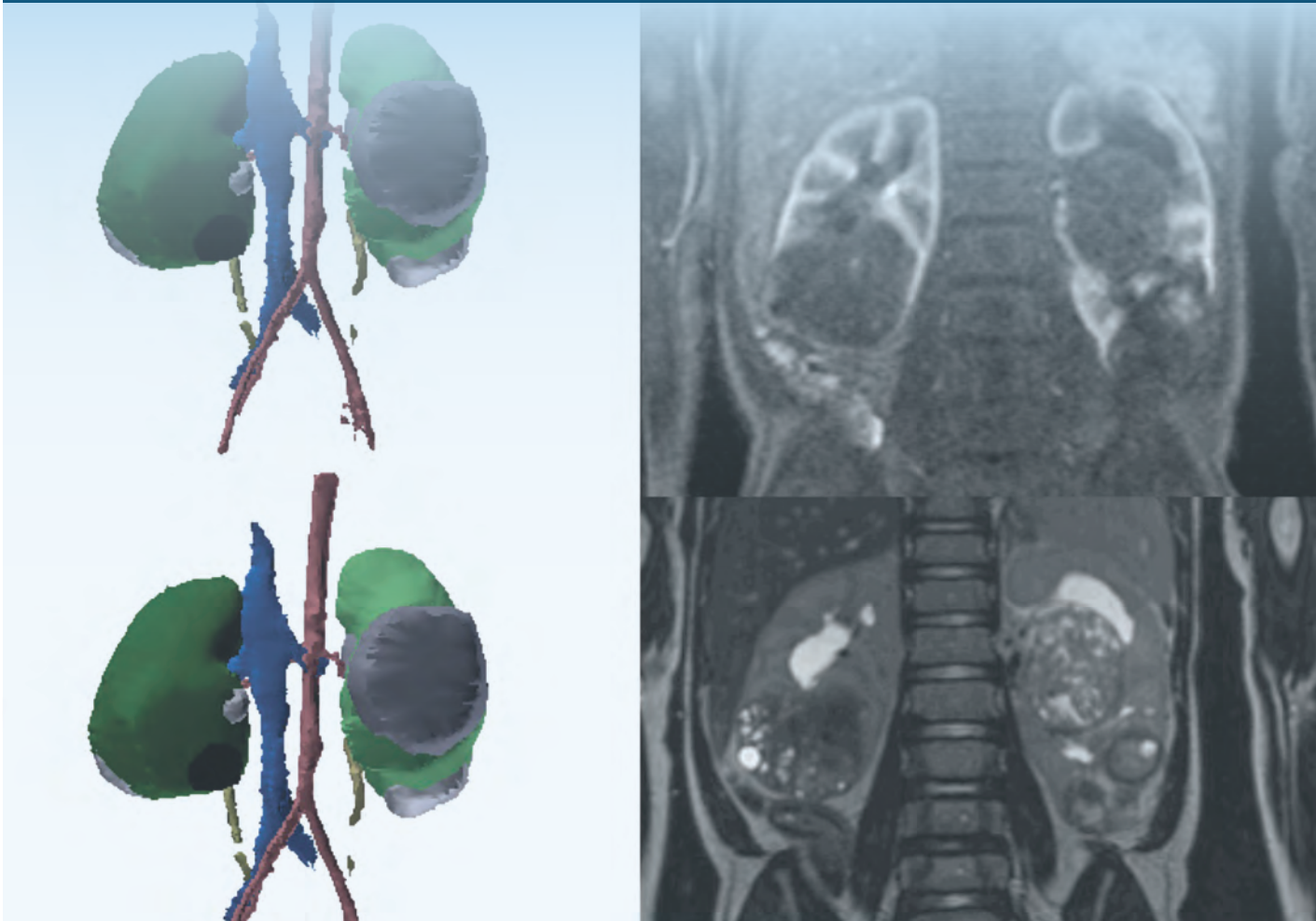




THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN UROLOGICAL ASSOCIATION

Renal Nephrometry in Childhood Wilms Tumor: What Is the Role?

Meghan F. Davis, MD, MPH; Christopher J. Long, MD; Thomas F. Kolon, MD; Sameer Mittal, MD, MSc



COMING SOON ONLINE

Fournier's Gangrene Reconstruction: Orchidopexy and Split-Thickness Skin Graft for Scrotal Defects

Fasciocutaneous Thigh Pouches for Scrotal Reconstruction Following Fournier's Gangrene

Transmeatal Endoscopic Management of Anterior Urethral Strictures: Thinking Outside the Box

Developing a Digital Tool to Aid Patients With Urinary Diversion Decisions After Radical Cystectomy

A Patient-Partnered Approach to Identifying Drivers and Barriers to PSA Screening of Black Americans

Decoding Idiopathic Male Infertility and Hypogonadism: The APHRODITE Criteria as a New Frontier in Treatment

Sandro C. Esteves, MD, PhD

GROUP 1
Reduced FSH/LH levels, TT < 350 ng/dL, azoospermia or severe oligozoospermia (Hypo-Hypo - acquired or congenital)

TREATMENT: FSH + hCG
Acquired: hCG (FSH, if needed)

GROUP 2
Lowered semen parameters (including NOA), normal FSH (sUNL) and TT levels (≥ 350 ng/dL) (Reduced Gn action & functional hypogonadism)

TREATMENT: FSH monotherapy

GROUP 3

Lowered semen parameters (including NOA), normal FSH levels (sUNL), & reduced TT levels (s350 ng/dL) (Reduced Gn action & biochemical hypogonadism)

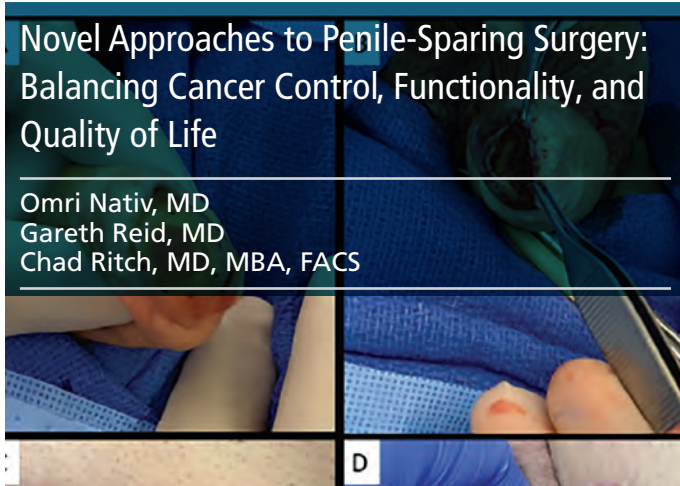
TREATMENT: FSH (+ hCG)

GROUP 4

Lowered semen parameters (incl. NOA)

Novel Approaches to Penile-Sparing Surgery: Balancing Cancer Control, Functionality, and Quality of Life

Omri Nativ, MD
Gareth Reid, MD
Chad Ritch, MD, MBA, FACS



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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 BCR¹

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

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

²The 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}

³Includes 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)

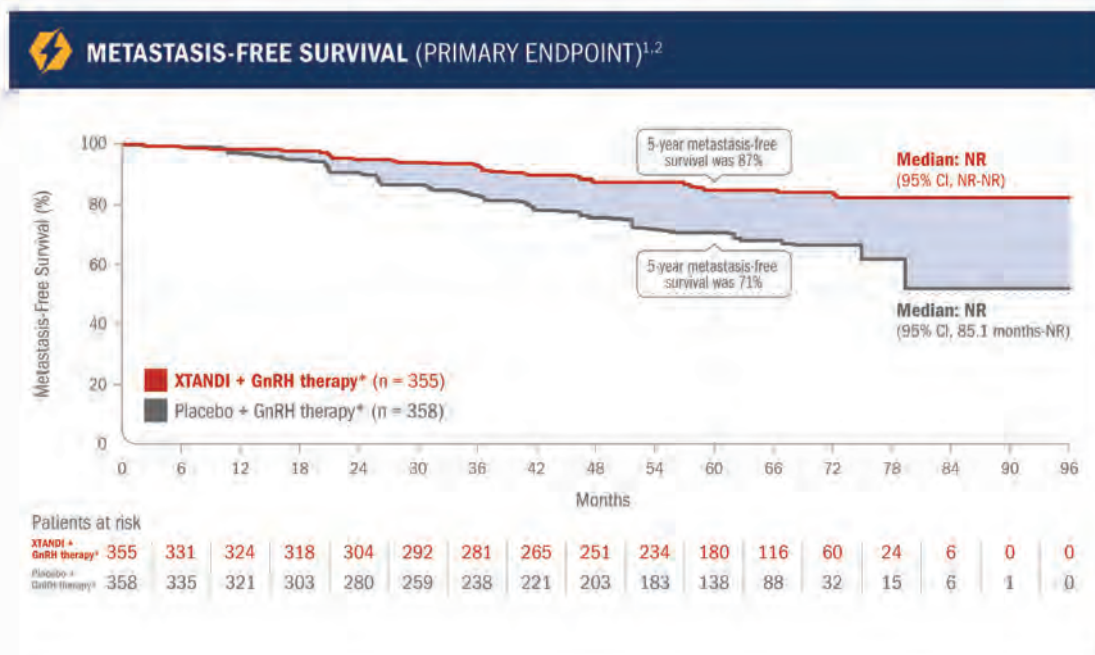
In the data from the five randomized placebo-controlled trials, the most common ARs ($\geq 10\%$) that occurred more frequently ($\geq 2\%$ over placebo) in XTANDI-treated patients were musculoskeletal pain, fatigue, hot flush, constipation, decreased appetite, diarrhea, hypertension, hemorrhage, fall, fracture, and headache. In the bicalutamide-controlled study, the most common ARs ($\geq 10\%$) 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

EMBARC 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 THERAPY¹



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 $\geq 5\%$ (Grade 1-4) or $\geq 2\%$ (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-naïve 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-naïve 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 $\geq 5\%$ 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



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



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.

EMBARC: XTANDI versus Placebo in Nonmetastatic CSPC Patients with High-risk BCR

EMBARC 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 Treatment¹ | | | |
| 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 [CL_{cr}] ≥ 30 mL/min). XTANDI has not been studied in patients with severe renal impairment (CL_{cr} < 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).

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 10017

Revised: November 2023

392224-XTA-USA

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076-8882-PM 12/23

Renal Nephrometry in Childhood Wilms Tumor: What Is the Role?

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Wilms tumor (WT) is the most common malignant renal tumor in children. Survival has improved with standardization of treatment from guidelines and clinical trials through the International Society of Pediatric Oncology and Children's Oncology Group. While these groups take different approaches, surgical resection remains the mainstay of treatment.¹ Radical nephrectomy has been the standard of care, with nephron-sparing surgery (NSS) advocated for in cases of bilateral WT (BWT), multifocal unilateral disease, or those with Wilms predisposition syndromes.¹ NSS is aimed at preserving functional renal tissue and preventing long-term declines in renal function. While the 20-year risk of end-stage renal disease (ESRD) for unilateral WT is 0.7%, the 3-year risk of ESRD is 4% for patients with metasynchronous disease and 19% for patients with BWT.² For patients with BWT and metasynchronous disease, these high rates of ESRD are thought to be driven by aggressive disease in a solitary remaining kidney, which then requires further surgical excision to prevent progression or metastasis.² Aside from renal mass loss, nephrotoxic chemotherapy and radiation-induced kidney injury likely also contribute to declines in renal function in patients with WT.² Renal insufficiency has been tied to higher risk of cardiovascular disease, hospitalization, and death amongst adults³; hence NSS is increasingly a consideration in pediatric patients with renal malignancy.

Recent International Society of Pediatric Oncology protocols permit partial nephrectomy for select patients with unilateral WT.⁴ A meta-analysis of 66 studies comparing partial nephrectomy to radical nephrectomy for WT found equivalent rates of tumor rupture, tumor

recurrence, and overall survival.⁵ However, the authors caution that patients selected for NSS were more likely to have lower-stage disease. With respect to renal function, a second meta-analysis of 20 studies demonstrated improved postoperative renal function for partial nephrectomy compared with radical nephrectomy.⁶ While tumor size and stage are reported in most of the included studies, interpretation is limited by our ability to make more detailed comparisons about the anatomic complexity of the renal masses, which in turn may have driven the decision to perform a NSS.⁶

While there is likely an expanding role for NSS in WT, this must be done so carefully, balancing the preservation of functional renal tissue with potential for increased complications, positive margins, and tumor recurrence. When considering NSS, nephrometry scores, which quantify multiple anatomic characteristics of a renal mass, can aid in surgical planning and decision-making. Nephrometry scores have been widely studied in adult tumors to quantify the risk of complications following partial nephrectomy with the R.E.N.A.L. (for radius, exophytic/endophytic, nearness of tumor to collecting system, anterior/posterior, location relative to polar line) score being the most used and best correlated with perioperative outcomes.⁷ In considering a nephron-sparing approach, nephrometry scores are one part of the decision. These scores can be coupled with 3D models (Figure) to aid in surgical planning and intraoperative decision making.^{1,8}

Preliminary studies have applied this score to pediatric patients,⁹ but it is not widely utilized. Our group showed moderate-good agreement when multiple raters scored consecutive patients undergoing NSS using the R.E.N.A.L. nephrometry score.¹⁰ Additionally, the cohort's median nephrometry score was 9, indicating intermediate-high complexity tumors undergoing NSS. Higher scores were associated with longer length of stay and operative time, but without a difference in 30-

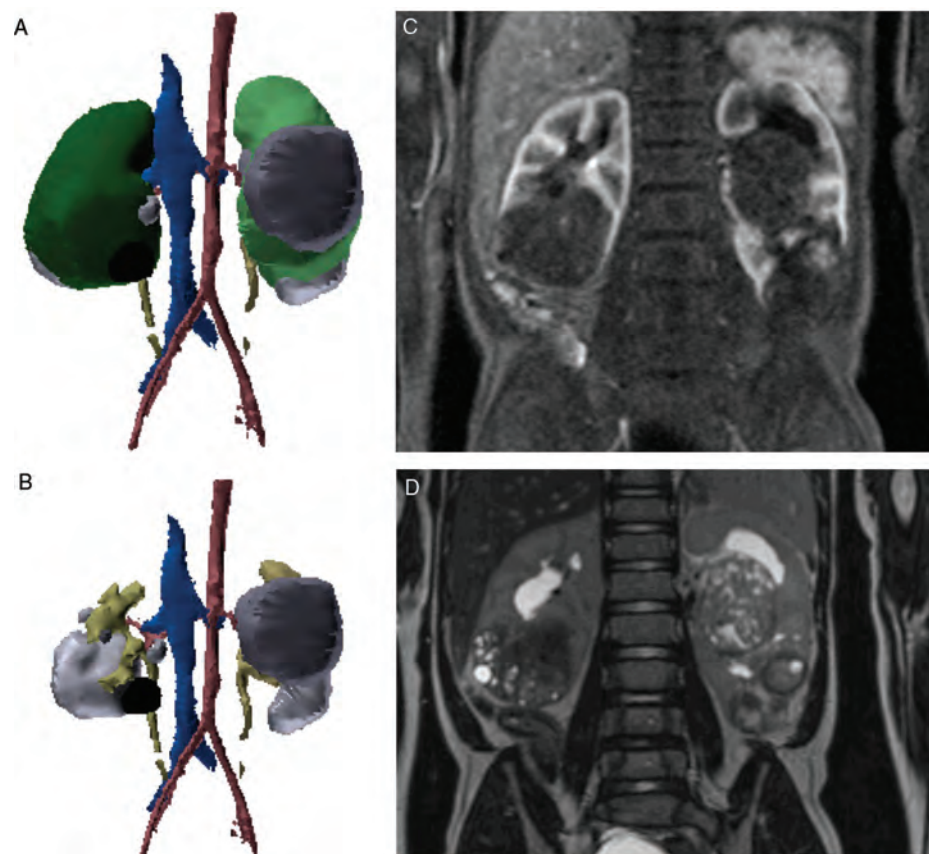


Figure. A, B, A 3D model was generated from an abdominal/pelvic MRI for a child with multiple renal masses in preparation for nephron-sparing surgery. The renal masses appear in gray. B, The normal renal parenchyma is subtracted out. C, D, Select images from the same patient's abdominal/pelvic MRI.

day complications.¹⁰ At 35-month follow-up, 78% remained cancer free, 17.9% had died, and 3.6% had a recurrence.

Currently, utilization of NSS has been surgeon and center specific. Widespread use of nephrometry scores would allow for improved analysis of this approach.¹⁰ As we seek to better understand how partial nephrectomy fits into the management paradigm for WT, standard use and reporting of nephrometry scores will be paramount for our community to compare mass complexity across institutional series. Nephrometry scores are easily reproducible and, much like adult urologic oncology literature, should be included in all reports to allow for more meaningful conclusions with the goal of improving outcomes for children with WT. ■

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Decoding Idiopathic Male Infertility and Hypogonadism: The APHRODITE Criteria as a New Frontier in Treatment

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The APHRODITE criteria—short for “Addressing Male Patients With Hypogonadism and/or Infertility Owing to Altered, Idiopathic Testicular Function”—present a novel system for describing and managing male infertility, particularly in hypogonadal males with idiopathic infertility.¹ Named after the Greek goddess of fertility and male sexuality, these criteria offer a structured framework that uses clinical characteristics, hormone levels, and semen analysis to categorize patients. The classification includes 5 distinct groups, each posing unique therapeutic challenges and opportunities, with hormonal treatments showing promise in improving spermatogenesis. While more research is required to establish the full potential of this approach, the APHRODITE criteria represent an essential first step aimed at enhancing communication between health care providers and paving the way for novel treatments for male infertility.

The Need for Improved Classification

Male infertility has long been a source of frustration for both patients and clinicians, particularly in cases of idiopathic infertility where progress has been limited. Many practitioners resort to intracytoplasmic sperm injection as the primary solution, often without exploring other treatment options.² The APHRODITE criteria aim to change this paradigm by offering a more systematic and detailed approach to classifying and treating men with infertility and hypogonadism, specifically those who may benefit from hormonal interventions.

Hormonal Regulation of Spermatogenesis

Understanding the APHRODITE criteria requires a basic knowledge

of spermatogenesis—the intricate process that takes approximately 75 days by which sperm is produced. This process is primarily regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH)—mediated testosterone production.³ These hormones are crucial in regulating spermatogenesis and form the foundation of the APHRODITE classification system.

The Role of LH, Testosterone, and FSH in Sperm Production

Gonadotropin-releasing hormone, secreted by the hypothalamus, signals the pituitary to release FSH and LH, which act on Sertoli and Leydig cells in the testes. LH is crucial for stimulating testosterone production in Leydig cells, while testosterone, in turn, activates androgen receptors on Sertoli cells to support spermatogenesis. Testosterone is particularly critical in the final phases of spermatogenesis, transforming round spermatids into mature sperm. FSH works in tandem with testosterone and LH, acting on Sertoli cells to ensure proper support for sperm production.³

Hypogonadism and Infertility

Many cases of male infertility arise from inadequate testicular stimulation due to insufficient FSH and/or LH production or action.⁴ Hypogonadism, characterized by deficient gonadal function—typically associated with low testosterone production—can result from various factors, including testicular disease, systemic illnesses, infections, congenital abnormalities, aging, or poor lifestyle choices.¹ The condition is classified as idiopathic when no underlying cause is identified. Despite the complexity, hypogonadism is often treatable, potentially allowing for the improvement of testicular function.

Table 1. Laboratory Tests and Interpretation According to the APHRODITE Criteria

| | | |
|---------------------------------|-------------|--|
| Semen analysis parameters | Normal | Percentages of motile and morphologically normal spermatozoa and concentration of spermatozoa in the ejaculate that is equal to or above the fifth percentile of the data from the 2021 WHO semen analysis manual reference limits ^a |
| | Lowered | Reduced percentages of motile and morphologically normal spermatozoa and concentration of spermatozoa in the ejaculate that is lower than the fifth percentile of the data from the 2021 WHO semen analysis manual reference limits ^a |
| | Azoospermia | Absence of spermatozoa in the ejaculate ^b |
| FSH level | Normal | FSH within the normal range of the assessing laboratory (eg, between 1.5-12.0 IU/L ^c) |
| | Reduced | FSH below the normal range of the assessing laboratory (eg, <1.5 IU/L) |
| | Elevated | FSH above the upper limit of the normal range of the assessing laboratory (eg, >12 IU/L) |
| Testosterone level ^d | Normal | Testosterone above the lower limit of the normal range of the assessing laboratory (suggested cutoff: ≥350 ng/dL ^e) |
| | Reduced | Testosterone below the lower limit of the normal range of the assessing laboratory (suggested cutoff: <350 ng/dL ^e) |

Abbreviation: FSH, follicle-stimulating hormone.

Adapted from Esteves et al, APHRODITE criteria: addressing male patients with hypogonadism and/or infertility owing to altered idiopathic testicular function, *Reprod Biomed Online* 2024, with permission (under the terms of the Creative Commons CC-BY license).¹

^aSperm concentration: 16×10^6 /mL; total motility: 42%; progressive motility: 30%; normal forms: 4%.

^bAfter examination of the centrifuged pellet.

^cTypical reference values by chemiluminescence immunoassays.

^dTotal testosterone.

^eCutoff for biochemical hypogonadism as recommended by the European Academy of Andrology, European Association of Urology, International Consultation for Sexual Medicine, and International Society for the Study of the Aging Male.

Breaking Down the APHRODITE Criteria

Developed through a collaborative effort among experts in male infertility, the APHRODITE criteria build upon concepts from the POSEIDON criteria for female infertility.^{1,5} The system relies on clinical characteristics and routine lab tests, such as semen analysis and hormonal assessments, with a focus on FSH and testosterone levels (Table 1).¹ It classifies male infertility into 5 groups, each with specific treatment recommendations and endpoints (Figure; Table 2).¹

“Despite the complexity, hypogonadism is often treatable, potentially allowing for the improvement of testicular function.”

DECODING IDIOPATHIC MALE INFERTILITY AND HYPOGONADISM

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APHRODITE Criteria: Five Groups in a Nutshell

APHRODITE is a novel stratification system for infertile men with testicular dysfunction, for whom fertility prospects may improve after hormonal therapy

APHRODITE criteria aim to provide guidance on improving semen quantity and/or quality for natural or ART conception, based on:

1. Routine clinical history/ physical exam
2. Semen analysis parameters
3. FSH & TT profile

GROUP 1

Reduced FSH/LH levels, TT < 350 ng/dL, azoospermia or severe oligozoospermia (**Hypo-Hypo - acquired or congenital**)

TREATMENT:

Congenital: FSH + hCG

Acquired: hCG (FSH, if needed)

GROUP 2

Lowered semen parameters (including NOA), normal FSH (\leq ULN) and TT levels (\geq 350 ng/dL) (**Reduced Gn action & functional hypogonadism**)

TREATMENT: FSH monotherapy

GROUP 3

Lowered semen parameters (including NOA), normal FSH levels (\leq ULN), & reduced TT levels (\leq 350 ng/dL) (**Reduced Gn action & biochemical hypogonadism**)

TREATMENT: FSH (+ hCG)

GROUP 4

Lowered semen parameters (incl. NOA), elevated FSH ($>$ ULN), normal or reduced TT levels (**Functional hypogonadism**)

TREATMENT: hCG (+ FSH if needed)

GROUP 5

Normal FSH, TT, and semen analysis parameters (**Unexplained male infertility in the context of unexplained couple infertility**)

TREATMENT: FSH monotherapy?

ART: Assisted Reproductive Technology;
FSH: follicle-stimulating hormone;
Gn: gonadotropin;
hCG: human chorionic gonadotropin;
NOA: non-obstructive azoospermia;
TT: total testosterone;
ULN: upper limit of normal



Addressing male Patients with Hypogonadism and/or Infertility Owing to altered Idiopathic Testicular Function

Sandro C. Esteves, Peter Humaidan, Filippo M. Ubaldi, Carlo Alviggi, Leen Antonio, Christopher LR Barratt, Hermann M. Behre, Niels Jørgensen, Allan Pacey, Manuela Simoni, Daniele Santi.
<https://doi.org/10.1016/j.rbmo.2023.103647>



Figure. Overview of the APHRODITE criteria and the 5 male infertility groups. Adapted from Esteves et al, APHRODITE criteria: addressing male patients with hypogonadism and/or infertility owing to altered idiopathic testicular function, *Reprod Biomed Online* 2024, with permission (under the terms of the Creative Commons CC-BY license).¹ ART indicates assisted reproductive technology; FSH, follicle-stimulating hormone; Gn, gonadotropin; hCG, human chorionic gonadotropin; LH, luteinizing hormone; NOA, nonobstructive azoospermia; TT, total testosterone; ULN, upper limit of normal.

Group 1: Hypogonadotropic Hypogonadism

Patients in this group present with low FSH, LH, and testosterone lev-

els, often associated with azoospermia.⁶ Typically caused by congenital or acquired conditions affecting gonadotropin secretion, these patients

can benefit from gonadotropin therapy (human chorionic gonadotropin and FSH), which may restore spermatogenesis in up to 90% of cases.⁶

“These patients can benefit from gonadotropin therapy (human chorionic gonadotropin and FSH), which may restore spermatogenesis in up to 90% of cases.”⁶

Group 2: Idiopathic Male Infertility

This group primarily includes men with idiopathic oligozoospermia and certain cases of idiopathic nonobstructive azoospermia.^{1,3,7} Despite normal physical exams and lab results, these patients show signs of functional hypogonadism. FSH therapy has demonstrated effectiveness³ and is recognized by the AUA/American Society for Reproductive Medicine guidelines as a valid medical intervention to be considered in men with idiopathic infertility for enhancing spermatogenesis and improving pregnancy prospects.⁸

Group 3: Biochemical Hypogonadism

Biochemical hypogonadism, characterized by low testosterone levels, distinguishes these patients from those in Group 2. Hormonal therapy combining human chorionic gonadotropin—to boost intratesticular testosterone production—with FSH is suggested to help enhance spermatogenesis.^{1,3} Patients with nonobstructive azoospermia in this group have shown improvements in sperm retrieval rates after treatment.⁹

Group 4: Hypergonadotropic Hypogonadism

Patients in this group exhibit high FSH and low or compensated testosterone levels, indicating diminished testicular reserve.⁷ Although

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DECODING IDIOPATHIC MALE INFERTILITY AND HYPOGONADISM

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Table 2. Characteristics of the 5 APHRODITE Groups

| Classification | Definition | Prevalence | Suggested Gonadotropin Regimen | Endpoints ^a |
|---|---|---|--------------------------------|--|
| Group 1: Hypogonadotropic hypogonadism (acquired and congenital) | <ul style="list-style-type: none"> Gonadal failure associated with reduced gametogenesis and reduced gonadal steroid production due to reduced gonadotropin production or action FSH levels below reference ranges and reduced LH levels, reduced T levels (eg, <350 ng/dL) and lowered semen analysis parameters (eg, OAT or azoospermia) | ~1.9% of azoospermia cases and 1.6% of male infertility cases overall | hCG (+/-) FSH ^b | Semen parameters or sperm retrieval rates, T levels, QoL, pregnancy rates |
| Group 2: Lowered semen analysis parameters, normal serum FSH, and normal serum total testosterone | <ul style="list-style-type: none"> Functional hypogonadism with reduced gonadotropin action Lowered semen analysis parameters, including NOA FSH levels within the reference range^b and normal T levels (eg, ≥350 ng/dL) | Idiopathic male infertility: up to 44% of male infertility cases | FSH alone ^c | Semen parameters or sperm retrieval rates, SDF rates, QoL, pregnancy rates |
| Group 3: Lowered semen analysis parameters, normal FSH, and reduced total testosterone levels | <ul style="list-style-type: none"> Functional hypogonadism with reduced gonadotropin action and reduced T production Lowered semen analysis parameters, including NOA FSH levels within the reference range and reduced T (eg, <350 ng/dL) | ~20% of the total idiopathic male infertility | FSH ^c (+/-) hCG | Semen parameters or sperm retrieval rates, T levels, SDF rates, QoL, pregnancy rates |
| Group 4: Lowered semen analysis parameters, elevated FSH levels, and normal or reduced total testosterone levels | <ul style="list-style-type: none"> Functional hypergonadotropic hypogonadism Lowered semen analysis parameters, mainly NOA FSH levels above the upper limit of the reference range and normal or reduced T levels (excluding genetic causes) | Up to 10% | hCG (+/-) FSH ^d | Semen parameters or sperm retrieval rates, T levels, SDF rates, QoL, pregnancy rates |
| Group 5: Unexplained male infertility in the context of unexplained couple infertility | <ul style="list-style-type: none"> FSH levels within the reference range, T levels within the normal range, and normal semen analysis parameters | 15% of couples present with unexplained infertility | FSH alone ^e | SDF rates, pregnancy rates |

Abbreviations: FSH, follicle-stimulating hormone; hCG, human chorionic gonadotropin; LH, luteinizing hormone; NOA, nonobstructive azoospermia; OAT, oligoasthenoteratospermia; QoL, quality of life; SDF, sperm DNA fragmentation; T, total testosterone.

Adapted from Esteves et al, APHRODITE criteria: addressing male patients with hypogonadism and/or infertility owing to altered idiopathic testicular function, *Reprod Biomed Online* 2024, with permission (under the terms of the Creative Commons CC-BY license).¹

^aSperm parameters are the primary outcome of hormonal treatment.

^bRegimen can be tailored according to the congenital or acquired forms of hypogonadotropic hypogonadism.

^cFSH treatment might improve DNA fragmentation and sperm quality.

^dIf FSH levels drop below the lower reference limit during hCG treatment, treatment with exogenous FSH can be considered.

^eThe suggestion for FSH alone is based on empirical evidence.

more challenging, some evidence suggests hormonal therapy may improve sperm retrieval outcomes in certain cases.^{3,9}

Group 5: Unexplained Male Infertility

This group includes men with normal semen analysis, hormone levels, and physical exams (along with unremarkable findings in the female partner's evaluation) who remain infertile for unknown reasons. It is hypothesized that FSH stimulation could enhance sperm production in these patients by optimizing spermatogenesis, which may not be functioning at its full capacity. While further research is

needed to validate this approach, it is well-known that higher sperm counts are associated with a shorter time to natural conception,¹⁰ thereby providing a rationale for the potential benefit of FSH therapy to boost spermatogenesis.

Challenges and Future Directions

While initial data support the effectiveness of gonadotropin therapy in Groups 1, 2, and 3, further studies are needed to establish broader applications. Additionally, alternative treatments using selective estrogen receptor modulators and aromatase inhibitors—alone or combined with gonadotropins—

could be explored to enhance reproductive hormone balance. The APHRODITE criteria may significantly advance classifying and treating male infertility, fostering clearer communication among clinicians, researchers, and patients. By guiding future clinical trials, these criteria can also offer hope to countless couples seeking new treatment avenues for infertility.

Author's Note

I am deeply honored to have been part of the distinguished panel that developed the APHRODITE criteria. I also want to express my heartfelt gratitude to the AUA for granting me an invaluable oppor-

tunity nearly 30 years ago after completing my urology residency as one of the first international scholars from South America in the AUA/Confederación Americana de Urología exchange program. The knowledge and insight I gained through this program and the subsequent fellowship at the Glickman Urological and Kidney Institute at the Cleveland Clinic have shaped my clinical expertise and academic journey in male infertility and reproductive medicine. This experience has laid the foundation for my contributions to the field, and I remain deeply thankful for these early opportunities that continue to influence my work today.

Acknowledgments

The author thanks Chloé Xilinas and Josefina Zamarbide from MedEA for their help with the artwork. ■

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Novel Approaches to Penile-Sparing Surgery: Balancing Cancer Control, Functionality, and Quality of Life

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Penile cancer is a rare malignancy, accounting for less than 1% of male cancers in developed countries, but its incidence is higher in certain regions of South America, Africa, and Asia. The most common type is squamous cell carcinoma, which typically arises on the glans, foreskin, or shaft of the penis. Etiology is multifactorial, with key risk factors including human papillomavirus (HPV) infection, poor hygiene, phimosis, chronic inflammation, and tobacco use.¹ Despite its rarity, penile cancer significantly impacts patients' quality of life due to the emotional and physical consequences of traditional treatments such as partial or total penectomy. While survival rates vary based on the stage at diagnosis, the 5-year survival rate for early-stage disease is over 85%, but it drops to 30% to 50% for advanced or metastatic cases. Penile-sparing surgery (PSS) has emerged as a viable option for

“Modern advances in imaging and surgical techniques have made this approach feasible with good outcomes, allowing patients to preserve both cosmetic appearance and functionality without compromising cancer control.”

treating localized penile cancers while maintaining organ function, appearance, and emotional well-being. Modern advances in imaging and surgical techniques have made this approach feasible with good outcomes, allowing patients to preserve both cosmetic appearance and functionality without compromising cancer control. This article reviews the novel approaches for penile-sparing techniques, highlighting outcomes such as negative margins, quality of life, cosmesis, and emotional well-being.

Preoperative Evaluation

Assessing the extent of penile cancer is crucial for selecting appropriate candidates for PSS.

The role of MRI in assessing penile cancer is not well defined, and it is a challenging examination even for experienced radiologists. However, prior to organ preservation, MRI has 86% sensitivity and 89% specificity for identifying T1 vs T2 disease. Hence, it can be considered prior to penile preservation treatment.² Penile Doppler ultrasound with an artificial erection is another imaging modality that can provide detailed information on the depth of tumor invasion and was found similar to penile MRI for detecting infiltration of corpora cavernosa prior to penile preservation surgery.³ For superficial lesions, especially in HPV-positive patients, peniscopy combined with acetic acid (5%) staining may help delineate the tumor margins and depth preoperatively, giving the surgeon a clearer understanding of the cancer's extent when considering organ preservation. These assessments are critical for both superficial and low-grade invasive tumors.

Penile Preservation Techniques

Penile preservation techniques fall into 2 broad categories: topical and laser treatments and surgical excision.

Topical and Laser Therapies: These are effective for

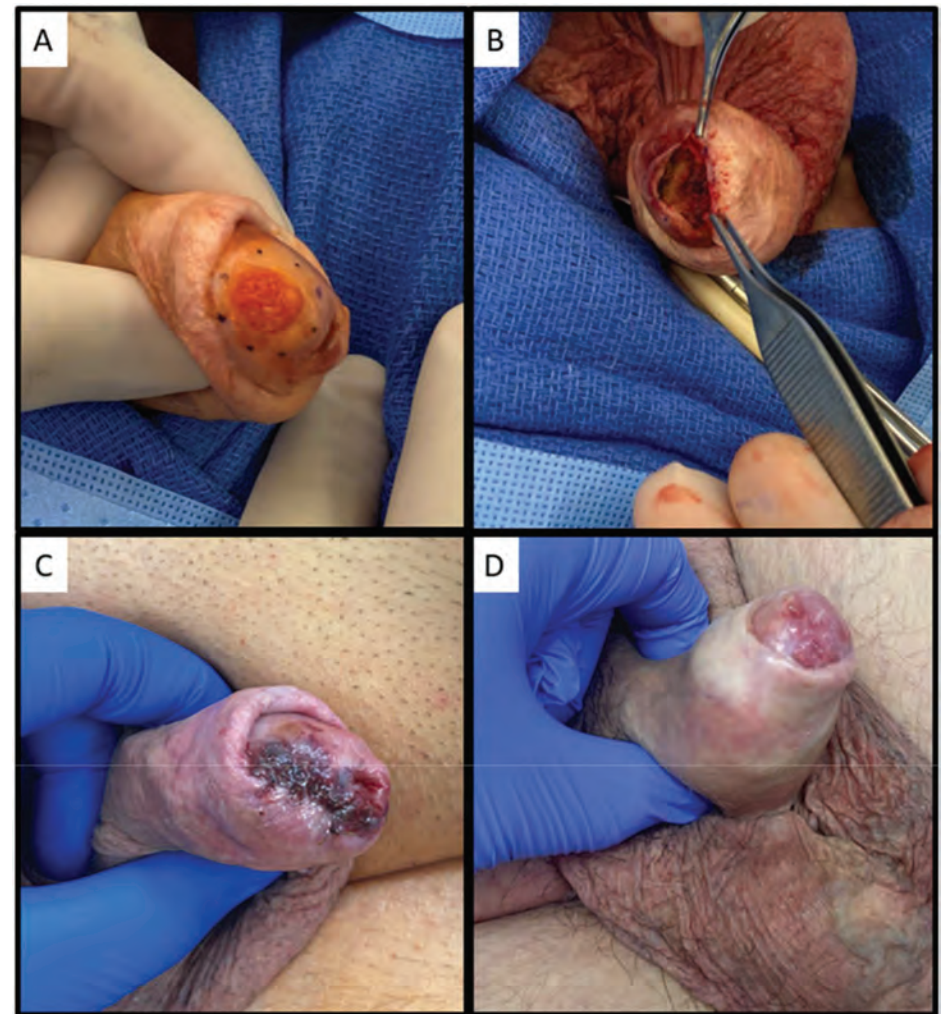


Figure 1. Tumor wedge excision (A and B) covered by a foreskin flap (C and D).

superficial lesions, such as carcinoma in situ. Topical therapies include fluorouracil 5% and imiquimod 5% cream. Fluorouracil is a type of antimetabolite that interferes with the synthesis of nucleic acids and selectively targets rapidly dividing cells. Imiquimod is an immune response modifier that activates toll-like receptor 7 on immune cells, particularly macrophages and dendritic cells, leading to the release of cytokines that promote an antitumor immune response. For superficial lesions reaching the epidermis and superficial dermis layers, laser therapy (such as CO₂, Nd, or KTP lasers) has shown synergistic effects, particularly in HPV-positive patients. Acetic acid can be used before these treatments to highlight tumor borders and guide therapy.

These modalities offer excellent cosmetic results with minimal scarring. However, a recent systematic

review on treatment for carcinoma in situ reported response rates for laser therapies to be 52% to 100%, with recurrences in 7% to 48% of cases, and a change in penile sensitivity in 50% of cases.⁴ Combining imiquimod and laser therapy can reduce recurrence risk, with patients reporting satisfaction in terms of both appearance and sexual function.⁵

Surgical Treatments: For low-grade invasive tumors (T1), surgical excision remains the mainstay therapy. Techniques include Mohs surgery, wedge resection (wide local excision), and partial penectomy.

1. Mohs surgery: The tumor is resected utilizing a microsurgical approach in layers. Every layer is examined in real time until no residual cancer is identified. For selected patients, this approach has good long-term

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1. ANKTIVA Prescribing Information. ImmunityBio Inc., 2024; Represents the upper limit of the range of duration of response.

INDICATION AND IMPORTANT SAFETY INFORMATION

INDICATION AND USAGE: ANKTIVA is an interleukin-15 (IL-15) receptor agonist indicated with Bacillus Calmette-Guerin (BCG) for the treatment of adult patients with BCG-unresponsive non-muscle invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) with or without papillary tumors. **WARNINGS AND PRECAUTIONS: Risk of Metastatic Bladder Cancer with Delayed Cystectomy.** Delaying cystectomy can lead to the development of muscle invasive or metastatic bladder cancer, which can be lethal. If patients with CIS do not have a complete response to treatment after a second induction course of ANKTIVA with BCG, reconsider cystectomy. **DOSAGE AND ADMINISTRATION: For Intravesical Use Only.** Do not administer by subcutaneous or intravenous routes. Instill intravesically only after dilution. Total time from vial puncture to the completion of the intravesical instillation should not exceed 2 hours. **USE IN SPECIFIC POPULATIONS: Pregnancy:** May cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception. **ADVERSE REACTIONS:** The most common ($\geq 15\%$) adverse reactions, including laboratory test abnormalities, are increased creatinine, dysuria, hematuria, urinary frequency, micturition urgency, urinary tract infection, increased potassium, musculoskeletal pain, chills and pyrexia.

For more information about ANKTIVA, please see the Full Prescribing Information at www.anktiva.com.

You are encouraged to report negative side effects of prescription drugs to FDA. Visit www.FDA.gov/medwatch or call 1-800-332-1088. You may also contact ImmunityBio at 1-877-ANKTIVA (1-877-265-8482)

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ANK-00139-US Jan 2025

NOVEL APPROACHES TO PENILE-SPARING SURGERY: BALANCING CANCER CONTROL, FUNCTIONALITY, AND QUALITY OF LIFE

→ Continued from page 14

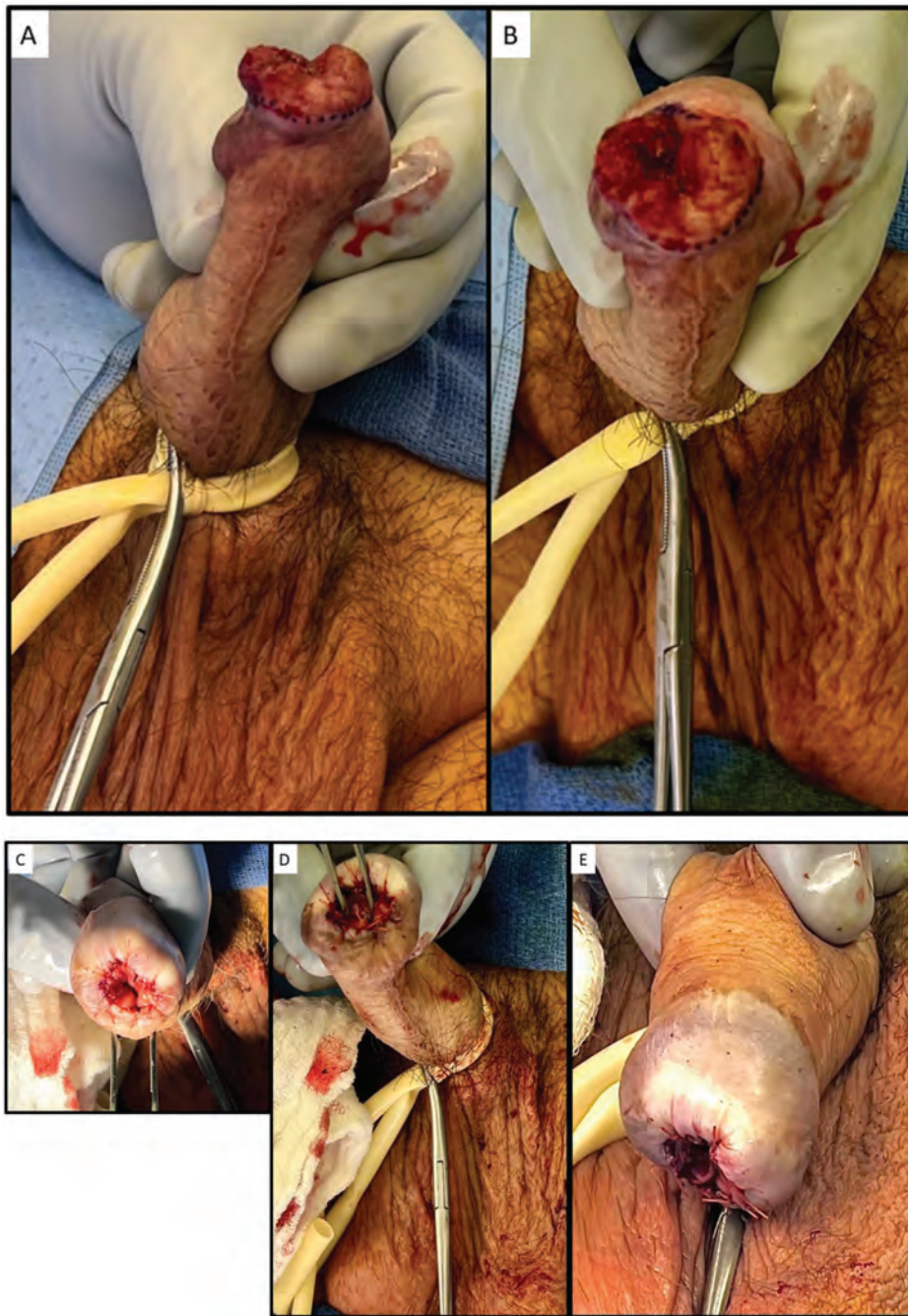


Figure 2. Tumor in proximity to the urethral meatus. The tumor is widely excised (A and B) with a portion of the fossa navicularis. Distal urethral mobilization is performed with wide spatulation of the urethra to avoid stenosis (C to E).

recurrence-free survival rates and excellent cosmesis.⁶

2. Wedge resection: Indicated for discrete lesions on the glans or shaft, this technique allows for margin control using frozen sections. In contrast to past recommendations for a 2-cm margin, current evidence suggests that even a 1-mm tumor-free margin may be sufficient for cancer control. Skin flaps (from the foreskin or prepuce) are often used to cover defects, contributing to improved cosmesis and functionality (Figure 1). Five-year local recurrence-free survival is about 73.6%, with good cosmetic outcomes and preservation of sexual function.⁷

“For low-grade invasive tumors (T1), surgical excision remains the mainstay therapy.”

3. Partial penectomy: For select lesions involving the corpus spongiosum and urethral meatus, penile-sparing techniques are possible. Tumors in proximity to the urethral meatus would typically be treated using a partial penectomy/glansectomy. However, these lesions are also

amenable to wide local excision with reconstructive techniques and can lead to reasonable oncological outcomes when combined with frozen sections (Figure 2).

Partial penectomy is typically reserved for more extensive disease and has very good oncological outcomes. However, it generally results in undesirable cosmesis compared to other forms of organ preservation. A partial penectomy typically leaves a penile stump of 3 to 4 cm to ensure the patient can urinate while standing upright. The emotional impact is significant, with some patients experiencing feelings of loss or decreased self-esteem due to the procedure’s more disfiguring nature.⁸

Oncological and Quality of Life Outcomes

While PSSs may carry a higher risk of local recurrence compared to radical and partial penectomy, cancer-specific survival is reasonably good in well-selected patients. In particular, combination therapies and organ-sparing surgical techniques can provide excellent functional outcomes with minimal impact on quality of life.⁹

Sexual function can be significantly impacted with radical or partial penectomy. A systematic review of the literature found that in patients undergoing partial penectomy, based on the International Index of Erectile Function domains, erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction can be decreased. Preservation of penile length was one of the significant factors that allowed for improvement in sexual function following partial penectomy. With better surgical technique and an understanding of a decreased required surgical margin, penile length can be significantly improved, and as such, function may be preserved.¹⁰ The emotional and psychological aspects of penile surgery cannot be overstated. Patient counseling is essential to help manage expectations and address concerns related to body image, sexual function, and overall quality of life. Studies

suggest that men who undergo PSS report greater satisfaction with their appearance and emotional well-being compared to those who undergo partial penectomy.

Conclusion

PSSs offer a well-balanced approach to treating localized penile cancer, providing favorable oncological outcomes while maintaining cosmesis and functionality. Combined topical and laser therapies are particularly effective for superficial tumors, while wedge resection with reconstruction offers an excellent option for localized, well-selected tumors. By reducing the size of necessary surgical margins and employing reconstructive techniques, surgeons can offer patients outcomes that are not only oncologically sound, but also cosmetically and emotionally satisfactory for patients. ■

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