1.1
Psychiatric Disorders				
Insomnia	8	0.1	6	0
Renal and Urinary Disorders				
Hematuria	9	1.3	6	1.3
Injury, Poisoning and Procedural Complications				
Fall	13	1.6	5	0.7
Non-Pathological Fracture	9	2.1	3	1.1
Metabolism and Nutrition Disorders				
Decreased Appetite	19	0.3	16	0.7
Investigations				
Weight Decreased	12	0.8	8	0.2
Reproductive System and Breast Disorders				
Gynecomastia	3.4	0	1.4	0

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: 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 reaction as the primary reason were reported for 8% of XTANDI-treated patients and 6% 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	7	4.2
Gastrointestinal Disorders				
Nausea	14	0	18	0
Constipation	13	1.1	13	0.5
Diarrhea	12	0	9	1.1
Infections and Infestations				
Upper Respiratory Tract Infection[4]	12	0	6	0.5
Investigational				
Weight Loss	11	0.5	8	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: 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 randomized 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 reactions. 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 reactions 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 reaction as the primary reason were reported for 9% of XTANDI-treated patients and 6% of placebo-treated patients. Of these, the most common adverse reaction 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	10	0.2	3.9	0.2
Nervous System Disorders				
Dizziness[2]	12	0.5	5	0
Headache	9	0.2	4.5	0
Cognitive and Attention Disorders[3]	4.6	0.1	1.5	0
Vascular Disorders				
Hot Flush	13	0.1	8	0
Hypertension	12	4.6	5	2.2
Gastrointestinal Disorders				
Nausea	11	0.3	9	0
Constipation	9	0.2	7	0.4
General Disorders and Administration Site Conditions				
Asthenic Conditions[4]	40	4	20	0.9
Investigations				
Weight Decreased	6	0.2	1.5	0
Injury, Poisoning and Procedural Complications				
Fall	11	1.3	4.1	0.6
Fractures[5]	10	2	4.9	1.7
Psychiatric Disorders				
Anxiety	2.8	0.2	0.4	0

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: XTANDI versus Placebo in Metastatic CSPC Patients

ARCHES randomized 1150 patients with mCSPC, of whom 1146 received at least one dose of study drug. All patients received either a gonadotropin-releasing hormone (GnRH) analog concurrently or had bilateral orchiectomy. Patients received either XTANDI at a dose of 160 mg once daily (N = 572) or placebo (N = 574). 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.

Overall, 10 patients (1.7%) receiving XTANDI died from adverse reactions. The reasons for death in ≥ 2 patients included heart disease (n = 3), sepsis (n = 2) and pulmonary embolism (n = 2). Eight patients (1.4%) receiving placebo died from adverse reactions. The reasons for death in ≥ 2 patients included heart disease (n = 2) and sudden death (n = 2). Grade 3 or higher adverse reactions were reported in 24% of patients treated with XTANDI. Permanent discontinuation due to adverse reactions as the primary reason was reported in 4.9% of XTANDI-treated patients and 3.7% of placebo-treated patients. The most common adverse reactions resulting in permanent discontinuation in XTANDI-treated patients were alanine aminotransferase increased, aspartate aminotransferase elevation, and seizure, each in 0.3%. The most common adverse reactions leading to permanent discontinuation in placebo-treated patients were arthralgia, and fatigue, each in 0.3%.

Dose reductions due to an adverse reaction occurred in 4.4% of patients who received XTANDI. Fatigue/asthenia was the most frequent adverse reaction requiring dose reduction in 2.1% of XTANDI-treated patients and 0.7% of placebo-treated patients.

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
Nervous System Disorders				
Cognitive and Memory Impairment[2]	4.5	0.7	2.1	0
Restless Legs Syndrome	2.4	0	0.3	0
Vascular Disorders				
Hot Flush	27	0.3	22	0
Hypertension	8	3.3	6	1.7
General Disorders and Administration Site Conditions				
Asthenic conditions[3]	24	1.7	20	1.6
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain	6	0.2	4	0.2
Injury, Poisoning and Procedural Complications				
Fractures[4]	6	1.0	4.2	1

1. CTCAE v 4.03.
2. Includes memory impairment, amnesia, cognitive disorder, dementia, disturbance in attention, transient global amnesia, dementia alzheimer's type, mental impairment, senile dementia and vascular dementia.
3. Includes asthenia and fatigue.
4. Includes Fracture related preferred terms under high level terms: fractures NEC; fractures and dislocations NEC; limb fractures and dislocations; pelvic fractures and dislocations; skull and brain therapeutic procedures; skull fractures, facial bone fractures and dislocations; spinal fractures and dislocations; thoracic cage fractures and dislocations.

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

EMBARK enrolled 1068 patients with high-risk BCR, of whom 1061 patients received at least one dose of study drug. Patients received XTANDI at a dose of 160 mg once daily concurrently with leuprolide (N = 353), XTANDI at a dose of 160 mg once daily as open-label monotherapy (N = 354), or placebo concurrently with leuprolide (N = 354). 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 (≥0.2 ng/mL) at week 36, treatment continued without suspension until permanent treatment discontinuation criteria were met.

Table 6 shows the total duration of treatment for the three treatment arms.

Table 6. Drug Treatment and Suspension in EMBARK

	XTANDI + Leuprolide (N = 353)	**Placebo + Leuprolide (N = 354)**	**XTANDI (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	18.0	16.6	9.4
Range, months	1.4 – 87.9	3.4 – 83.0	2.0 – 77.7
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 leuprolide, 8 patients (2.3%) receiving XTANDI as a single agent, and 3 patients (0.8%) receiving placebo plus leuprolide. The reason for death in ≥ 2 patients receiving XTANDI plus leuprolide was infection (n = 2), and the reason for death in ≥ 2 patients receiving XTANDI as a single agent was arterial thromboembolism (n=2).

Grade 3 or higher adverse reactions during the total duration of treatment were reported in 46% of patients treated with XTANDI plus leuprolide, 50% of patients receiving XTANDI as a single agent, and 43% of patients receiving placebo plus leuprolide. Permanent treatment discontinuation due to adverse reactions during the total duration of treatment as the primary reason was reported in 21% of patients treated with XTANDI plus leuprolide, 18% of patients receiving XTANDI as a single agent, and 10% of patients receiving placebo plus leuprolide. The most common adverse reactions resulting in permanent discontinuation included fatigue (3.4% of patients treated with XTANDI plus leuprolide, 3.7% of patients receiving XTANDI as a single agent, and 1.4% of patients receiving placebo plus leuprolide), hot flush (2% of patients treated with XTANDI plus leuprolide, 0% of patients receiving XTANDI as a single agent, and 1.1% of patients receiving placebo plus leuprolide), nausea (1.1% of patients treated with XTANDI plus leuprolide, 0.6% of patients receiving XTANDI as a single agent, and 0.3% of patients receiving placebo plus leuprolide), and cognitive disorder (1.1% of patients treated with XTANDI plus leuprolide, 1.4% of patients receiving XTANDI as a single agent, and 0.8% of patients receiving placebo plus leuprolide).

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

Table 7 shows adverse reactions reported in EMBARK that occurred at a ≥ 5% (Grade 1-4) or ≥ 2% (Grade 3-4) higher frequency in either of the XTANDI arms than in the placebo arm.

Table 7. Adverse Reactions in EMBARK

	XTANDI + Leuprolide (N = 353)		Placebo + Leuprolide (N = 354)		XTANDI (N = 354)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Nervous System Disorders						
Cognitive Disorder[2]	10	0.3	4.8	0.6	10	0.3
Syncope	4.8	4.2	2.3	1.7	2.5	2
Vascular Disorders						
Hot Flush	69	0.6	57	0.8	22	0.3
Hemorrhage[2]	20	3.4	15	1.7	21	3.7
Gastrointestinal Disorders						
Diarrhea[2]	15	0.6	9	0.8	14	0.3
Nausea	12	0.3	8	0.3	15	0.6
Investigations						
Weight Decreased	7	0.3	3.4	0	11	0.3
General Disorders and Administration Site Conditions						
Fatigue[2]	50	4	38	1.7	54	4.8
Musculoskeletal and Connective Tissue Disorders						
Musculoskeletal Pain[2]	50	4.8	43	2.3	48	3.1
Osteoarthritis	6	2.8	4.2	0.6	5	0.6
Injury, Poisoning and Procedural Complications						
Fall	21	1.1	14	1.1	16	2
Fracture[2]	18	4	13	2.5	11	2
Reproductive System and Breast Disorders						
Gynecomastia[2]	9	0	10	0	49	0.8
Breast tenderness[2]	5	0	2.8	0	35	0
Cardiac Disorders						
Ischemic Heart Disease[2]	5	4	6	3.1	9	6

1. CTCAE v 4.03.
2. Includes multiple terms.

Clinically relevant adverse reactions that did not meet criteria for inclusion in Table 7 include hypertension (XTANDI plus leuprolide, 25%; XTANDI as a single agent, 21%), angioedema (XTANDI plus leuprolide, 2.5%; XTANDI as a single agent, 2%), and seizure (XTANDI plus leuprolide, 1.1%; XTANDI as a single agent, 0.8%).

Laboratory Abnormalities

Table 8 shows laboratory abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies.

Table 8. Laboratory Abnormalities

	XTANDI (N = 3526)		Placebo (N = 2636)	
	Grade 1-4 (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Hematology				
Hemoglobin decreased	50	1.8	47	1.5
Neutrophil count decreased	20	1	17	0.5
White blood cell decreased	18	0.5	11	0.2
Chemistry				
Hyperglycemia	86	3.7	78	4.3
Hypermagnesemia	17	0.1	14	0.3
Hyponatremia	14	1.6	9	1.4
Hypophosphatemia	10	1.4	7	0.8
Hypercalcemia	8	0.1	5	0.1

Hypertension

In the combined data from five randomized placebo-controlled clinical trials, hypertension was reported in 14% of patients receiving XTANDI and 7% of patients receiving placebo. Medical history of hypertension was balanced between arms. Hypertension led to study discontinuation in < 1% of patients in each arm.

6.2 Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of XTANDI. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal Disorders: vomiting, dysphagia (including choking related to XTANDI product size)

Immune System Disorders: hypersensitivity (edema of the face, tongue, lip, or pharynx)

Neurological Disorders: posterior reversible encephalopathy syndrome (PRES), dysgeusia

Skin and Subcutaneous Tissue Disorders: rash, severe cutaneous adverse reactions (including Stevens-Johnson syndrome (SJS), erythema multiforme, toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) and acute generalized exanthematous pustulosis (AGEP))

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on XTANDI

Strong CYP2C8 Inhibitors

The coadministration of XTANDI with gemfibrozil (a strong CYP2C8 inhibitor) increases plasma concentrations of enzalutamide plus N-desmethyl enzalutamide, which may increase the incidence and severity of adverse reactions of XTANDI. Avoid the coadministration of XTANDI with strong CYP2C8 inhibitors. If the coadministration of XTANDI with a strong CYP2C8 inhibitor cannot be avoided, reduce the dosage of XTANDI *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)].*

Strong CYP3A4 Inducers

The coadministration of XTANDI with rifampin (a strong CYP3A4 inducer and a moderate CYP2C8 inducer) decreases plasma concentrations of enzalutamide plus N-desmethyl enzalutamide, which may decrease the efficacy of XTANDI. Avoid the coadministration of XTANDI with strong CYP3A4 inducers. If the coadministration of XTANDI with a strong CYP3A4 inducer cannot be avoided, increase the dosage of XTANDI *[see Dosage and Administration (2.3), Clinical Pharmacology (12.3)]*.

7.2 Effect of XTANDI on Other Drugs

Certain CYP3A4, CYP2C9, or CYP2C19 Substrates

XTANDI is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer. The coadministration of XTANDI decreases the concentrations of certain CYP3A4, CYP2C9, or CYP2C19 substrates *[see Clinical Pharmacology (12.3)]*, which may reduce the efficacy of these substrates. Avoid the coadministration of XTANDI with certain CYP3A4, CYP2C9, or CYP2C19 substrates for which a minimal decrease in concentration may lead to therapeutic failure of the substrate. If the coadministration cannot be avoided, increase the dosage of these substrates in accordance with their Prescribing Information. In cases where active metabolites are formed, there may be increased exposure to the active metabolites.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of XTANDI have not been established in females. Based on animal reproductive studies and mechanism of action, XTANDI can cause fetal harm and loss of pregnancy. There are no human data on the use of XTANDI in pregnant females. In animal reproduction studies, oral administration of enzalutamide in pregnant mice during organogenesis caused adverse developmental effects at doses lower than the maximum recommended human dose *(see Data)*.

Data

Animal Data

In an embryo-fetal developmental toxicity study in mice, enzalutamide caused developmental toxicity when administered at oral doses of 10 or 30 mg/kg/day throughout the period of organogenesis (gestational days 6-15). Findings included embryo-fetal lethality (increased post-implantation loss and resorptions) and decreased anogenital distance at ≥ 10 mg/kg/day, and cleft palate and absent palatine bone at 30 mg/kg/day. Doses of 30 mg/kg/day caused maternal toxicity. The doses tested in mice (1, 10 and 30 mg/kg/day) resulted in systemic exposures (AUC) approximately 0.04, 0.4 and 1.1 times, respectively, the exposures in patients. Enzalutamide did not cause developmental toxicity in rabbits when administered throughout the period of organogenesis (gestational days 6-18) at dose levels up to 10 mg/kg/day (approximately 0.4 times the exposures in patients based on AUC).

In a pharmacokinetic study in pregnant rats with a single oral 30 mg/kg enzalutamide administration on gestation day 14, enzalutamide and/or its metabolites were present in the fetus at a C_{max} that was approximately 0.3 times the concentration found in maternal plasma and occurred 4 hours after administration.

8.2 Lactation

Risk Summary

The safety and efficacy of XTANDI have not been established in females. There is no information available on the presence of XTANDI in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Enzalutamide and/or its metabolites were present in milk of lactating rats *(see Data)*.

Data

Following a single oral administration in lactating rats on postnatal day 14, enzalutamide and/or its metabolites were present in milk at a C_{max} that was 4 times higher than concentrations in the plasma and occurred 4 hours after administration.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI *[see Use in Specific Populations (8.1)]*.

Infertility

Males

Based on animal studies, XTANDI may impair fertility in males of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of XTANDI in pediatric patients have not been established.

8.5 Geriatric Use

Of 5110 patients who received XTANDI in eight randomized, controlled clinical trials, 78% were 65 and over, while 33% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

8.6 Renal Impairment

No dosage modification is recommended for patients with mild to moderate renal impairment (creatinine clearance [CLcr] ≥ 30 mL/min). XTANDI has not been studied in patients with severe renal impairment (CLcr < 30 mL/min) or end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

No dosage modification is recommended for patients with mild, moderate, or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*.

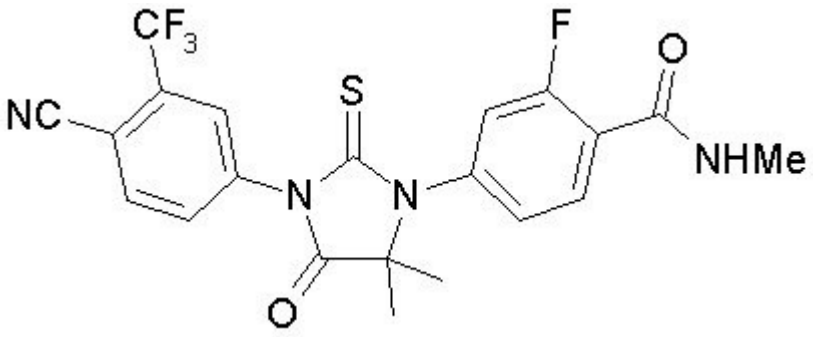
10 OVERDOSAGE

In the event of an overdosage, stop treatment with XTANDI and initiate general supportive measures taking into consideration the half-life of 5.8 days. In a dose escalation study, no seizures were reported at ≤ 240 mg daily, whereas 3 seizures were reported, 1 each at 360 mg, 480 mg, and 600 mg daily. Patients may be at increased risk of seizure following an overdosage.

11 DESCRIPTION

Enzalutamide is an androgen receptor inhibitor. The chemical name is 4-{3-[4-cyano-3-(trifluoromethyl)phenyl]-5,5-dimethyl-4-oxo-2-sulfanylideneimidazolidin-1-yl}-2-fluoro-*N*-methylbenzamide.

The molecular weight is 464.44 and molecular formula is $C_{21}H_{16}F_4N_4O_2S$. The structural formula is:



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

XTANDI is available as liquid-filled soft gelatin capsules for oral administration. Each capsule contains 40 mg of enzalutamide as a solution in caprylocaproyl polyoxylglycerides. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

XTANDI is also available as film-coated tablets for oral administration. Each tablet contains 40 mg or 80 mg of enzalutamide. The inactive ingredients are hypromellose acetate succinate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate. The tablet film-coat contains hypromellose, talc, polyethylene glycol, titanium dioxide, and ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enzalutamide is an androgen receptor inhibitor that acts on different steps in the androgen receptor signaling pathway. Enzalutamide has been shown to competitively inhibit androgen binding to androgen receptors; and consequently, inhibits nuclear translocation of androgen receptors and their interaction with DNA. A major metabolite, N-desmethyl enzalutamide, exhibited similar *in vitro* activity to enzalutamide. Enzalutamide decreased proliferation and induced cell death of prostate cancer cells *in vitro*, and decreased tumor volume in a mouse prostate cancer xenograft model.

12.2 Pharmacodynamics

Once daily dosing of 160 mg enzalutamide in addition to ADT reduced PSA levels to undetectable levels (< 0.2 ng/mL) in 68% of patients with mCSPC (ARCHES).

Based on the efficacy results of AFFIRM after once daily dosing of 160 mg enzalutamide, no exposure-response relationship for the efficacy endpoint of overall survival could be identified. In addition, there was no clinically meaningful exposure-response relationship for adverse effects (e.g. fatigue, flushing, headache, or hypertension) within the limited exposure range for 160 mg/day.

Cardiac Electrophysiology

At the recommended dosage, XTANDI does not cause large mean increases (i.e., > 20 msec) in the QT interval.

12.3 Pharmacokinetics

Enzalutamide achieves steady-state by Day 28 and its AUC accumulates approximately 8.3-fold relative to a single dose. At steady-state, the mean (%CV) maximum concentration (C_{max}) for enzalutamide and N-desmethyl enzalutamide are 16.6 µg/mL (23%) and 12.7 µg/mL (30%), respectively, and the mean (%CV) minimum concentrations (C_{min}) are 11.4 µg/mL (26%) and 13.0 µg/mL (30%), respectively.

Enzalutamide showed approximately dose proportional pharmacokinetics over the daily dose range of 30 (0.2 times the approved recommended dosage) to 360 mg (2.25 times the approved recommended dosage).

Absorption

The median T_{max} is 1 hour (0.5 to 3 hours) following a single 160 mg dose of capsules and 2 hours (0.5 to 6 hours) following a single 160 mg dose of tablets.

Effect of Food

There was no clinically meaningful effect on enzalutamide or N-desmethyl enzalutamide pharmacokinetics following the administration of XTANDI with a high-fat meal (approximately 150 calories from protein, 250 calories from carbohydrates, and 500 to 600 calories from fat).

Distribution

The mean (%CV) volume of distribution after a single oral dose is 110 L (29%).

Enzalutamide is 97% to 98% bound to plasma proteins, primarily albumin. N-desmethyl enzalutamide is 95% bound to plasma proteins.

Elimination

Enzalutamide is primarily eliminated by hepatic metabolism.

The mean apparent clearance (CL/F) of enzalutamide after a single dose is 0.56 L/h (0.33 to 1.02 L/h). The mean terminal half-life ($t_{1/2}$) for enzalutamide after a single oral dose is 5.8 days (2.8 to 10.2 days). The mean terminal $t_{1/2}$ for N-desmethyl enzalutamide is approximately 7.8 to 8.6 days.

Metabolism

Enzalutamide is metabolized by CYP2C8 and CYP3A4. CYP2C8 is primarily responsible for the formation of the active metabolite (N-desmethyl enzalutamide). Carboxylesterase 1 metabolizes N-desmethyl enzalutamide and enzalutamide to the inactive carboxylic acid metabolite.

Specific Populations

No clinically meaningful differences in the pharmacokinetics of enzalutamide were observed based on age (41 to 92 years), race (White, Chinese, and Japanese), body weight (46 kg to 163 kg), mild to moderate renal impairment (CLcr ≥ 30 mL/min) and hepatic impairment (Child-Pugh A, B, and C). Severe renal impairment and end stage renal disease (CLcr < 30 mL/min) have not been studied.

Drug Interaction Studies

Clinical Studies

Effect of CYP2C8 Inhibitors on XTANDI: The coadministration of XTANDI 160 mg with gemfibrozil (strong CYP2C8 inhibitor) increased the AUC of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold with minimal effect on C_{max}.

Effect of CYP3A4 and CYP2C8 Inducers on XTANDI: The coadministration of XTANDI 160 mg after multiple oral doses of rifampin (strong CYP3A4 and moderate CYP2C8 inducer) decreased the AUC of enzalutamide plus N-desmethyl enzalutamide by 37% with no effect on C_{max}.

Effect of CYP3A4 Inhibitors on XTANDI: The coadministration of XTANDI 160 mg after multiple oral doses of itraconazole (strong CYP3A4 inhibitor) increased the AUC of enzalutamide plus N-desmethyl enzalutamide by 1.3-fold with no effect on C_{max}.

Effect of XTANDI on Other Drugs:

The coadministration of XTANDI 160 mg orally once daily with midazolam (a sensitive CYP3A4 substrate) decreased midazolam AUC by 86% and C_{max} by 77%.

Coadministration of XTANDI 160 mg orally once daily with warfarin (a sensitive CYP2C9 substrate) decreased S-warfarin AUC by 56% and C_{max} by 17%.

Coadministration of XTANDI 160 mg orally once daily with omeprazole (a sensitive CYP2C19 substrate) decreased omeprazole AUC by 72% and C_{max} by 62%.

Coadministration of XTANDI 160 mg orally once daily with digoxin (a P-glycoprotein substrate) increased digoxin AUC by 33% and C_{max} by 17%.

No clinically meaningful changes in exposure of pioglitazone (a sensitive CYP2C8 substrate), caffeine (a sensitive CYP1A2 substrate), dextromethorphan (a sensitive CYP2D6 substrate), or rosuvastatin (a BCRP substrate) were observed following coadministration with XTANDI.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Enzalutamide induces CYP2B6 at clinically achievable concentrations.

Transporter Systems: Enzalutamide, N-desmethyl enzalutamide, and the major inactive carboxylic acid metabolite are not substrates for P-glycoprotein or BCRP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

A two-year carcinogenicity study was conducted in male and female rats at oral enzalutamide doses of 10, 30, and 100 mg/kg/day. Enzalutamide increased the incidence of benign Leydig cell tumors in the testes at all dose levels tested (≥ 0.3 times the human exposure based on AUC) and combined incidence of urothelial papilloma and carcinoma in the urinary bladder in male rats at 100 mg/kg/day (1.4 times the human exposure based on AUC). The findings in the testes are considered to be related to the pharmacological activity of enzalutamide. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Administration of enzalutamide to male and female rasH2 transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day.

Enzalutamide did not induce mutations in the bacterial reverse mutation (Ames) assay and was not genotoxic in either the *in vitro* mouse lymphoma thymidine kinase (Tk) gene mutation assay or the *in vivo* mouse micronucleus assay.

Based on nonclinical findings in repeat-dose toxicology studies, which were consistent with the pharmacological activity of enzalutamide, male fertility may be impaired by treatment with XTANDI. In a 26-week study in rats, atrophy of the prostate and seminal vesicles was observed at ≥ 30 mg/kg/day (equal to the human exposure based on AUC). In 4-, 13-, and 39-week studies in dogs, hypospermatogenesis and atrophy of the prostate and epididymides were observed at ≥ 4 mg/kg/day (0.3 times the human exposure based on AUC).

14 CLINICAL STUDIES

The efficacy of XTANDI in patients with CRPC (N = 4692), mCSPC (N = 1150), or nmCSPC with high-risk BCR (N = 1068) was demonstrated in six randomized, multicenter clinical trials. Patients received concomitant GnRH therapy or had prior bilateral orchiectomy, unless otherwise indicated.

AFFIRM (NCT00974311): XTANDI versus Placebo in Metastatic CRPC Following Chemotherapy

In AFFIRM, a total of 1199 patients who had received prior docetaxel-based chemotherapy were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 800) or placebo orally once daily (N = 399). Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event, or clinical progression), initiation of new systemic antineoplastic treatment, unacceptable toxicity, or withdrawal. Patients with a previous history of seizure, taking medicines known to decrease the seizure threshold, or with other risk factors for seizure were not eligible *[see Warnings and Precautions (5.1)]*.

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 92.7% White, 3.9% Black, 1.1% Asian, and 2.1% Other. Ninety-two percent of patients had an ECOG performance status score of 0-1 and 28% had a mean Brief Pain Inventory score of ≥ 4. Ninety-one percent of patients had metastases in bone and 23% had visceral involvement in the lung and/or liver. Fifty-nine percent of patients had radiographic evidence of disease progression and 41% had PSA-only progression on study entry. All patients had received prior docetaxel-based therapy and 24% had received two cytotoxic chemotherapy regimens. During the trial, 48% of patients on the XTANDI arm and 46% of patients on the placebo arm received glucocorticoids.

A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis at the time of 520 deaths in patients on the XTANDI arm compared to patients on the placebo arm (Table 9 and Figure 1).

Table 9. Overall Survival of Patients Treated with Either XTANDI or Placebo in AFFIRM

	XTANDI (N = 800)	Placebo (N = 399)
Number of 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 baseline ECOG performance status score (0-1 vs. 2) and mean baseline pain score (BPI-SF score < 4 vs. ≥ 4).
2. Hazard Ratio is derived from a stratified proportional hazards model. Hazard Ratio < 1 favors XTANDI.

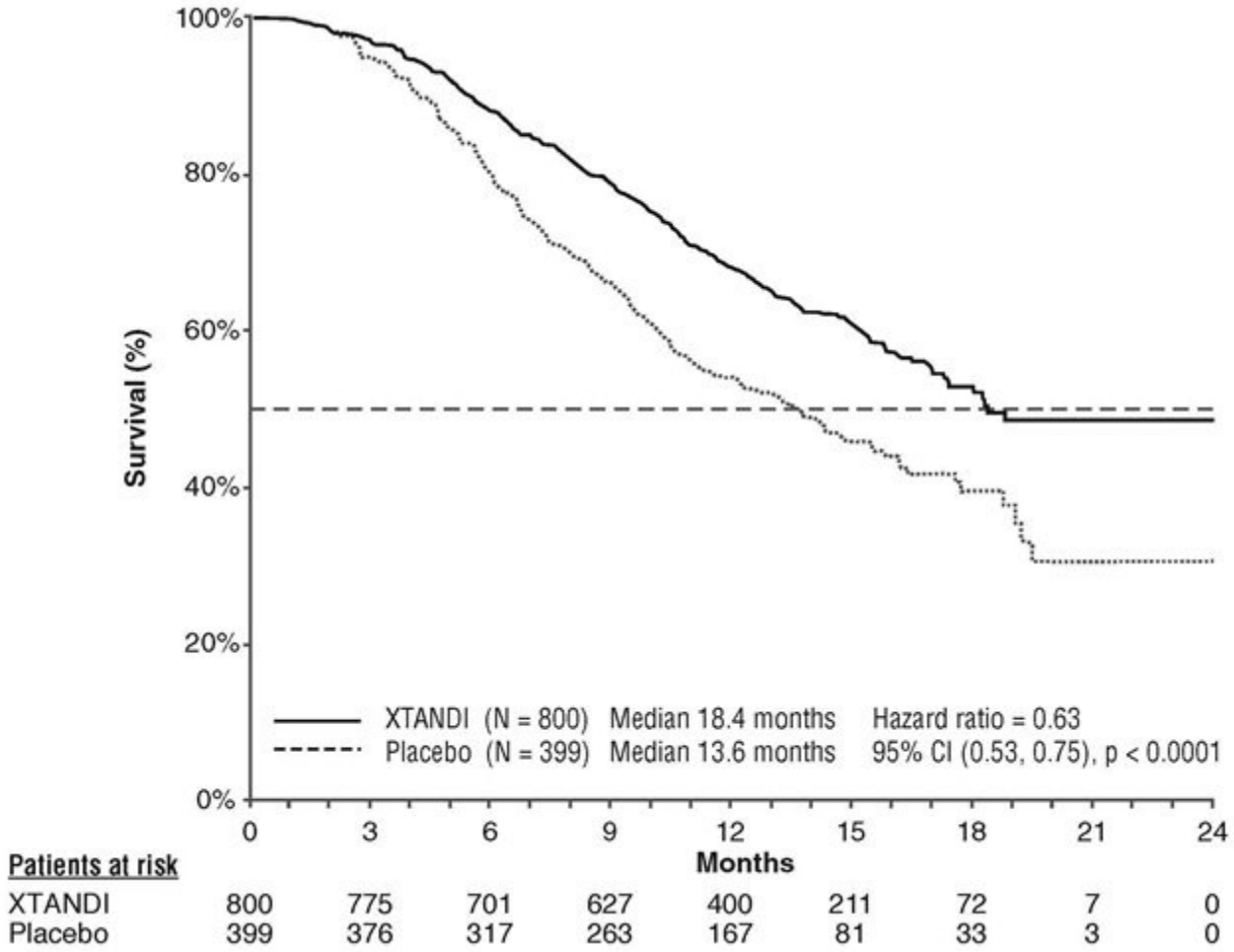


Figure 1. Kaplan-Meier Curves of Overall Survival in AFFIRM

PREVAIL (NCT01212991): XTANDI versus Placebo in Chemotherapy-naïve Metastatic CRPC

In PREVAIL, 1717 chemotherapy-naïve patients were randomized 1:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 872) or placebo orally once daily (N = 845). Patients with visceral metastases, 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 a cytotoxic chemotherapy or an investigational agent, unacceptable toxicity, or withdrawal. Overall survival and radiographic progression-free survival (rPFS) were assessed. Radiographic progression was assessed with the use of sequential imaging and was defined by bone scan identification of 2 or more new bone lesions with confirmation (Prostate Cancer Clinical Trials Working Group 2 criteria) and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria for progression of soft tissue lesions. The primary analysis of rPFS utilized centrally reviewed radiographic assessment of progression.

Patient demographics and baseline disease characteristics were balanced between the treatment arms at entry. The median age was 71 years (range 42-93) and the racial distribution was 77% White, 10% Asian, 2% Black and 11% Other. The ECOG performance status score was 0 for 68% of patients, and 1 for 32% of patients. 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 at study entry). Fifty-four percent of patients had radiographic evidence of disease progression and 43% had PSA-only progression. Twelve percent of patients had visceral (lung and/or liver) disease involvement. During the study, 27% of patients on the XTANDI arm and 30% of patients on the placebo arm received glucocorticoids for varying reasons.

A statistically significant improvement in overall survival was demonstrated at the pre-specified interim analysis, conducted after 540 deaths, in patients treated with XTANDI compared to those treated with placebo (Table 10). Forty percent of XTANDI-treated and 70% of placebo-treated patients received subsequent therapies for metastatic CRPC that may prolong overall survival. An updated survival analysis was conducted when 784 deaths were observed. The median follow-up time was 31 months. Results from this analysis were consistent with those from the pre-specified interim analysis (Table 10, Figure 2). At the updated analysis, 52% of XTANDI-treated and 81% of placebo-treated patients had received subsequent therapies that may prolong overall survival in metastatic CRPC. XTANDI was used as a subsequent therapy in 2% of XTANDI-treated patients and 29% of placebo-treated patients.

Table 10. Overall Survival of Patients Treated with Either XTANDI or Placebo in PREVAIL

	XTANDI (N = 872)	**Placebo (N = 845)**
Pre-specified Interim Analysis[1]		
Number of Deaths (%)	241 (28)	299 (35)
Median Survival, months (95% CI)	32.4 (30.1, NR)	30.2 (28.0, NR)
P-value[2]	$p < 0.0001$	
Hazard Ratio (95% CI)[3]	0.71 (0.60, 0.84)	
Updated Survival Analysis[4]		
Number of Deaths (%)	368 (42)	416 (49)
Median Survival, months (95% CI)	35.3 (32.2, NR)	31.3 (28.8, 34.2)
Hazard Ratio (95% CI)[3]	0.77 (0.67, 0.88)	

NR = Not reached.

1. The data cut-off date is 16 Sep 2013.
2. P-value is derived from an unstratified log-rank test.
3. Hazard Ratio is derived from an unstratified proportional hazards model. Hazard Ratio < 1 favors XTANDI.
4. The data cut-off date is 1 Jun 2014. The planned number of deaths for the final overall survival analysis was ≥ 765.

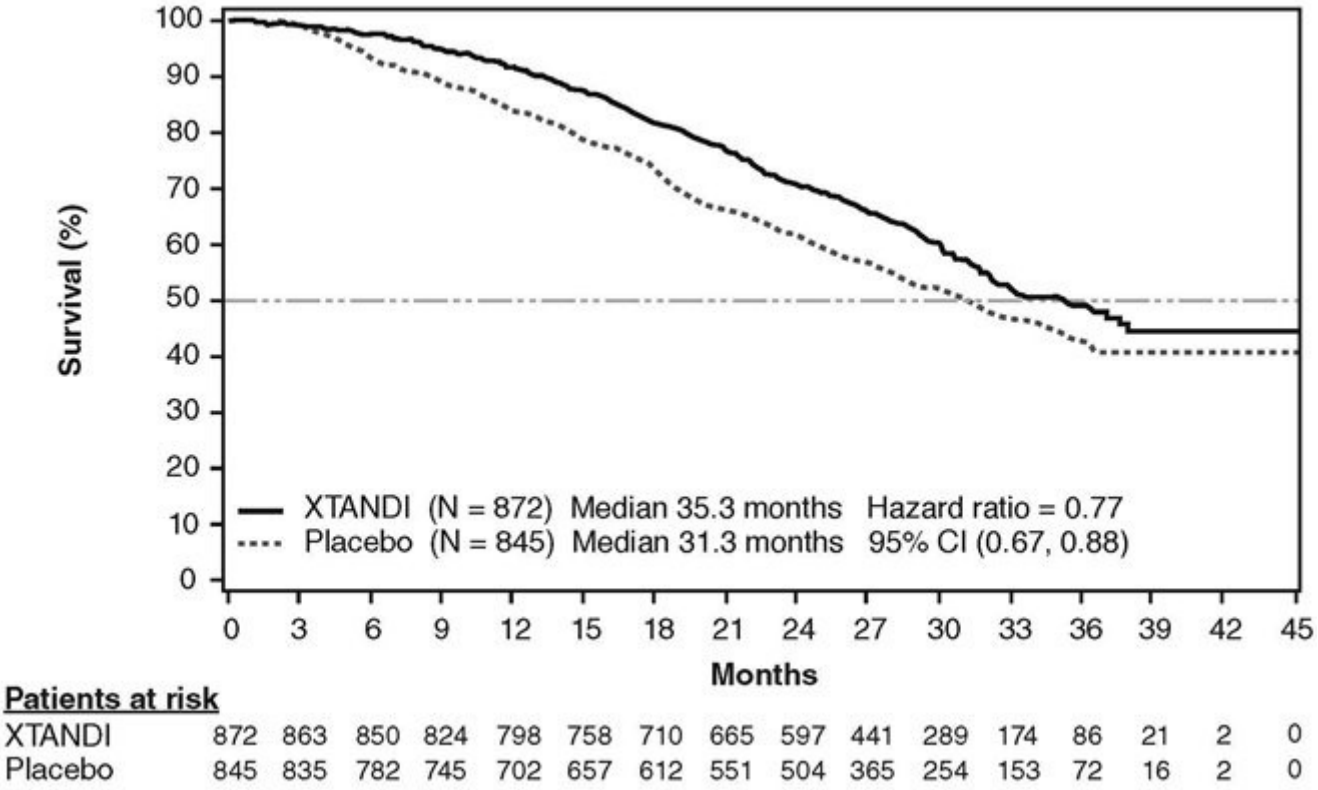


Figure 2. Kaplan-Meier Curves of Overall Survival in PREVAIL

A statistically significant improvement in rPFS was demonstrated in patients treated with XTANDI compared to patients treated with placebo (Table 11, Figure 3).

Table 11. Radiographic Progression-free Survival of Patients Treated with Either XTANDI or Placebo in PREVAIL

	XTANDI (N = 832)	**Placebo (N = 801)**
Number of Progression or Deaths (%)	118 (14)	320 (40)
Median rPFS (months) (95% CI)	NR (13.8, NR)	3.7 (3.6, 4.6)
P-value[1]	$p < 0.0001$	
Hazard Ratio (95% CI)[2]	0.17 (0.14, 0.21)	

NR = Not reached.

Note: As of the cut-off date for the rPFS analysis, 1633 patients had been randomized.

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 favors XTANDI.

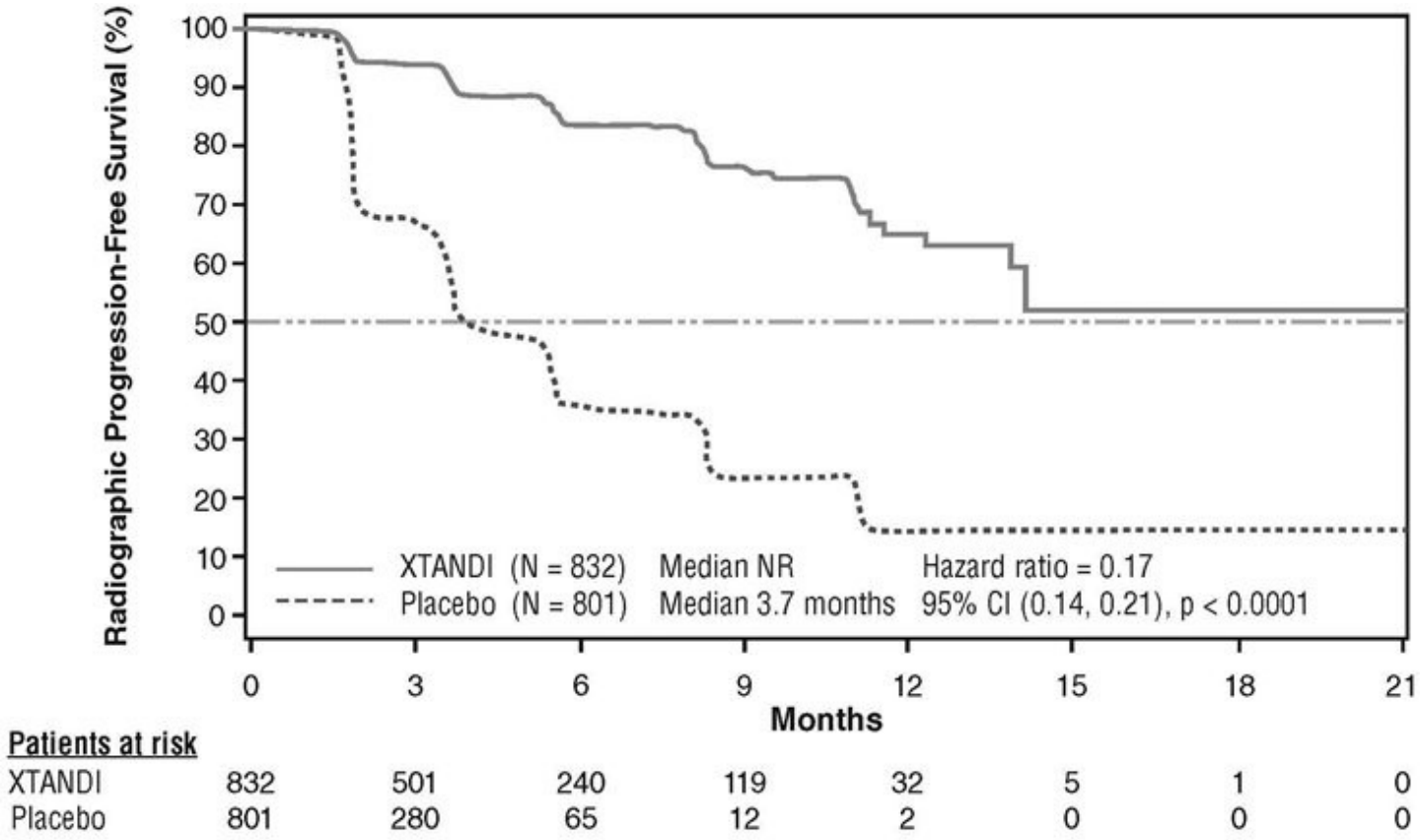


Figure 3. Kaplan-Meier Curves of Radiographic Progression-free Survival in PREVAIL

Time to initiation of cytotoxic chemotherapy was prolonged after XTANDI treatment, with a median of 28.0 months for patients on the XTANDI arm versus a median of 10.8 months for patients on the placebo arm [HR = 0.35 (95% CI: 0.30, 0.40), $p < 0.0001$].

The median time to first skeletal-related event was 31.1 months for patients on the XTANDI arm versus 31.3 months for patients on the placebo arm [HR = 0.72 (95% CI: 0.61, 0.84), $p < 0.0001$]. 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.

TERRAIN (NCT01288911): XTANDI versus Bicalutamide in Chemotherapy-naïve Metastatic CRPC

TERRAIN was conducted in 375 chemotherapy-naïve patients who were randomized 1:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 184) or bicalutamide orally at a dose of 50 mg once daily (N = 191). Patients with a previous history of seizure or a condition that might predispose to seizure and patients with moderate to severe pain from prostate cancer were excluded. Patients could have received prior bicalutamide, but those whose disease had progressed on prior antiandrogen therapy (e.g., bicalutamide) were excluded. Study treatment continued until disease progression (evidence of radiographic progression, a skeletal-related event), the initiation of subsequent antineoplastic agent, unacceptable toxicity, or withdrawal. Radiographic disease progression was assessed by Independent Central Review (ICR) using the Prostate Cancer Clinical Trials Working Group 2 criteria and/or Response Evaluation Criteria in Solid Tumors (RECIST v 1.1) criteria for progression of soft tissue lesions. Radiographic progression-free survival (rPFS) was defined as the time from randomization to the first objective evidence of radiographic progression as assessed by ICR or death, whichever occurred first.

Patient demographics and baseline disease characteristics were balanced between the treatment arms at entry. The median age was 71 years (range 48-96) and the racial distribution was 93% White, 5% Black, 1% Asian and 1% Other. The ECOG performance status score was 0 for 74% of patients and 1 for 26% of patients. Baseline pain assessment was 0-1 (asymptomatic) in 58% of patients, and 2-3 (mildly symptomatic) in 36% of patients as defined by the Brief Pain Inventory Short Form Question 3 (worst pain over past 24 hours at study entry). Ninety-eight percent of patients had objective evidence of disease progression at study entry. Forty-six percent of patients had received prior treatment with bicalutamide while no patients received prior treatment with XTANDI.

An improvement in rPFS was demonstrated in patients treated with XTANDI compared to patients treated with bicalutamide (Table 12, Figure 4).

Table 12. Radiographic Progression-free Survival of Patients in TERRAIN

	XTANDI (N = 184)	**Bicalutamide (N = 191)**
Number of Progression or Deaths (%)	72 (39)	74 (39)
Median rPFS (months) (95% CI)	19.5 (11.8, NR)	13.4 (8.2, 16.4)
Hazard Ratio (95% CI)[1]	0.60 (0.43, 0.83)	

NR = Not reached.

1. Hazard Ratio is derived from an unstratified proportional hazards model. Hazard Ratio < 1 favors XTANDI.

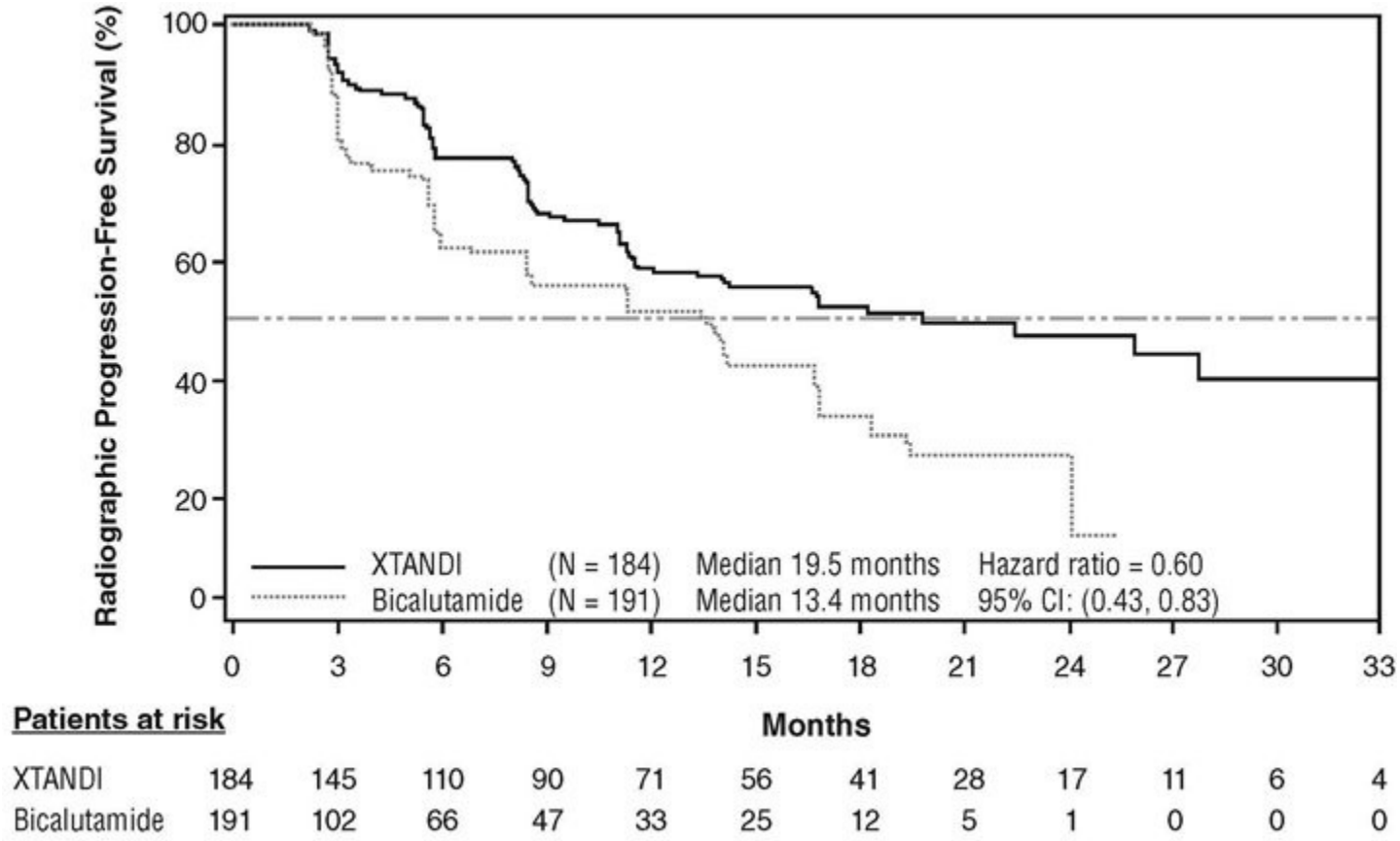


Figure 4. Kaplan-Meier Curves of Radiographic Progression-free Survival in TERRAIN

PROSPER (NCT02003924): XTANDI versus Placebo in Non-metastatic CRPC

PROSPER enrolled 1401 patients with non-metastatic CRPC who were randomized 2:1 to receive either XTANDI orally at a dose of 160 mg once daily (N = 933) or placebo orally once daily (N = 468). All patients in the PROSPER trial received a gonadotropin-releasing hormone (GnRH) analog or had a prior bilateral orchiectomy. Patients were stratified by Prostate Specific Antigen (PSA) Doubling Time (PSADT) and the use of bone-targeting agents. 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). PSA results were blinded and were not used for treatment discontinuation. Patients randomized to either arm discontinued treatment for radiographic disease progression confirmed by BICR, 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 randomization was 74 years (range 50-95) and 23% were 80 years of age or older. The racial distribution was 71% White, 16% Asian, and 2% Black. A majority of patients had a Gleason score of 7 or higher (77%). The median PSADT was 3.7 months. Fifty-four percent (54%) of patients received prior treatment for prostate cancer with either surgery or radiation. Sixty-three percent (63%) of patients received prior treatment with an anti-androgen; 56% of patients received bicalutamide and 11% of patients received flutamide. All patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0 or 1 at study entry.

The major efficacy outcome of the study was metastasis-free survival (MFS), defined as the time from randomization to whichever of the following occurred first 1) loco-regional and/or distant radiographic progression per BICR or 2) death up to 112 days after treatment discontinuation without evidence of radiographic progression. A statistically significant improvement in MFS and OS was demonstrated in patients randomized to receive XTANDI compared with patients randomized to receive placebo. Consistent MFS results were observed when considering only distant radiographic progression events or deaths regardless of the cut-off date. Consistent MFS results were also observed in pre-specified and stratified patient sub-groups of PSADT (< 6 months or ≥ 6 months) and use of a prior bone-targeting agent (yes or no). The efficacy results from PROSPER are summarized in Table 13, Figure 5 and Figure 6.

Table 13. Summary of Efficacy Results in PROSPER (Intent-to-treat Population)

	XTANDI (N = 933)	**Placebo (N = 468)**
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[2]	p < 0.0001	
Overall survival[3]		
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]	0.73 (0.61, 0.88)	
P-value[2]	p = 0.0011	

NR = Not reached.

1. Based on Kaplan-Meier estimates.
2. Hazard ratio from a Cox regression model (with treatment as the only covariate) and p-value from a log-rank test are stratified by PSA doubling time and prior or concurrent use of a bone targeting agent.
3. The pre-specified final analysis of OS occurred 27 months after the MFS analysis.

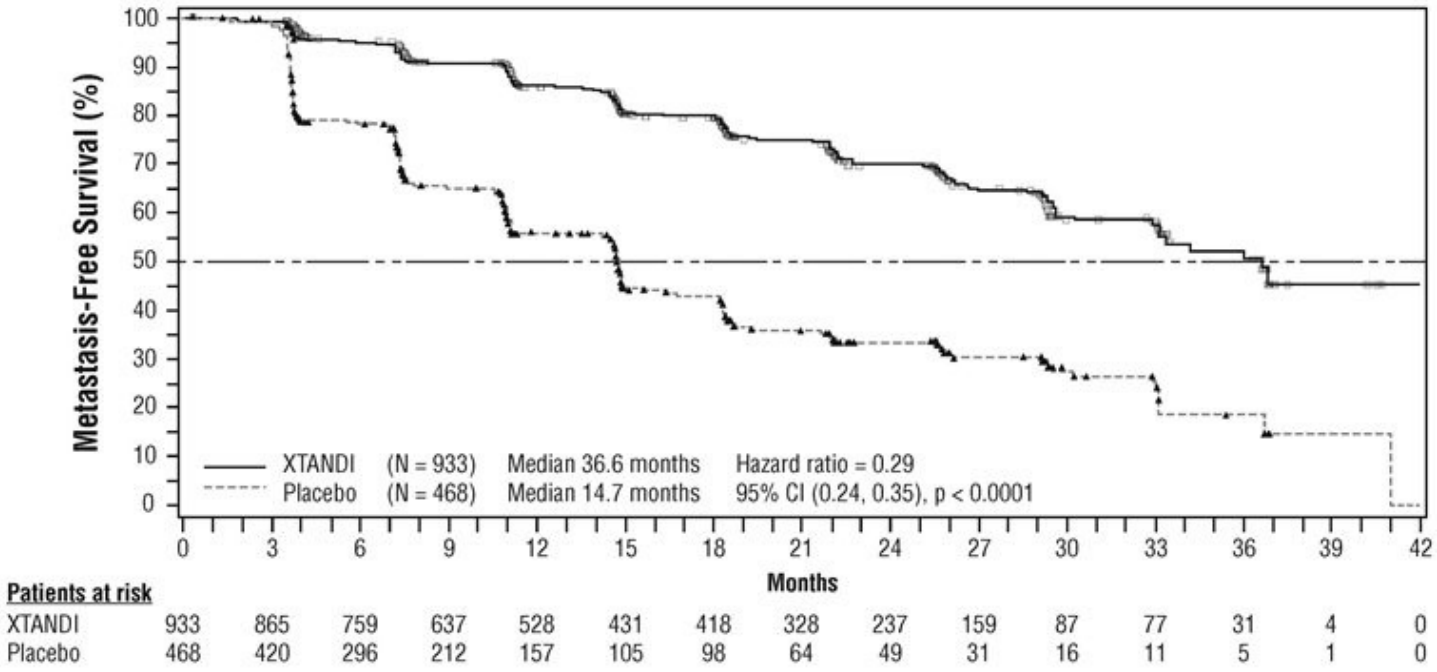


Figure 5. Kaplan-Meier Curves of Metastasis-free Survival in PROSPER

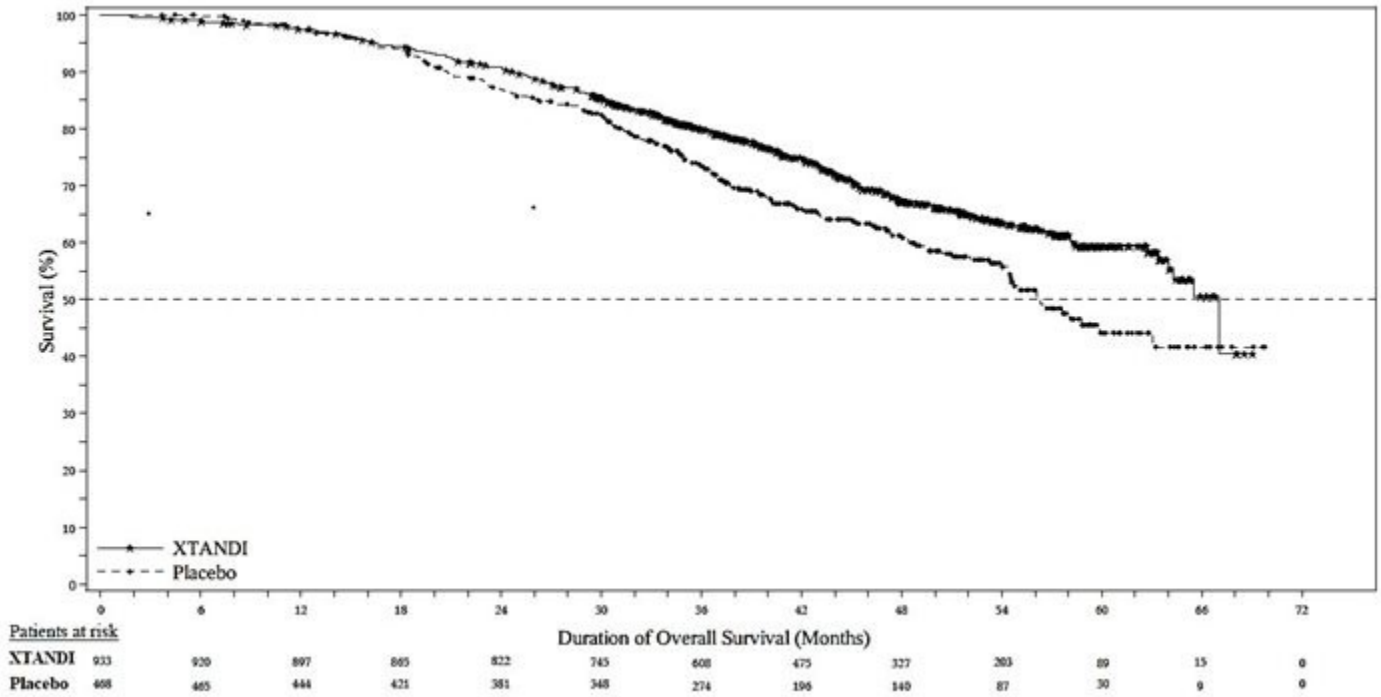


Figure 6. Kaplan-Meier Curves of Overall Survival in PROSPER

The primary efficacy outcome was also supported by a statistically significant delay in time to first use of new antineoplastic therapy (TTA) for patients in the XTANDI arm compared to those in the placebo arm. The median TTA was 39.6 months for patients on XTANDI and was 17.7 months for patients on placebo (HR = 0.21; 95% CI: [0.17, 0.26], $p < 0.0001$).

ARCHES (NCT02677896): XTANDI versus Placebo in Metastatic CSPC

ARCHES enrolled 1150 patients with mCSPC who were randomized 1:1 to receive XTANDI orally at a dose of 160 mg once daily (N = 574) or placebo orally once daily (N = 576). All patients in the trial received a GnRH 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). 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. Treatment with concurrent docetaxel was not allowed. 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 randomization was 70 years (range: 42-92) and 30% were 75 years of age or older. The racial distribution was 81% White, 14% Asian, and 1% Black. Sixty-six percent (66%) of patients 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. 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. Twelve percent (12%) of patients received concomitant bone-targeted agents (bisphosphonates or RANKL inhibitors) which included both prostate and non-prostate cancer indications. 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.

The major efficacy outcome measure was radiographic progression-free survival (rPFS) based on blinded independent central review (BICR). Radiographic progression-free survival was defined as the time from randomization to radiographic disease progression at any time or death within 24 weeks after study drug discontinuation. Radiographic disease progression was defined by identification of 2 or more new bone lesions on a bone scan with confirmation (Prostate Cancer Working Group 2 criteria) and/or progression in soft tissue disease. Time to new antineoplastic therapy and OS were additional efficacy endpoints.

XTANDI demonstrated a statistically significant improvement in rPFS and OS compared to placebo. Consistent rPFS results were observed in patients with high or low volume of disease and patients with and without prior docetaxel therapy. Efficacy results for rPFS and OS from ARCHES are summarized in Table 14, Figure 7 and Figure 8.

Table 14. Efficacy Results in ARCHES (Intent-to-Treat Analysis)

	XTANDI (N = 574)	Placebo (N = 576)
Radiographic Progression-free Survival[1]		
Number of events (%)	89 (15.5)	198 (34.4)
Radiographic disease progression	77 (13.4)	185 (32.1)
Death within 24 weeks after treatment discontinuation	12 (2.1)	13 (2.3)
Median, months (95% CI)[2]	NR	19.4 (16.6, NR)
Hazard ratio (95% CI)[3]	0.39 (0.30, 0.50)	
P-value[4]	p < 0.0001	
Overall Survival		
Number of events (%)	154 (26.8)	202 (35.1)
Median, months (95% CI)[2]	NR (NR, NR)	NR (49.7, NR)
Hazard ratio (95% CI)[3]	0.66 (0.53, 0.81)	
P-value[4]	p < 0.0001	

NR = Not reached.

1. Based on BICR.
2. Based on Kaplan-Meier estimates.
3. Hazard Ratio is based on a Cox regression model stratified by volume of disease (low vs high) and prior docetaxel use (yes vs no).
4. P-value is based on a stratified log-rank test by volume of disease (low vs high) and prior docetaxel use (yes or no).

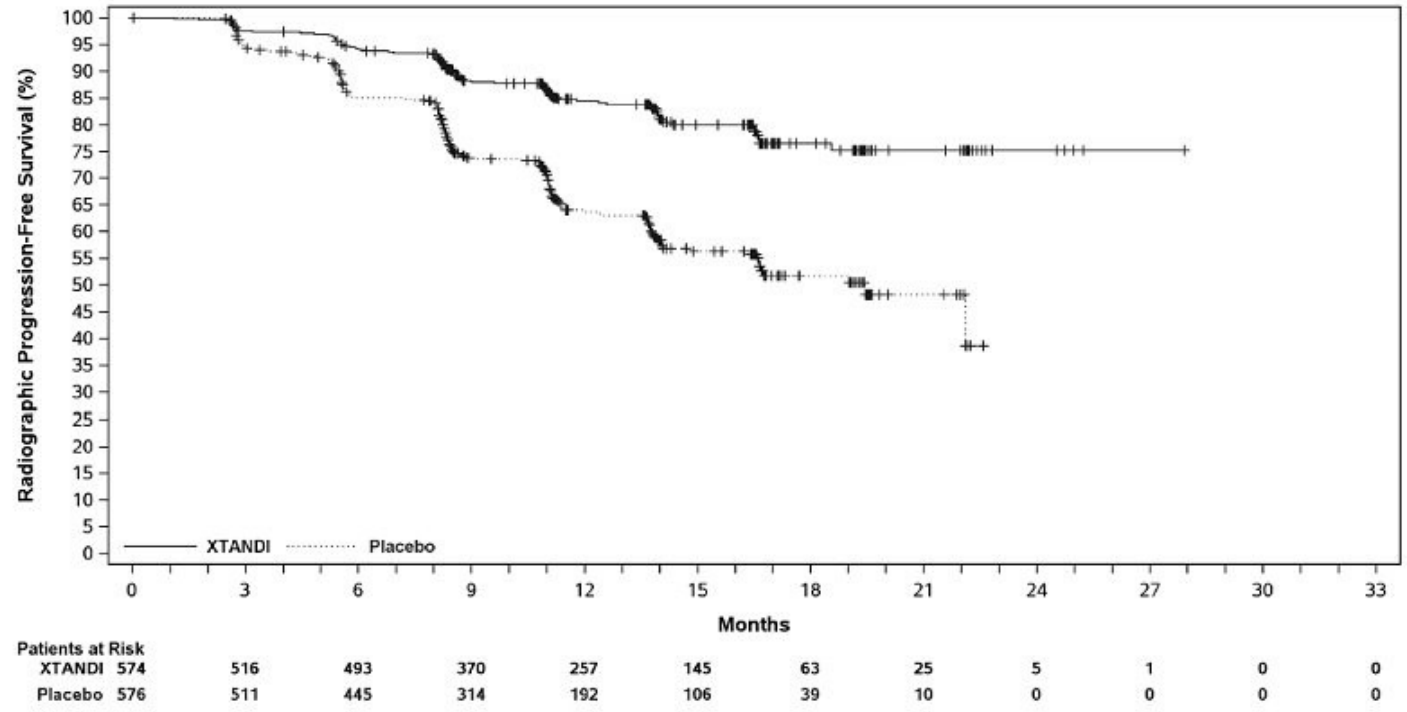


Figure 7. Kaplan-Meier Curves of rPFS in ARCHES (Intent-to-Treat Analysis)

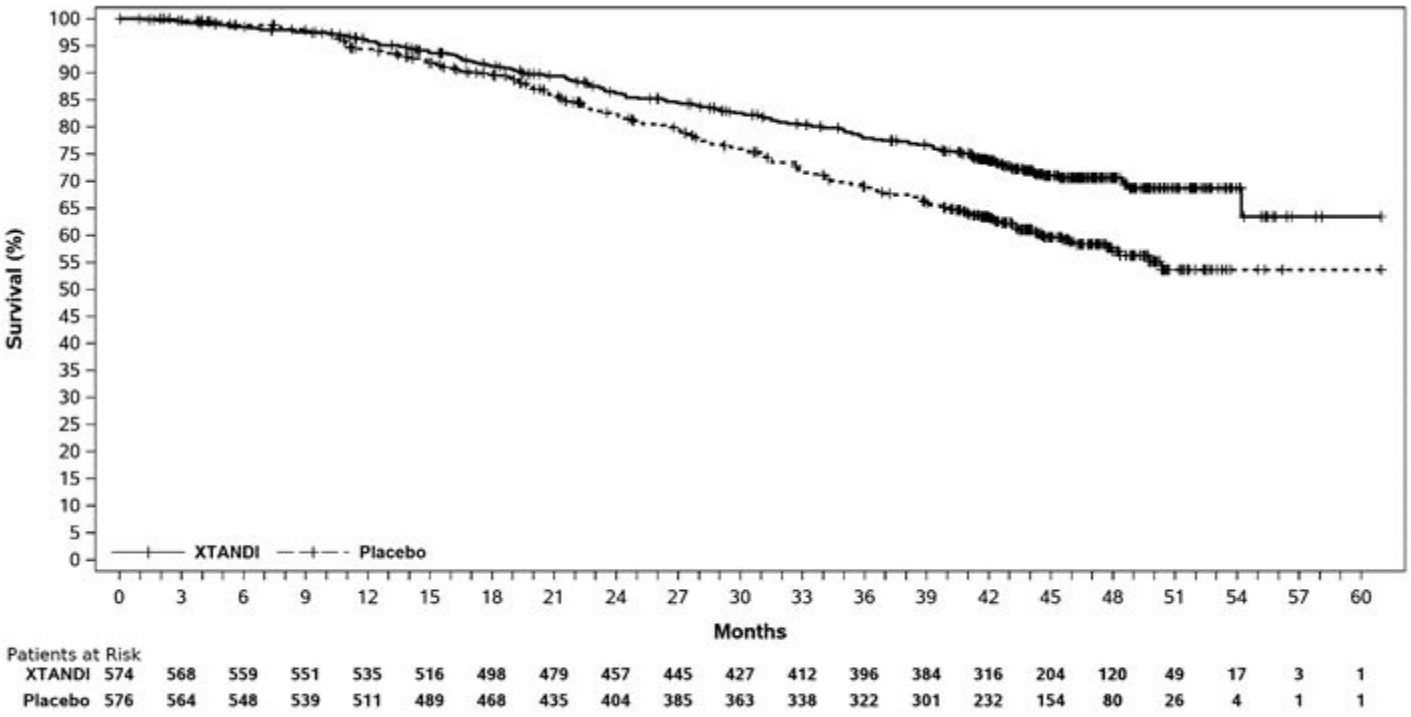


Figure 8. Kaplan-Meier Curves of Overall Survival in ARCHES

A statistically significant improvement was also reported on the XTANDI arm compared to placebo in time to initiation of a new antineoplastic therapy (HR = 0.28 [95% CI: 0.20, 0.40]; $p < 0.0001$).

EMBARK (NCT02319837): XTANDI versus Placebo in Non-metastatic CSPC with High-Risk BCR

EMBARK enrolled 1068 patients with nmCSPC with high-risk BCR who were randomized 1:1:1 to receive XTANDI orally at a dose of 160 mg once daily concurrently with leuprolide (N = 355), XTANDI orally at a dose of 160 mg once daily as open-label as a single agent (N = 355), or placebo orally once daily concurrently with leuprolide (N = 358). All patients had prior definitive therapy with radical prostatectomy or radiotherapy (including brachytherapy) with curative intent, or both. Patients were not candidates for salvage radiotherapy at the time of enrollment. 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. 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 (≥0.2 ng/mL) at week 36, treatment continued without suspension until permanent treatment discontinuation criteria were met. For all patients, treatment was permanently discontinued upon radiographic disease progression confirmed by BICR, initiation of new treatment, unacceptable toxicity, or withdrawal.

The median age at randomization was 69 years (range: 49-93) and 23% were 75 years of age or older. The racial distribution was 83% White, 7% Asian, 4% Black, 2.3% Others, and 2.7% not reported; 5.5% of patients were Hispanic or Latino. The median PSADT was 4.9 months. Seventy-four percent (74%) of patients had prior definitive therapy with radical prostatectomy, 34% of patients had prior primary radiotherapy (including brachytherapy), and 49% of patients had prior therapy with both surgery and radiotherapy (including adjuvant and salvage radiotherapy). Thirty-two percent (32%) of patients had a Gleason score of ≥ 8. The ECOG PS score was 0 for 92% of patients and 1 for 8% of patients at study entry.

The major efficacy outcome measure was metastasis-free survival (MFS) in patients randomized to receive XTANDI plus leuprolide compared to patients randomized to receive placebo plus leuprolide. MFS was defined as the time from randomization to whichever of the following occurred first 1) radiographic progression per BICR or 2) death. MFS in patients randomized to receive XTANDI as a single agent compared to patients randomized to receive placebo plus leuprolide and overall survival (OS) were additional efficacy outcome measures.

A statistically significant improvement in MFS was demonstrated in patients randomized to receive XTANDI plus leuprolide compared with patients randomized to receive placebo plus leuprolide. A statistically significant improvement in MFS was also demonstrated in patients randomized to receive XTANDI as a single agent compared with patients randomized to receive placebo plus leuprolide. The results are summarized in Table 15 and Figure 9.

Table 15. Metastasis-free Survival Based on BICR in EMBARK (Intent-to-treat Population)

	XTANDI + Leuprolide (N = 355)	Placebo + Leuprolide (N = 358)	XTANDI (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 Leuprolide (95% CI)[3]	0.42 (0.30, 0.61)	--	0.63 (0.46, 0.87)
P-value for comparison to Placebo + Leuprolide[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.

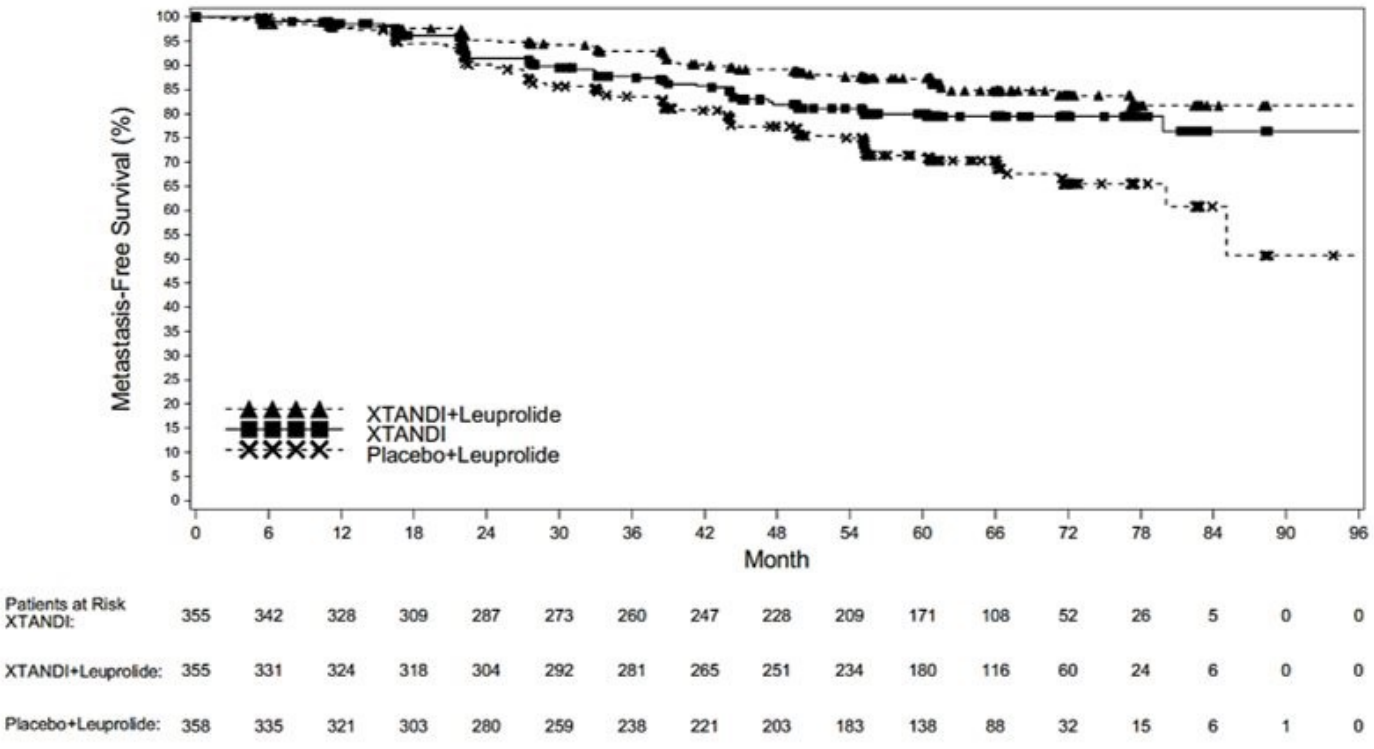


Figure 9. Kaplan-Meier Curves of Metastasis-free Survival in the XTANDI plus Leuprolide vs. Placebo plus Leuprolide vs. XTANDI Treatment Arms in EMBARK

OS data were not mature at the time of MFS analysis (12.2% deaths across the overall population of 1068 patients).

16 HOW SUPPLIED/STORAGE AND HANDLING

XTANDI (enzalutamide) 40 mg capsules are supplied as white to off-white oblong soft gelatin capsules imprinted in black ink with ENZ and are available in the following package size:

- Bottles of 120 capsules with child resistant closures (NDC 0469-0125-99)

XTANDI (enzalutamide) 40 mg tablets are supplied as yellow, round, film-coated tablets debossed with E 40, and are available in the following package size:

- Bottles of 120 tablets with child resistant closures (NDC 0469-0625-99)

XTANDI (enzalutamide) 80 mg tablets are supplied as yellow, oval, film-coated tablets debossed with E 80, and are available in the following package size:

- Bottles of 60 tablets with child resistant closures (NDC 0469-0725-60)

Store XTANDI capsules and tablets at 20°C to 25°C (68°F to 77°F) in a dry place and keep the container tightly closed. Excursions permitted from 15°C to 30°C (59°F to 86°F).

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Seizure

- Inform patients that XTANDI has been associated with an increased risk of seizure. Discuss conditions that may predispose to seizures and medications that may lower the seizure threshold. Advise patients of the risk of engaging in any activity where sudden loss of consciousness could cause serious harm to themselves or others. Inform patients to contact their healthcare provider right away if they have loss of consciousness or seizure *[see Warnings and Precautions (5.1)]*.

Posterior Reversible Encephalopathy Syndrome (PRES)

- Inform patients to contact their healthcare provider right away if they experience rapidly worsening symptoms possibly indicative of PRES such as seizure, headache, decreased alertness, confusion, reduced eyesight, or blurred vision *[see Warnings and Precautions (5.2)]*.

Hypersensitivity

- Inform patients that XTANDI may be associated with hypersensitivity reactions that include swelling of the face, lip, tongue, or throat *[see Warnings and Precautions (5.3)]*. Advise patients who experience these types of symptoms of hypersensitivity to discontinue XTANDI and promptly contact their healthcare provider.

Ischemic Heart Disease

- Inform patients that XTANDI has been associated with an increased risk of ischemic heart disease. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur *[see Warnings and Precautions (5.4)]*.

Falls and Fractures

- Inform patients that XTANDI is associated with an increased incidence of dizziness/vertigo, falls, and fractures. Advise patients to report these adverse reactions to their healthcare provider *[see Warnings and Precautions (5.5)]*.

Dysphagia or Choking

- Inform patients that the size of XTANDI capsules and tablets has been associated with severe dysphagia or choking.
- Advise patients to take each capsule or tablet as instructed in Dosage and Administration.
- Advise patients to inform their healthcare provider if experiencing difficulty swallowing XTANDI *[see Warnings and Precautions (5.7)]*.

Hypertension

- Inform patients that XTANDI is associated with an increased incidence of hypertension *[see Adverse Reactions (6.1)]*.

Dosage and Administration

- Inform patients who have not undergone bilateral orchiectomy and are receiving GnRH therapy that they need to maintain this treatment during the course of treatment with XTANDI.
- Instruct patients to take their dose at the same time each day (once daily). XTANDI can be taken with or without food. Advise patients to take each capsule or tablet whole with a sufficient amount of water to ensure that all medication is successfully swallowed. Do not chew, dissolve, or open the capsules. Do not cut, crush, or chew the tablets *[see Warnings and Precautions (5.7)]*.
- Inform patients that they should not interrupt, modify the dose, or stop XTANDI without first consulting their healthcare provider.
- Inform patients that if they miss a dose, then they should take it as soon as they remember. If they forget to take the dose for the whole day, then they should take their normal dose the next day. They should not take more than their prescribed dose per day *[see Dosage and Administration (2.1)]*.

Embryo-Fetal Toxicity

- Inform patients that XTANDI can be harmful to a developing fetus and can cause loss of pregnancy.
- Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI. Advise male patients to use a condom if having sex with a pregnant woman *[see Warnings and Precautions (5.6)]*.

Infertility

- Inform male patients that XTANDI may impair fertility *[see Use in Specific Populations (8.3)]*.

Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062

Marketed by:
Astellas Pharma US, Inc., Northbrook, IL 60062 Pfizer Inc., New York, NY 10001
430539-XTA-USA

Rx Only

PATIENT INFORMATION

XTANDI® (ex TAN dee) **(enzalutamide)** **capsules**	**XTANDI® (ex TAN dee)** **(enzalutamide)** **tablets**

What is XTANDI®?

XTANDI is a prescription medicine used to treat men with prostate cancer that:

- no longer responds to a hormone therapy or surgical treatment to lower testosterone
  OR
- has spread to other parts of the body and responds to a hormone therapy or surgical treatment to lower testosterone
  OR
- has not spread to other parts of the body and responds to a hormone therapy or surgical treatment to lower testosterone, and who are at high risk of cancer spreading to other parts of the body

It is not known if XTANDI is safe and effective in females.

It is not known if XTANDI is safe and effective in children.

Before taking XTANDI, tell your healthcare provider about all your medical conditions, including if you:

- have a history of seizures, brain injury, stroke, or brain tumors.
- have a history of heart disease.
- have high blood pressure.
- have abnormal amounts of fat or cholesterol in your blood (dyslipidemia).
- are pregnant or plan to become pregnant. XTANDI can cause harm to your unborn baby and loss of pregnancy (miscarriage).
- have a partner who is pregnant or may become pregnant.
  - Males who have female partners who are able to become pregnant should use effective birth control (contraception) during treatment with XTANDI and for 3 months after the last dose of XTANDI.
  - Males must use a condom during sex with a pregnant female.
- are breastfeeding or plan to breastfeed. It is not known if XTANDI passes into your breast milk.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. XTANDI may affect the way other medicines work, and other medicines may affect how XTANDI works.

You should not start or stop any medicine before you talk with the healthcare provider that prescribed XTANDI.

Know the medicines you take. Keep a list of them with you to show your healthcare provider and pharmacist when you get a new medicine.

How should I take XTANDI?

- Take XTANDI exactly as your healthcare provider tells you.
- Take your prescribed dose of XTANDI 1 time a day, at the same time each day.
- Your healthcare provider may change your dose if needed.
- Do not change or stop taking your prescribed dose of XTANDI without talking with your healthcare provider first.
- XTANDI can be taken with or without food.
- Swallow each XTANDI capsule or tablet whole with enough water to make sure that you can swallow all of the medicine successfully. **Do not** chew, dissolve, or open the capsules. **Do not** cut, crush, or chew the tablets. Your healthcare provider may change your treatment to a smaller tablet size or stop your treatment with XTANDI if you have swallowing problems with capsules or tablets.
- If you are receiving gonadotropin-releasing hormone (GnRH) therapy, you should continue with this treatment during your treatment with XTANDI unless you have had a surgery to lower the amount of testosterone in your body (surgical castration).
- If you miss a dose of XTANDI, take your prescribed dose as soon as you remember that day. If you miss your daily dose, take your prescribed dose at your regular time the next day. Do not take more than your prescribed dose of XTANDI each day.
- If you take too much XTANDI, call your healthcare provider or go to the nearest emergency room right away. You may have an increased risk of seizure if you take too much XTANDI.

What are the possible side effects of XTANDI?

XTANDI may cause serious side effects including:

- **Seizure.** If you take XTANDI you may be at risk of having a seizure. You should avoid activities where a sudden loss of consciousness could cause serious harm to yourself or others. Tell your healthcare provider right away if you have loss of consciousness or seizure.
- **Posterior Reversible Encephalopathy Syndrome (PRES).** If you take XTANDI you may be at risk of developing a condition involving the brain called PRES. Tell your healthcare provider right away if you have a seizure or quickly worsening symptoms such as headache, decreased alertness, confusion, reduced eyesight, blurred vision or other visual problems. Your healthcare provider will do a test to check for PRES.
- **Allergic Reactions.** Allergic reactions have happened in people who take XTANDI. Stop taking XTANDI and get medical help right away if you develop swelling of the face, tongue, lip or throat.
- **Heart disease.** Blockage of the arteries in the heart (ischemic heart disease) that can lead to death has happened in some people during treatment with XTANDI. Your healthcare provider will monitor you for signs and symptoms of heart problems during your treatment with XTANDI. Call your healthcare provider or go to the nearest emergency room right away if you get chest pain or discomfort at rest or with activity or shortness of breath during your treatment with XTANDI.
- **Falls and bone fractures.** XTANDI treatment may increase your risk for falls and bone fractures. Falls were not caused by loss of consciousness (fainting) or seizures. Your healthcare provider will monitor your risks for falls and bone fractures during treatment with XTANDI.
- **Swallowing problems or choking.** Severe swallowing problems or choking, including life-threatening problems or death can happen in people during treatment with XTANDI because of the size of the XTANDI capsules and tablets. Swallow each XTANDI capsule or tablet whole with enough water to make sure that you can swallow all of the medicine successfully. See "**How should I take XTANDI?**"

Your healthcare provider will stop treatment with XTANDI if you have serious side effects.

The most common side effects of XTANDI include:

- muscle and joint pain
- feeling more tired than usual
- hot flashes
- constipation
- decreased appetite
- diarrhea
- high blood pressure
- bleeding problems
- falls
- bone fractures
- headache

XTANDI may cause fertility problems in males, which may affect the ability to father children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of XTANDI. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store XTANDI?

- XTANDI capsules and tablets come in a child-resistant bottle.
- Store XTANDI capsules and tablets between 68°F to 77°F (20°C to 25°C).
- Keep XTANDI capsules and tablets dry and in a tightly closed container.

Keep XTANDI and all medicines out of the reach of children.

General information about the safe and effective use of XTANDI.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use XTANDI for a condition for which it was not prescribed. Do not give XTANDI to other people, even if they have the same symptoms that you have. It may harm them. You can ask your healthcare provider or pharmacist for information about XTANDI that is written for health professionals.

What are the ingredients in XTANDI?

XTANDI capsules

Active ingredient: enzalutamide

Inactive ingredients: caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatin, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, black iron oxide.

XTANDI tablets

Active ingredient: enzalutamide

Inactive ingredients: hypromellose acetate succinate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, and magnesium stearate.

The tablet film-coat contains hypromellose, talc, polyethylene glycol, titanium dioxide, and ferric oxide.

Manufactured for and Distributed by: Astellas Pharma US, Inc., Northbrook, IL 60062
Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062 Pfizer Inc., New York, NY 10001
430539-XTA-USA

For more information go to www.Xtandi.com or call 1-800-727-7003.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: Mar 2025