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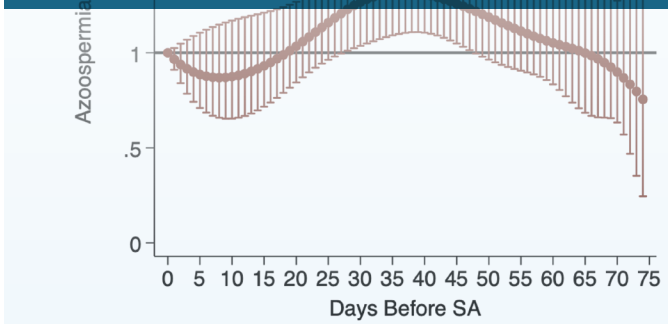
The SHARE Cohort: Investigating Genetic, Epigenetic, and Environmental Mechanisms of Subfertility

Joemy M. Ramsay, MS, PhD; Hunter LaCouture, MD; Jason Kunisaki, BA; James M. Hotaling, MD, MS, FECSM



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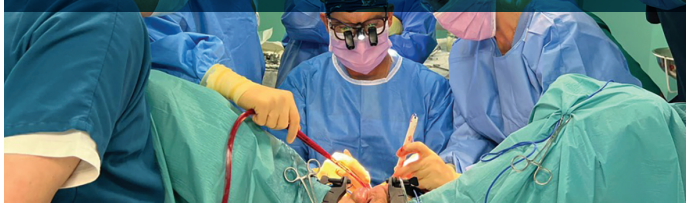
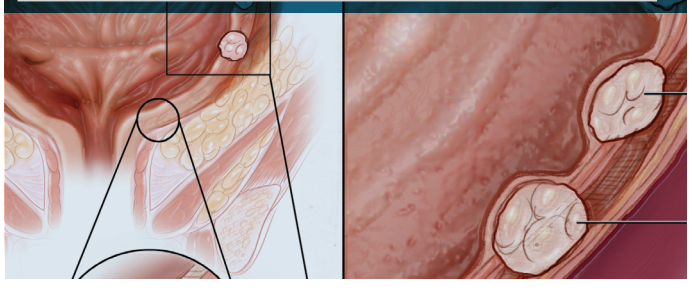


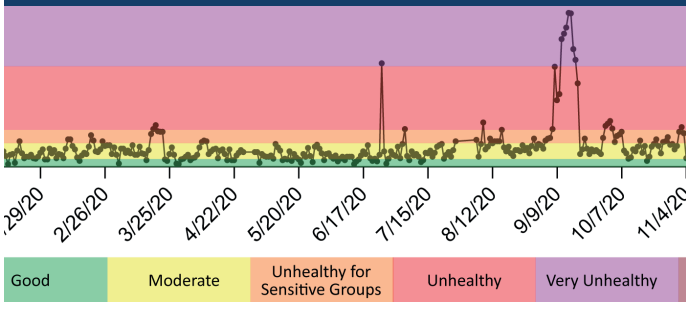
Updates on High-Grade Nonmuscle-Invasive Bladder Cancer Clinical Trials

Gal Wald, MD
Eugene Pietzak, MD



Studying the Impact of Wildfire Smoke on Human Sperm

Tristan M. Nicholson, MD, PhD



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Xtandi® (enzalutamide)

40 mg tablets | 80 mg tablets

XTANDI is indicated for the treatment of patients with nonmetastatic castration-sensitive prostate cancer (nmCSPC) with biochemical recurrence at high risk for metastasis (high-risk BCR), metastatic castration-sensitive prostate cancer (mCSPC), or castration-resistant prostate cancer (CRPC).[1]

For certain men with CSPC,

NOW IS THE TIME TO STRIKE

Strike early with the first and only ARi approved for patients with nmCSPC with high-risk BCR[1]

Patient population: All patients had prior definitive therapy with RP or RT (including brachytherapy) with curative intent, or both; confirmation of nonmetastatic disease by BICR; screening PSA ≥ 1 ng/mL after RP (with or without RT) as the primary treatment for prostate cancer or at least 2 ng/mL above the nadir after prior RT only; PSA doubling time ≤ 9 months; testosterone ≥ 150 ng/dL; ECOG Performance Status 0-1 at screening.[1,2]

Exclusion criteria (select): prior/current distant metastasis; prior hormonal therapy generally not allowed except for short courses ≤ 36 months in duration and ≥ 9 months before randomization; suitable candidate for salvage RT if prior prostatectomy; prior cytotoxic chemotherapy/systemic biologic therapy, including immunotherapy, for prostate cancer; history of seizure or any seizure-predisposing condition; and clinically significant cardiovascular disease.[3]

Patients were offered a treatment suspension once at Week 37 if PSA was < 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. In the XTANDI + GnRH therapy* and placebo + GnRH therapy* arms, GnRH therapy* was also suspended.[1]

Metastasis-free survival was defined as the time from randomization to whichever the following occurred first: 1) radiographic progression per BICR or 2) death.[1]

ARi, androgen receptor inhibitor; **BICR**, blinded independent central review; **CI,** confidence interval; **ECOG**, Eastern Cooperative Oncology Group; **GnRH**, gonadotropin-releasing hormone; **HR**, hazard ratio; **MFS**, metastasis-free survival; **PSA**, prostate-specific antigen; **RP**, radical prostatectomy; **RT**, radiotherapy.

***Leuprolide.**[1]

†Patients with nmCSPC with high-risk BCR receiving XTANDI may be treated with or without GnRH therapy.[1]

‡The EMBARK trial included 1068 patients who were randomized 1:1:1 among 3 study arms to receive XTANDI + GnRH therapy* (n = 355), placebo + GnRH therapy* (n = 358), or XTANDI (single agent) (n = 355). The primary endpoint was MFS in patients randomized to receive XTANDI + GnRH therapy* versus those receiving placebo + GnRH therapy.* MFS in patients randomized to receive XTANDI as a single agent versus those receiving placebo + GnRH therapy* was a key secondary endpoint.[1,2]

§Includes multiple terms.[1]

Important Safety Information

Warnings and Precautions

Seizure occurred in 0.6% of patients receiving XTANDI in eight randomized clinical trials. In a study of patients with predisposing factors for seizure, 2.2% of XTANDI-treated patients experienced a seizure. It is unknown whether anti-epileptic medications will prevent seizures with XTANDI. Patients in the study had one or more of the following predisposing factors: use of medications that may lower the seizure threshold, history of traumatic brain or head injury, history of cerebrovascular accident or transient ischemic attack, and Alzheimer's disease, meningioma, or leptomeningeal disease from prostate cancer, unexplained loss of consciousness within the last 12 months, history of seizure, presence of a space occupying lesion of the brain, history of arteriovenous malformation, or history of brain infection. Advise patients of the risk of developing a seizure while taking 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.

Posterior Reversible Encephalopathy Syndrome (PRES) There have been reports of PRES in patients receiving XTANDI. PRES is a neurological disorder that 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 MRI. Discontinue XTANDI in patients who develop PRES.

Hypersensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with XTANDI 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.

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 XTANDI versus 1.1% on placebo. Ischemic events led to death in 0.4% of patients on XTANDI compared to 0.1% on placebo. 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.

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. Fractures occurred in 13% of patients treated with XTANDI and in 6% of patients treated with placebo.

Embryo-Fetal Toxicity The safety and efficacy of XTANDI have not been established in females. 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.

Adverse Reactions (ARs)

In the data from the five randomized placebo-controlled trials, the most common ARs (≥ 10%) that occurred more frequently (≥ 2% over placebo) in XTANDI-treated patients were musculoskeletal pain, fatigue, hot flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture, and headache. In the bicalutamide-controlled study, the most common ARs (≥ 10%) reported in XTANDI-treated patients were asthenia/fatigue, back pain, musculoskeletal pain, hot flush, hypertension, nausea, constipation, diarrhea, upper respiratory tract infection, and weight loss.

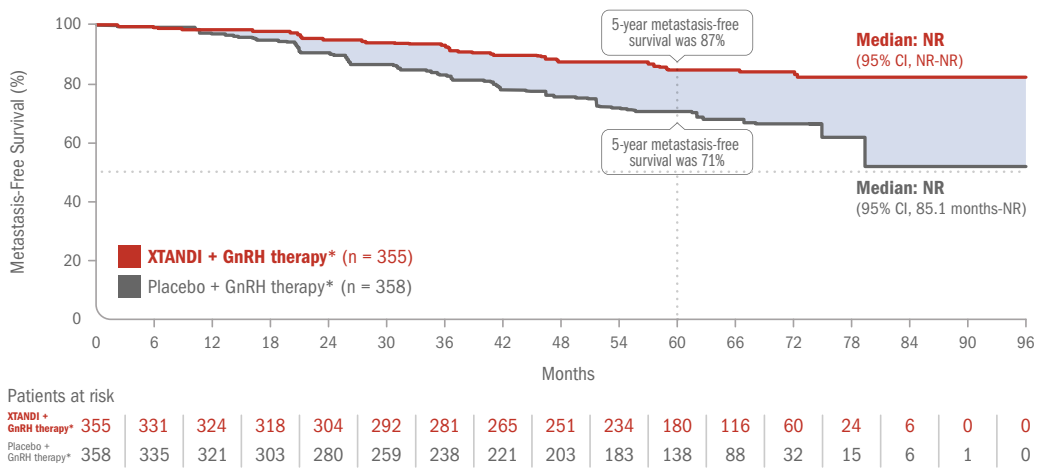
In AFFIRM, the placebo-controlled study of metastatic CRPC (mCRPC) patients who previously received docetaxel, Grade 3 and higher ARs were reported among 47% of XTANDI-treated

HARNESS THE POWER OF XTANDI + GnRH THERAPY*† FOR YOUR APPROPRIATE PATIENTS WITH nmCSPC WITH HIGH-RISK BCR

EMBARK was a randomized phase 3 trial that assessed the efficacy and safety of XTANDI + GnRH therapy* vs placebo + GnRH therapy* in 1068‡ patients with nmCSPC with high-risk BCR[1,2]

XTANDI + GnRH THERAPY* SIGNIFICANTLY IMPROVED METASTASIS-FREE SURVIVAL VS PLACEBO + GnRH THERAPY[1]

METASTASIS-FREE SURVIVAL (PRIMARY ENDPOINT)[1,2]



METASTASIS-FREE SURVIVAL

58% **reduction in the risk of metastasis or death**

with XTANDI + GnRH therapy* vs placebo + GnRH therapy* (HR = 0.42 [95% CI, 0.30-0.61]; *P* < 0.0001)[1]

- Number of events: 45 (12.7%) with XTANDI + GnRH therapy* vs 92 (25.7%) with placebo + GnRH therapy*[1]
- Median metastasis-free survival was not reached in either treatment arm*[1]
- The 5-year metastasis-free survival was 87% in the XTANDI + GnRH therapy* arm and 71% in the placebo + GnRH therapy* arm. This timepoint was not prespecified and is not in the US Full Prescribing Information for XTANDI[1,2]

Overall survival data were not mature at the time of metastasis-free survival analysis (12.2% deaths across the overall population of 1068‡ patients had been reported).[1]

In the EMBARK trial, the adverse reactions that occurred at ≥ 5% (Grade 1-4) or ≥ 2% (Grade 3-4) higher frequency in the XTANDI + GnRH therapy* arm than in the placebo + GnRH therapy* arm were hot flush (Grade 1-4: 69% vs 57%; Grade 3-4: 0.6% vs 0.8%), fatigue§ (Grade 1-4: 50% vs 38%; Grade 3-4: 4% vs 1.7%), musculoskeletal pain§ (Grade 1-4: 50% vs 43%; Grade 3-4: 4.8% vs 2.3%), fall (Grade 1-4: 21% vs 14%; Grade 3-4: 1.1% vs 1.1%), hemorrhage§ (Grade 1-4: 20% vs 15%; Grade 3-4: 3.4% vs 1.7%), fracture§ (Grade 1-4: 18% vs 13%; Grade 3-4: 4% vs 2.5%), diarrhea§ (Grade 1-4: 15% vs 9%; Grade 3-4: 0.6% vs 0.8%), cognitive disorder§ (Grade 1-4: 10% vs 4.8%; Grade 3-4: 0.3% vs 0.6%), osteoarthritis (Grade 1-4: 6% vs 4.2%; Grade 3-4: 2.8% vs 0.6%), and syncope (Grade 1-4: 4.8% vs 2.3%; Grade 3-4: 4.2% vs 1.7%).[1]

Important Safety Information (Continued)

Adverse Reactions (ARs)

patients. Discontinuations due to ARs were reported for 16% of XTANDI-treated patients. In PREVAIL, the placebo-controlled study of chemotherapy-naive mCRPC patients, Grade 3-4 ARs were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to ARs were reported for 6% of XTANDI-treated patients. In TERRAIN, the bicalutamide-controlled study of chemotherapy-naive mCRPC patients, Grade 3-4 ARs were reported in 39% of XTANDI patients and 38% of bicalutamide patients. Discontinuations with an AR as the primary reason were reported for 8% of XTANDI patients and 6% of bicalutamide patients.

In PROSPER, the placebo-controlled study of nonmetastatic CRPC (nmCRPC) patients, Grade 3 or higher ARs were reported in 31% of XTANDI patients and 23% of placebo patients. Discontinuations with an AR as the primary reason were reported for 9% of XTANDI patients and 6% of placebo patients.

In ARCHES, the placebo-controlled study of metastatic CSPC (mCSPC) patients, Grade 3 or higher ARs were reported in 24% of XTANDI-treated patients. Permanent discontinuation due to ARs as the primary reason was reported in 5% of XTANDI patients and 4% of placebo patients.

In EMBARK, the placebo-controlled study of nonmetastatic CSPC (nmCSPC) with high-risk biochemical recurrence (BCR) patients, 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.

Lab Abnormalities: Lab 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 are hemoglobin decrease, neutrophil count decreased, white blood cell decreased, hyperglycemia, hypermagnesemia, hyponatremia, hyperphosphatemia, and hypercalcemia.

Hypertension: In the combined data from five randomized placebo-controlled clinical trials, hypertension was reported in 14.2% of XTANDI patients and 7.4% of placebo patients. Hypertension led to study discontinuation in < 1% of patients in each arm.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid coadministration with strong CYP2C8 inhibitors. If coadministration cannot be avoided, reduce the dosage of XTANDI.

Avoid coadministration with strong CYP3A4 inducers. If coadministration cannot be avoided, increase the dosage of XTANDI.

Effect of XTANDI on Other Drugs Avoid coadministration with certain CYP3A4, CYP2C9, and CYP2C19 substrates for which minimal decrease in concentration may lead to therapeutic failure of the substrate. If 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.

Please see adjacent pages for Brief Summary of Full Prescribing Information.

References: 1. XTANDI [package insert]. Northbrook, IL: Astellas Pharma US, Inc. **2.** Freedland SJ, de Almeida Luz M, De Giorgi U, et al. Improved outcomes with enzalutamide in biochemically recurrent prostate cancer. N Engl J Med 2023;389(16):1453-65. **3.** Freedland SJ, De Giorgi U, Gleave M, et al. A phase 3 randomised study of enzalutamide plus leuprolide and enzalutamide monotherapy in high-risk non-metastatic hormone-sensitive prostate cancer with rising PSA after local therapy: EMBARK study design. BMJ Open (Epub) 08-12-2021.

See more EMBARK trial data

astellas Pfizer Oncology

MAT-US-XTD-2024-01238 09/24

Xtandi® (enzalutamide)
40 mg capsules

Xtandi® (enzalutamide)
40 mg tablets | 80 mg tablets

XTANDI® (enzalutamide) capsules, for oral use
XTANDI® (enzalutamide) tablets, for oral use

Initial U.S. Approval: 2012

BRIEF SUMMARY OF PRESCRIBING INFORMATION

The following is a brief summary. Please see the package insert for full prescribing information.

INDICATIONS AND USAGE

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

- castration-resistant prostate cancer
- metastatic castration-sensitive prostate cancer
- nonmetastatic castration-sensitive prostate cancer with biochemical recurrence at high-risk for metastasis

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

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.

Posterior Reversible Encephalopathy Syndrome (PRES)

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XTANDI. 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.

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.

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.

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.

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.

ADVERSE REACTIONS

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. 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
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

Table 1. Adverse Reactions in AFFIRM (cont'd)

	XTANDI (N = 800)		Placebo (N = 399)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
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

Table 2. Adverse Reactions in PREVAIL (cont'd)

	XTANDI (N = 871)		Placebo (N = 844)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
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. Includes asthenia and fatigue.
3. Includes musculoskeletal pain and pain in extremity.
4. Includes 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

Table 5. Adverse Reactions in ARCHES (cont'd)

	XTANDI (N = 572)		Placebo (N = 574)	
	Grade 1-4[1] (%)	Grade 3-4 (%)	Grade 1-4 (%)	Grade 3-4 (%)
Injury, Poisoning and Procedural Complications				
Fractures[4]	6	1	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 Nonmetastatic 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	20.2	16.8	11.1
Range, months	5.7 – 87.9	3.4 – 83.0	2.3 – 84.9
Patients who had Drug Treatment Suspended at Week 37			
Number of Patients (%)	321 (90.9)	240 (67.8)	304 (85.9)

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

Overall, deaths from adverse reactions during the total duration of treatment occurred in 6 patients (1.7%) receiving XTANDI plus 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.

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.

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
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))

DRUG INTERACTIONS

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.

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 a strong CYP3A4 inducer with strong CYP3A4 inducers. If the coadministration of XTANDI cannot be avoided, increase the dosage of XTANDI.

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, 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.

USE IN SPECIFIC POPULATIONS

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.

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.

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.

Infertility

Males

Based on animal studies, XTANDI may impair fertility in males of reproductive potential.

Pediatric Use

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

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.

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.

Hepatic Impairment

No dosage modification is recommended for patients with mild, moderate, or severe hepatic impairment.

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.

NONCLINICAL TOXICOLOGY

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).

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The SHARE Cohort: Investigating Genetic, Epigenetic, and Environmental Mechanisms of Subfertility

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At least 1 in 5 couples are impacted by subfertility, with a male factor implicated in at least half of these cases. Although there are several risk factors for male infertility, the etiology is frequently unknown. The Subfertility, Health, Assisted Reproduction, and the Environment (SHARE) cohort is a powerful dataset with a long history of uncovering key environmental, molecular, genetic, and clinical features associated with male infertility. This rich database combines medical, genealogic, and administrative data with biobanked specimens and semen analysis results from men undergoing fertility assessment collected by the University of Utah and Intermountain Healthcare beginning in 1996. Additionally, the SHARE cohort is linked to the Utah Population Database (UPDB), allowing for the identification of age- and sex-matched "fertile" control population, integration of demographic information, and longitudinal follow-up. UPDB is a comprehensive statewide population registry that links demographic, residential, clinical, and vital status information across several data sources.[1] This statewide database is further able to identify family structures, allowing for identification and inclusion of first- to third-degree relatives of men in the SHARE cohort, allowing for individual and family-based analyses into the factors underlying reduced sperm production in infertile men.

Increasing evidence suggests that male subfertility does not only impact reproduction but could serve as a biomarker for overall somatic health. Poor semen quality has been linked to various adverse health outcomes, including increased risk of hospitalization and mortality from chronic conditions, decreased lifespan, and increased risk of cardiovascular disease, metabolic syndrome, some cancers, and autoimmune conditions (Figure 1).[2,3] Evidence that male subfertility may serve as a somatic health marker for family members is also growing. Familial risk associations can suggest heritable genetic factors, shared environmental exposures and health behaviors, or combined genetic and environmental risk components as mechanisms underlying the relationship between male infertility and poor somatic health. However, analyses of familial associations between fertility and health are still rare, and the majority of these analyses were carried out within SHARE.[3-6]

SHARE leverages this unique population-level data resource, UPDB, to investigate the impact of male subfertility on familial patterns of disease. One such analysis described novel multicancer risk patterns among the families of severely subfertile men (<1.5 M/mL sperm) that manifest across generations. Distinct overall multicancer risk and familial multicancer patterns were observed, suggesting heterogeneity in cancer risk by type of subfertility and within subfertility type (Table).[6] A majority (66%) of the families of azoospermic men (0 M/mL sperm) showed population-level cancer risks. However, the remaining families formed 12 unique multicancer patterns with elevated risk for 2 to 7 cancer types. Twelve multicancer patterns were identified among the families of severely oligozoospermic men (>0-1.5 M/mL sperm), all of whom showed an increased risk for 1 to 3 cancer types. Increased odds of cancer diagnoses at young ages were seen in several of the multicancer patterns among families of both azoospermic and severely oligozoospermic men.

In addition to familial cancer risk assessment, SHARE was used to describe mortality in relatives of men undergoing fertility assessment.[7] Family members of men undergoing fertility assessment were classified by the total sperm count as azoospermic (0 M sperm), oligozoospermic (<39 M sperm), or normozoospermic (≥39 M). Relative to normozoospermia families, all-cause mortality risk increased in azoospermia and oligozoospermia families (Figure 2). First- and second-degree relatives of azoospermic and oligozoospermic men had the highest all-cause and cause-specific mortality risks, including death due to cardiovascular disease, sudden infant death syndrome, and congenital birth conditions. These results suggest that familial all-cause mortality risk may differ by fertility phenotype and motivate future investigations to uncover shared genetic and/or environmental factors that may influence both fertility and somatic health.

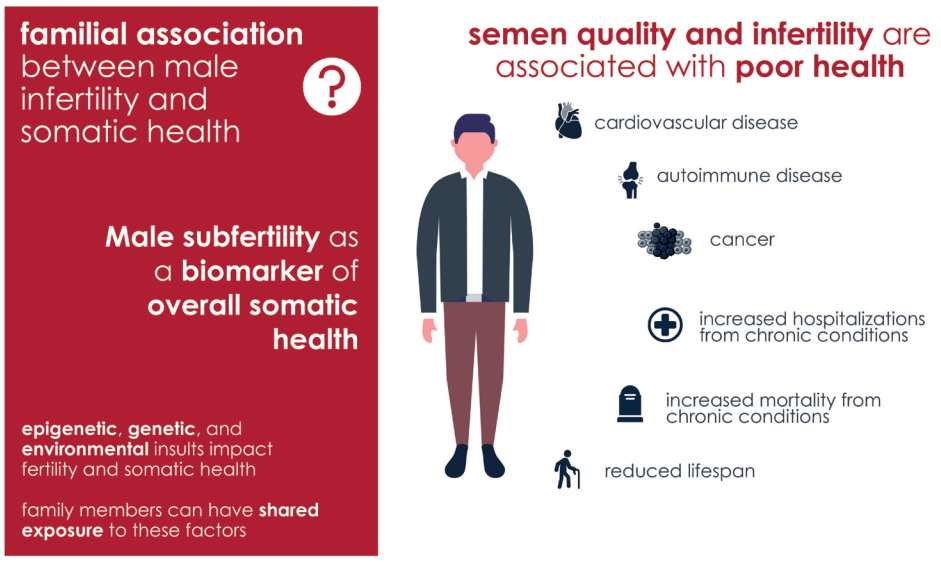

Figure 1. Semen quality and infertility are associated with poor health.

> "First- and second-degree relatives of azoospermic and oligozoospermic men had the highest all-cause and cause-specific mortality risks, including death due to cardiovascular disease, sudden infant death syndrome, and congenital birth conditions."

SHARE was also used to examine the impact of sociodemographic and environmental exposures on fertility and reproductive outcomes. Recent studies have demonstrated how environmental exposures can disrupt the male germline's epigenetic landscape and negatively influence male reproductive health. Using SHARE and UPDB, we have found that even chronic low-level environmental exposure to endocrine-disrupting chemicals found in industrial air pollution was associated with decreased semen quality, with the strongest associations seen for increased odds of azoospermia and declines in total

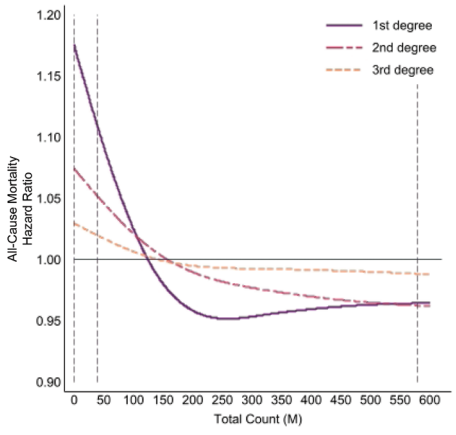

Figure 2. All-cause mortality risk is highest in first-degree relatives of subfertile men. The risk declines with increasing total sperm count and increasing distance in the relationship.

→ Continued on page 11

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THE SHARE COHORT: INVESTIGATING GENETIC, EPIGENETIC, AND ENVIRONMENTAL MECHANISMS OF SUBFERTILITY

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Table. Summary of Familial Multicancer Risk Patterns for Azoospermia and Severe Oligozoospermia Cohorts

Families in multicancer pattern		Increased diagnoses at young ages		Significant cancer phenotypes in familial multicancer pattern	
		Pediatric[a]	AYA[b]	No.	
Azoospermia cohort					
1	66.0%			0	
2	5.2%		X	2	Breast, Hodgkin lymphoma
3	3.8%	X	X	7	Small intestine, bone/joint, melanoma, other skin, breast, other leukemia, thyroid
4	3.8%			2	Soft tissue, ovarian
5	3.5%		X	3	Cervical, other female genital, renal
6	3.3%		X	3	Prostate, thyroid, other endocrine
7	3.1%		X	2	Testis, non-Hodgkin lymphoma
8	2.3%			2	Soft tissue, other skin
9	2.3%			3	Stomach, small intestine, thyroid
10	2.3%	X	X	2	Extrathoracic, acute lymphocytic leukemia
11	1.6%			2	Other digestive, thyroid
12	1.4%			2	Uterine, eye
13	1.4%			2	Other male genital, thyroid
Severe oligozoospermia cohort					
1	62.4%			2	Colon, liver[c]
2	7.5%		X	1	Testis
3	5.0%			2	Colon, liver
4	4.7%			3	Soft tissue, melanoma, testis
5	4.5%		X	2	Hodgkin lymphoma, myeloma
6	3.3%	X		2	Bone/joint, breast
7	2.8%		X	2	Myeloma, other endocrine
8	2.5%			3	Stomach, small intestine, non-Hodgkin lymphoma
9	2.5%			3	Other female genital, testis, eye
10	1.7%	X		2	Colon, acute lymphocytic leukemia
11	1.7%			1	Other skin
12	1.4%			1	Other male genital

Abbreviations: AYA, adolescent and young adult.
Azoospermia indicates sperm concentration of 0 M/mL. Severe oligozoospermia indicates sperm concentration <1.5 M/mL.
[a]Pediatric age range (<15 years); significantly increased risk relative to control families.
[b]AYA age range (15-39 years); significantly increased risk relative to control families.
[c]Significantly decreased familial risk for liver cancers.

motility and volume.[8] Exposure to wildfire smoke was also associated with decreased semen quality, including increased odds of azoospermia and decreased number of normal heads (Figure 3).[9]

The many epidemiologic associations that were made possible by analyzing the SHARE cohort in combination with the UPDB highlight the need to understand precise genetic, epigenetic, and environmental mechanisms contributing to spermatogenic impairment and its association with poor somatic health. To examine the genetic underpinnings of these relationships, we used error-corrected duplex DNA sequencing to investigate single nucleotide de novo mutations derived from the sperm and blood of oligozoospermic and normozoospermic men in the SHARE cohort.[10] This analysis builds upon prior research implicating dysfunction in DNA repair pathways, the same ones involved in human cancers, as candidate mechanisms underlying impaired spermatogenesis and poor somatic health in male infertility. From our analysis, we observed a significant 1.34- to 2.01-fold increase in age-adjusted mutation frequencies in the sperm of oligozoospermic men, suggesting that their germlines are predisposed to hypermutation by the onset of puberty. Conversely, we did not observe consistently elevated mutation rates in the blood of oligozoospermic men. While initially unexpected, this finding correlates with our familial multicancer clustering analyses, which showed that somatic comorbidities are not ubiquitous across infertile and subfertile men but exhibit a family-specific pattern across unrelated individuals.

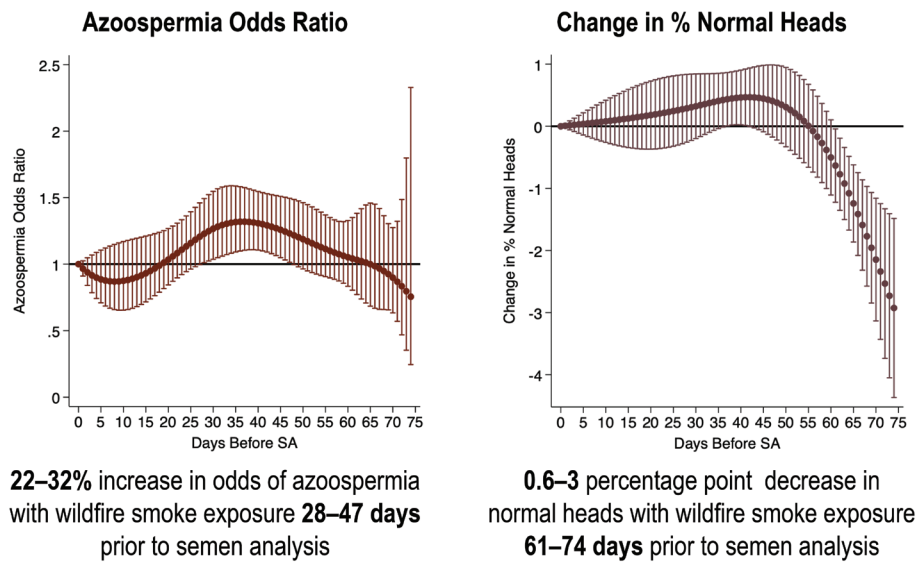

Figure 3. Exposure to wildfire smoke adversely impacts semen quality. SA indicates semen analysis.

SHARE provides a powerful platform for investigating the intricate web of genetic, epigenetic, and environmental mechanisms contributing to male subfertility. These advances will yield comprehensive insights that may lead to improved diagnostic, preventative, and therapeutic strategies for male subfertility, and advance our understanding of broader implications such a diagnosis could have for predicting family health. This endeavor stands at the forefront of reproductive health research, aiming not just to address subfertility, but to elucidate the larger picture of male health and well-being in diverse populations. ■

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Tips and Tricks for Stone Surgery Positioning in the Contracted Patient

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Surgical management of urolithiasis in patients with limb contractures presents a unique challenge, as a dysmorphic body habitus may limit optimal access to the bladder or upper urinary tract from either a retrograde or antegrade approach. The anatomic complexity of these cases is further compounded by the high-risk nature of surgery due to comorbidities, adverse social situations, and limited access to care in these patients.[1] As such, meticulous surgical planning is essential to ensure adequate stone clearance while minimizing complications.

Preoperative evaluation and planning are the keys to successful stone surgery in patients with a challenging body habitus. In-person visits are encouraged to allow for direct physical examination and discussion with the patient and their caregiver. A thorough physical examination should evaluate the extent of limb contractures and other musculoskeletal deformities to determine the optimal position that allows access to the kidneys, ureters, and bladder and will maximize stone clearance with the least morbidity. Furthermore, endoscopy of a urinary diversion may be considered in patients with prior lower urinary tract reconstruction to determine whether retrograde access to the ureter is feasible.

For patients with moderate-sized renal or ureteral stones in whom ureteroscopy is the preferred surgical treatment modality, the dorsal lithotomy position is typically the preferred position, as it allows the use of both flexible and rigid instrumentation. This position is best accomplished by placing the legs in stirrups, with the weight on the heels, minimizing pressure on the calves. Most stirrups provide enough range of motion to accommodate mild contractures of the hips, knees, and ankles. Alternatively, candy-cane stirrups may provide adequate lower limb separation and create a working space.

> "Access to the distal ureter is best accomplished with a semirigid ureteroscope. If positioning precludes that, flexible ureteroscopy, or even antegrade ureteroscopy, may be necessary."

If this is not possible or optimal, retrograde access via the supine position with a flexible cystoscope to obtain guidewire access for ureteroscopy is often feasible.

Access to the distal ureter is best accomplished with a semirigid ureteroscope. If positioning precludes that, flexible ureteroscopy, or even antegrade ureteroscopy, may be necessary. In some cases, severe limb contractures may preclude adequate access to the urethra in both men and women or may not allow fluoroscopic imaging of the kidneys and ureters because of interference by the legs (Figure 1). In such cases,

Figure 1. Patient with a history of spina bifida and lower limb contractures in whom a dorsal lithotomy position was not feasible and who underwent flexible ureteroscopy in a supine position.

Figure 2. Configurable surgical table with spreader bars that can be adjusted individually to accommodate patients with leg contractures.

particularly in women, prone split-leg positioning using spreader bars and lowering the individual spreader bars as necessary to achieve up to a 90° angle with the horizontal bed can provide surprisingly good access to the urethra for flexible endoscopy (Figure 2). Each leg can be adjusted individually to accommodate differential contractures.

For large and/or complex stones for which percutaneous nephrolithotomy is the optimal surgical modality, patient positioning is generally based on the experience and comfort of the surgeon. No position—flank, supine, or prone—has been shown to be superior to the others.[2] However, in patients with limb contractures, body habitus and anesthesia considerations may demand one position over another. If neither the prone or supine position can be easily achieved, or if adequate ventilation is precluded in either position, a modified flank position may provide access to the flank and the urethra

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TIPS AND TRICKS FOR STONE SURGERY POSITIONING IN THE CONTRACTED PATIENT

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while allowing for optimal ventilation. Although fluoroscopic-guided access may be a bit disorienting in this position, ultrasound-guided access is less unfamiliar.

Performing percutaneous nephrolithotomy in the modified flank position is appealing due to its versatility. Patients are placed in a lateral decubitus position, similar to that used for robotic-assisted nephrectomy. Familiarity with this positioning is helpful, as the process of positioning the patient can be streamlined by the operating room staff. Extra padding is used to protect pressure points. The ipsilateral arm is tucked against the chest. Malleable support, such as gel rolls, bolsters, or bean bags, are used to maintain the modified flank position at 45°. It is important that the patient be positioned at the edge of the bed to allow sufficient space around the access site to allow for unobstructed instrument movement. Likewise, it is critical to align the iliac crest with the break in the surgical table, as flexion of the table can open up the retroperitoneal space and improve access to the kidney. Furthermore, all-around adhesive strapping at the level of the torso/chest and lower limbs is recommended in the event the table needs to be tilted to improve ergonomics and/or renal access during the procedure.

Upper extremity contractures can also be challenging. Although in the prone position, we typically place the upper extremities with flexion at the elbow and the upper arm bent less than 90° from the shoulder, contractures may preclude that precise positioning. Tucking the arm alongside the body may be possible in some patients in which the arm cannot flex. However, in those for whom the arm is contracted in the flexed position at the elbow or is partially flexed across the chest, removing the cushion from the arm board or suspending the arm with towels and foam to a position lower than or even below the bed may allow the arms to remain flexed but out of the way.

It is evident from this discussion that the key to the successful management of these patients is a versatile operating room table with multiple points of flexion to accommodate the angulation of contracted extremities. Likewise, understanding the limitations of a patient's extremities is essential. In some cases where the patient will be positioned supine or in dorsal lithotomy, awake positioning allows the patient to vocalize discomfort with any particular position and avoids prolonged unfavorable positions during anesthesia.

In conclusion, a careful preoperative physical examination and thorough discussion with the patient and caregiver regarding the limitations of extremity movement and willingness to spend the time and effort to improvise during positioning to adjust each extremity for maximum comfort individually are key to safe and successful stone surgery in the contracted patient. ■

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Urological Reconstruction and Ukraine Humanitarianism

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"I will remember that I remain a member of society, with special obligations to all my fellow human beings…"[1] These words of the Hippocratic Oath recited by physicians for centuries have remained the cornerstone of our guiding principles. Current geopolitical events have far-reaching consequences beyond just identified conflicts. Since February 2022, the war in Ukraine has inextricably altered the health care domain through scarcity of resources and personnel for general citizens, creating unique challenges with complex injuries sustained on the battlefield. According to the WHO Surveillance System for Attacks on Health Care, there have been 1355 Russian attacks on Ukrainian health care facilities, resulting in damage to 630 facilities since the onset of the war.[2] The human toll for the Ukrainian population has also been staggering with reports of wartime casualties hovering around 31,000 with up to 120,000 injured.[3] Civilians also experience delays in care for routine care, which place further strain on the health care system. Taking this all into account, our group saw vulnerable populations in dire need of assistance.

Genitourinary trauma has been reported in 4.2% of modern-day battlefield injuries.[4] These include blast injuries and penetrating traumas. These injuries are complicated by extensive tissue loss, dense fibrosis, and fistulas. Following initial stabilization, patients require complex repairs, oftentimes necessitating adjunctive techniques such as autologous grafts, flaps, or creative operative approaches in settings of multiple previous operations.

The field of urological reconstruction in Ukraine is in its infancy. Unfortunately, due to the aforementioned injuries, this field is being forced to expand and evolve to address the needs of its population. Through partnership with both local civilian and military urologists, a reconstructive surgical mission

Figure. Drs Gupta and Mishra performing urethroplasty with local urologists. Multiple local urologists actively enaged in learning urethroplasty techniques in real time.

was created to address the disparities in comprehensive urological care. This initiative was launched following in-depth discussions with patients, nongovernmental organizations, and urologists to identify the most pressing needs, allowing for targeted interventions in areas requiring the most attention. Across 2 surgical missions in Kyiv and Lviv, Ukraine, 31 patients were treated in collaboration with local urologists and urology trainees (Figure). A key focus of the mission was the educational component, emphasizing the foundational principles of reconstructive urology. This approach ensures that high-quality care will continue to exist within the community, extending the impact well beyond the initial interventions and fostering long-term benefits.

The cases performed included urethroplasty with buccal mucosal grafts and/or gracilis muscle flaps, excision and primary anastomosis urethroplasty, staged perineal urethrostomy with pendulous urethral reconstruction, Orandi flap pendulous urethral reconstruction, rectourethral fistula repairs, simple cystectomy with urinary diversion, ureteral reconstruction with bowel interposition, ureteral reimplant with Boari flap, simple nephrectomy, corporal reconstruction, and penile prosthetics. The educational components encompassed not only intraoperative techniques but also preoperative decision-making and postoperative management, delivered through a series of in-person sessions and Zoom meetings. This comprehensive care has been longitudinal thanks to close communication with our partnering local urologists long after we returned stateside. We look forward to continuing our partnership, providing healing to those affected by the War in Ukraine, and further developing the field of reconstructive urology in the region. ■

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CLINICAL TRIALS

Updates on High-Grade Nonmuscle-Invasive Bladder Cancer Clinical Trials

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While bacillus Calmette-Guérin (BCG) remains the most effective treatment for high-grade nonmuscle invasive bladder cancer (NMIBC), up to 20% to 30% of patients do not respond to BCG monotherapy, and ~50% of initial responders will relapse within 5 years of treatment.[1] A number of new therapeutic approaches have recently been approved by the US Food and Drug Administration (FDA) for BCG-unresponsive NMIBC. Results from KEYNOTE-057 led to approval in 2020 of the intravenous PD1/PDL1 inhibitor pembrolizumab for treatment of BCG-unresponsive carcinoma in situ (CIS) in patients ineligible for, or who declined, radical cystectomy,[2] although the oncological efficacy of pembrolizumab was modest. Another PD1/PDL1 inhibitor, atezolizumab, was evaluated in SWOG S1605 and had similar oncologic

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UPDATES ON HIGH-GRADE NONMUSCLE-INVASIVE BLADDER CANCER CLINICAL TRIALS

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outcomes but failed to achieve the prespecified futility threshold.[3] Nadofaragene firadenovec, an intravesical vector-based gene therapy, and nogapendekin alfa inbakicept, an interleukin-15 superagonist administered with BCG, are now approved for BCG-unresponsive CIS with/without papillary tumors, but durable efficacy is still lacking. Cretostimogene grenadenorepvec, a conditionally replicating oncolytic adenovirus, received FDA Fast Track and Breakthrough Therapy designation for BCG-unresponsive disease based on preliminary results from the phase 1 BOND-003 study (NCT04452591). Intravesical cretostimogene monotherapy resulted in a 75% complete response rate at "any time," with 83% retaining an ongoing response at 12 months.[4]

FDA Breakthrough Therapy designation was also given to TAR-200, a novel osmotically driven intravesical drug delivery system. TAR-200 delivers sustained local release of gemcitabine into the bladder without detectable concentration in plasma. Several trials are underway to evaluate TAR-200 alone and in combination with immune checkpoint blockade (ICB). The SunRISe-1 trial (NCT04640623) randomized patients with BCG-unresponsive NMIBC CIS to 3 cohorts: TAR-200 alone, TAR-200 with cetrelimab (anti-PD1), and cetrelimab alone. Preliminary data demonstrated that TAR-200 monotherapy resulted in an 83% complete response rate at "any time" and an estimated 1-year duration of response rate of 75%.[5]

Notably, these have been single-arm, nonrandomized clinical trials with varying methodology and heterogeneous patient populations, limiting cross-trial comparisons. Randomized trials to determine the relative efficacy of these treatments should be prioritized by the urologic oncology community, although they will be challenging to conduct because pharmaceutical companies lack the incentive to participate when their drugs have already been FDA approved.

With the ongoing BCG shortage (since 2012), investigators have focused on identifying alternative formulations and intravesical treatment options, such as using strains other than TICE BCG (the only strain currently available in the United States). SWOG S1602 PRIME (NCT03091660) is a phase 3 trial randomizing patients to TICE BCG vs Tokyo-172 BCG with/without intradermal T-cell priming with the Tokyo-172 strain prior to intravesical therapy. While the trial's findings are still pending, results showing noninferiority of the Tokyo-172 strain may mean a new strain of BCG will be allowed into the United States. Among the most important studies investigating alternatives to BCG is the BRIDGE trial (ECOG-ACRIN EA8212/NCT05538663), which is randomizing 870 patients with newly diagnosed high-grade NMIBC to either BCG or gemcitabine with docetaxel (GemDoce).[6] A investigator-initiated phase 2 trial of GemDoce in the BCG-naïve setting found the combination was well tolerated and had a complete response rate of 100% (25/25) at 3 months and 92% recurrence-free survival at 12 months.[7]

Even if Tokyo-172 BCG does not get FDA approval, the shortage is expected to be resolved in 2026 with the opening of a new Merck TICE BCG manufacturing facility. In anticipation of the crisis being resolved, developing strategies to enhance the effectiveness of BCG is of the utmost importance.

Preclinical studies suggest that PD1/PDL1 overexpression may be a mechanism for BCG resistance. Three large industry-sponsored trials (KEYNOTE-676 cohort B [NCT03711032], CREST [NCT04165317], and POTOMAC [NCT03528694]) are testing whether the addition of ICB can enhance the effectiveness of BCG for patients with BCG-naïve NMIBC. The results of these trials are of great interest but need to be carefully analyzed to determine which patients with NMIBC represent justifiable risk/benefit trade-offs, given the 12% to 15% risk of developing immune-related major adverse events after ICB.[2,3] Additional data for identifying which patients with NMIBC are most likely to benefit from ICB will likely be provided by an ongoing investigator-initiated phase 2 trial testing the combination of pembrolizumab with BCG in 37 patients with BCG-naïve "very high risk T1" for whom the AUA and NCCN guidelines typically recommend immediate radical cystectomy (NCT03504163).

Another promising approach for NMIBC is combination chemoimmunotherapy regimens using BCG and intravesical chemotherapy. ANZUP 1301 (NCT02948543) is an international open-label phase 3 trial of standard BCG therapy vs BCG and passive instillation of mitomycin C (MMC) in 500 patients with high-risk BCG-naïve NMIBC. This trial builds upon a prior successful randomized clinical trial demonstrating the superiority of combination BCG+MMC, where MMC is delivered via electromotive drug administration.[8] Gemcitabine, a better tolerated, more effective, and less costly intravesical option, is also under investigation in combination with BCG. In a phase 1 trial (NCT04179162) of BCG-exposed high-grade NMIBC, 25 patients with BCG-exposed NMIBC (high-grade recurrence within 24 months of last BCG, but not meeting BCG-unresponsive criteria) received combination intravesical gemcitabine and BCG (GemBCG). Complete response at 6 and 12 months was 96% and 92%, respectively; no patient progressed to muscle-invasive disease or underwent cystectomy.[9] The phase 2 portion of this trial recently completed enrollment (n = 44) with promising preliminary results. A phase 3 trial (Alliance A032303; GAIN) set to open in May 2025 will randomize 330 patients with BCG-exposed NMIBC to receive gemcitabine and BCG or retreatment with BCG alone.

Ongoing investigations also include combinatorial strategies of novel intravesical therapies with/without ICB. For example, the phase 2 CORE-001 trial demonstrated 83% and 57% complete response rates at 3 and 12 months, respectively, in 35 patients with BCG-unresponsive CIS treated with intravesical cretostimogene and pembrolizumab.[10] Ultimately, randomized trials are needed to understand the additive benefits of component treatments, but trials adding ICB will need to be thoughtfully designed to enrich for NMIBC patients for whom the added toxicity is most justified. Efforts should also focus on conducting randomized comparisons of novel agents that were approved based on single-arm, nonrandomized studies, and concerted efforts should be made to develop predictive biomarkers to help select patients for these treatment approaches.

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Studying the Impact of Wildfire Smoke on Human Sperm

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I am humbled to be selected for the Urology Care Foundation™ Research Scholar Award, which supports my project studying the impact of wildfire smoke on human sperm under the guidance of my mentor, Thomas Walsh, MD, MS. The support of the Research Scholar Award provides the protected time needed to complete the project, present the work at conferences such as the Annual Meeting of the AUA and the Western Section of the AUA, write manuscripts, and submit grants. Moreover, the Research Scholar Award is allowing me to develop a unique niche as a surgeon-scientist focused on male infertility and environmental health.

I was born and raised in Seattle, Washington, just a few miles from the University of Washington, where I am a newly appointed assistant professor in the Department of Urology. I don't recall air quality issues affecting my childhood in Seattle, but in recent memory, unhealthy air quality associated with wildfire smoke has become a seasonal event in the Pacific Northwest. The wildfire smoke events that I personally experienced while growing my young family stimulated my interest in how wildfire smoke exposure affects human sperm. In early September 2020, high winds pushed smoke from eastern Washington wildfires into the Puget Sound region. The air smelled of smoke, and ash fell around Seattle while air quality in the Puget Sound region declined to hazardous levels.[1] In multiple regions of Oregon, aggressive wildfires burned nearly a million acres of forest and ultimately threatened Portland suburbs. September 2020 was a notable smoke event, and seasonal wildfire smoke events are now part of life in the Pacific Northwest. Wildfire smoke exposure is emerging as a national and global concern, with a particularly intense year of destructive and deadly wildfires worldwide in 2023. As climate change reduces winter snowpack and produces hotter and drier summers, wildfires are increasing in frequency and intensity.[2]

It is well established that wildfire smoke exposure is a major threat to human health and that most of the health effects are mediated by fine particulate matter from burning vegetation, synthetics, and other materials.[1-3] Wildfire smoke exposure has been linked to respiratory problems, heart attack, stroke, lung cancer, and cognitive impairment.[4] A higher risk of testis cancer has been observed among firefighters,[5] suggesting that the male reproductive tract may be a target of wildfire smoke. However, it is not known how wildfire smoke exposure affects human gametes and reproduction. Infertility affects 1 in 6 individuals worldwide, and a male factor is identified in up to 50% of couples.[6] In a study using mice, widespread epigenetic changes in sperm were observed after simulated wildfire smoke exposure.[7] A decrease in total motile sperm count was observed during the September 2020 Pacific Northwest wildfire smoke event in Portland, Oregon, among a small cohort of individuals undergoing intrauterine insemination (IUI), a common fertility treatment in which a purified motile sperm solution is placed into the partner's uterine cavity at the time of expected ovulation.[8] This is the first report, to my knowledge, of wildfire smoke exposure impacting human gametes. Couples with infertility undergoing treatment may be especially vulnerable to environmental exposures such as wildfire smoke events.

The overall hypothesis of our study is that wildfire smoke has harmful effects on human sperm. Our project focuses on a period of unhealthy air due to wildfire smoke that occurred in Seattle, Washington, in September 2020 (Figure). First, we are conducting a study of sperm donors who underwent serial sperm donations prior to, during, and in the 3 months after September 2020 in Seattle, given that spermatogenesis occurs over 74 days in humans.[9] Sperm donor subjects completed questionnaires to estimate their smoke exposure. Using banked samples from these sperm donors, we are performing sperm DNA integrity assessment with the comet assay, a single-cell gel electrophoresis assay that detects double-stranded DNA breaks.[10] This will allow us to evaluate changes in sperm DNA integrity associated with wildfire smoke exposure over time in the same sperm donor subjects. In the second part of our study, we are evaluating sperm quality at the time of IUI procedures performed in the period prior to, during, and after September 2020 in Seattle. We are comparing the total motile sperm count for patients who underwent IUI during or after the wildfire smoke event in September 2020 in Seattle to sperm parameters from the same subject at the time of their diagnostic semen analysis obtained prior to smoke exposure. Understanding whether sperm parameters at the time of IUI are affected by wildfire smoke exposure will be important for counseling patients to mitigate exposures. As wildfire smoke exposure events increase in intensity and frequency, it is critical to understand the impact of wildfire smoke on sperm quality and reproductive outcomes.

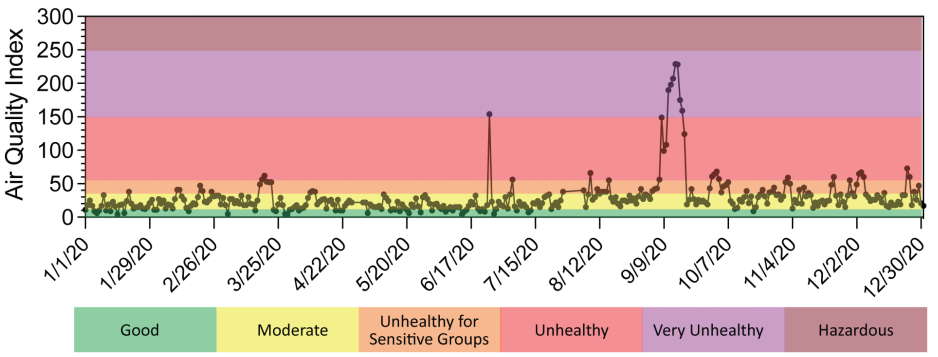

Figure. 24-Hour daily average Air Quality Index from the Environmental Protection Agency single outdoor sensor in Seattle, Washington, for the year 2020 (https://www.epa.gov/outdoor-air-quality-data/download-daily-data). Air Quality Index is a composite index that includes ground-level ozone, particle pollution, carbon monoxide, sulfur dioxide, and nitrogen dioxide, the 5 major pollutants regulated by the Environmental Protection Agency.

In addition to regular interactions with my research mentor, Dr Walsh, the support of the Research Scholar Award is allowing me to participate in several career development opportunities provided by the AUA. I am a mentee in the Urology Scientific Mentoring and Research Training Academy (USMART) program and have regular meetings with a new mentor outside my institution, Dr James Hotaling. I am also participating in the AUA's Early Career Investigator's Workshop in Linthicum, Maryland. I am very grateful to the AUA, the Urology Care Foundation™, and the Western Section for supporting my work on wildfire smoke and human sperm. I hope to publish this work in AUA journals such as the *The Journal of Urology*®. Ultimately, I expect this will provide preliminary data for a prospective study of wildfire smoke and male fertility. My next step will be to apply for an individual career development award from the National Institutes of Health toward my goal of developing an independent research program in male infertility and environmental health. ■

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