2021

Urology Pipeline Report

BLADDER CANCER
IL-15 superagonist N-803 shows clinical activity

OVERACTIVE BLADDER/INCONTINENCE
Biomarker emerges for Botox response in patients with overactive bladder

SEXUAL DYSFUNCTION
Higher T dosing may be required for patients with a higher BMI

KIDNEY CANCER
Radiation therapy as monotherapy is effective in oligometastatic RCC

PROSTATE CANCER
Real-world effectiveness with apalutamide in nmCRPC

BENIGN PROSTATIC HYPERPLASIA
Investigators examine effect of statins on LUTS secondary to BPH
XTANDI is indicated for the treatment of patients with castration-resistant prostate cancer (CRPC) or metastatic castration-sensitive prostate cancer (mCSPC).¹

When your patients present with mCSPC* or CRPC†... No need to wait. START XTANDI.

The first and only novel hormone therapy approved by the FDA in 3 advanced prostate cancer patient types--mCSPC, nmCRPC, and mCRPC¹

Important Safety Information

Warnings and Precautions

Seizure occurred in 0.5% of patients receiving XTANDI in seven 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.

Hyper sensitivity reactions, including edema of the face (0.5%), tongue (0.1%), or lip (0.1%) have been observed with XTANDI in seven 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 four randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.9% vs 1.3%). Grade 3-4 ischemic events occurred in 1.4% of patients on XTANDI versus 0.7% 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 four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Fractures occurred in 10% of patients treated with XTANDI and in 4% of patients treated with placebo.

Embryofetal 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 four randomized placebo-controlled trials, the most common ARs (≥ 10%) that occurred more frequently (≥ 2% over placebo) in XTANDI-treated patients were asthenia/fatigue, back pain,
with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, risk of developing a seizure while taking XTANDI and of engaging in any activity where sudden loss of consciousness may occur due to venous infarction 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 may occur due to venous infarction of the brain.

Anti-epileptic medications are not likely to prevent seizures with XTANDI. Patients in the study received anti-epileptic medications if seizures occurred. Seizures occurred in 0.5% of patients receiving XTANDI in seven randomized clinical trials. In a study of patients with PRES, seizures occurred in 0.5% of patients receiving XTANDI in seven randomized clinical trials.

Warnings and Precautions

Important Safety Information

† Castration-resistant prostate cancer is defined as disease progression on androgen deprivation therapy (LHRH therapy or prior bilateral orchiectomy) despite castrate levels of testosterone. 5

‡ Based on IQVIA NBRx rolling 4-week data, April 2020–March 26, 2021. THIS INFORMATION DOES NOT IMPLY SAFETY OR EFFICACY OF ANY PRODUCT; NO COMPARISONS SHOULD BE MADE.

#1 PREScribed BRANDED NOVEL HORMONE THERAPY IN mCSPC AND CRPC‡

PROVEN EFFICACY: XTANDI significantly extended radiographic progression-free survival§ in patients with mCSPC¹

ARCHES was a multinational, randomized, double-blind, placebo-controlled trial of XTANDI + LHRH therapy vs placebo + LHRH therapy in 1150 patients with mCSPC, stratified by volume of disease (low vs high) and prior docetaxel therapy for prostate cancer (none, 1 to 5, or 6 cycles). 1.3

Overall survival data were not mature at the time of radiographic progression-free survival analysis (7.3% of deaths in the intent-to-treat population had been reported)§¹

Eligibility criteria included mCSPC, ECOG Performance Status of 0 or 1.1

Exclusion criteria included predisposing factors for seizure and clinically significant cardiovascular disease. 4

§Radiographic progression-free survival was defined as the time from randomization to radiographic disease progression at any time or death within 24 weeks after study drug discontinuation. 1

||Or after bilateral orchiectomy. 1

†Defined as metastases involving the viscera or, in the absence of visceral lesions, ≥ 4 bone lesions, ≥ 1 of which must be in a bony structure beyond the vertebral column and pelvic bone. 1

#At the time of analysis, the median follow-up was 14.4 months. 3

Drug Interactions

Effect of Other Drugs on XTANDI Avoid strong CYP2C8 inhibitors, as they can increase the plasma exposure to XTANDI. If co-administration is necessary, reduce the dose of XTANDI. Avoid strong CYP3A4 inducers as they can decrease the plasma exposure to XTANDI. If co-administration is necessary, increase the dose of XTANDI.

Effect of XTANDI on Other Drugs Avoid CYP3A4, CYP2C8, and CYP2C9 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposures of these drugs. If XTANDI is co-administered with warfarin (CYP2C9 substrate), conduct additional INR monitoring.

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


For more information, please visit XtandiHCP.com

© 2021 Astellas Pharma US, Inc. and Pfizer Inc. All rights reserved. 076-7374-PM 1121

XTANDI, Astellas, and the flying star logo are registered trademarks of Astellas Pharma Inc.
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

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Seizure

Seizure occurred in 0.5% of patients receiving XTANDI in seven randomized clinical trials. In these trials, patients with predisposing factors for seizure were generally excluded. Seizure occurred from 13 to 1776 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 seven 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 four randomized, placebo-controlled clinical studies, ischemic heart disease occurred more commonly in patients on the XTANDI arm compared to patients on the placebo arm (2.9% vs 1.3%). Grade 3-4 ischemic events occurred in 1.4% of patients on the XTANDI arm compared to 0.7% 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 four randomized, placebo-controlled clinical studies, falls occurred in 11% of patients treated with XTANDI compared to 4% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Fractures occurred in 10% of patients treated with XTANDI and in 4% of patients treated with placebo. Grade 3-4 fractures occurred in 3% of patients treated with XTANDI and in 2% of patients treated with placebo. The median time to onset of fracture was 336 days (range: 2 to 1914 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 seven randomized, controlled trials [AFFIRM, PREVAIL, TERRAIN, PROSPER, ARCHES, Asian PREVAIL (NCT02234461), and STRIVE (NCT01664923)] that were pooled to conduct safety analyses in patients with CRPC (N=3569) or mCSPC (N=572) treated with XTANDI. Patients received XTANDI 160 mg (N=4081) or placebo orally once daily (N=2472) or bicalutamide 50 mg orally once daily (N=387). All patients continued androgen deprivation therapy (ADT). In these seven trials, the median duration of treatment was 13.8 months (range: <0.1 to 87.6) in the XTANDI group.

In four placebo-controlled trials (AFFIRM, PROSPER, PREVAIL, and ARCHES), the median duration of treatment was 14.3 months (range: <0.1 to 87.6) in the XTANDI group. In these four trials, the most common adverse reactions (≥10%) that occurred more frequently (≥2% over placebo) in the XTANDI-treated patients were asthenia/fatigue, back pain, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension.

AFFIRM (NCT00974311): 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 events 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 ≥10% over placebo.

Table 1. Adverse Reactions in AFFIRM

<table>
<thead>
<tr>
<th>Reaction Category</th>
<th>Grade 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td>XTANDI (N=800)</td>
<td>Placebo (N=399)</td>
</tr>
<tr>
<td>Headache</td>
<td>12.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Dizziness1</td>
<td>9.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Constipation and Diarrhea Syndrome</td>
<td>7.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Mental Impairment Disorders</td>
<td>4.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>12.0</td>
<td>5.5</td>
</tr>
</tbody>
</table>

Table 1. Adverse Reactions in AFFIRM

<table>
<thead>
<tr>
<th>Reaction Category</th>
<th>Grade 1-4 (%)</th>
<th>Grade 3-4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Disorders</td>
<td>XTANDI (N=800)</td>
<td>Placebo (N=399)</td>
</tr>
<tr>
<td>Headache</td>
<td>12.9</td>
<td>5.5</td>
</tr>
<tr>
<td>Dizziness1</td>
<td>9.5</td>
<td>7.5</td>
</tr>
<tr>
<td>Constipation and Diarrhea Syndrome</td>
<td>7.4</td>
<td>6.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>8.6</td>
<td>4.5</td>
</tr>
<tr>
<td>Mental Impairment Disorders</td>
<td>4.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>12.0</td>
<td>5.5</td>
</tr>
</tbody>
</table>
PREVAIL (NCT01212991): XTANDI versus Placebo in Chemotherapy-naive 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 events were reported for 6% of XTANDI-treated patients and 3% of bicalutamide-treated patients. The most common adverse reactions leading to treatment discontinuation was fatigue, which occurred in 1% of patients on each treatment arm. Table 2 includes adverse reactions reported in PREVAIL that occurred at ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm.

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

<table>
<thead>
<tr>
<th></th>
<th>XTANDI (N = 800)</th>
<th>Placebo (N = 1120)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Respiratory Tract And Lung Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pollakiuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Adverse Reactions in PREVAIL

<table>
<thead>
<tr>
<th></th>
<th>XTANDI (N = 871)</th>
<th>Placebo (N = 844)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysgeusia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental Impairment Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restless Legs Syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower Respiratory Tract And Lung Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Psychiatric Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Renal and Urinary Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Injury, Poisoning and Procedural Complications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Non-Pathological Fracture</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Table 3. Adverse Reactions in TERRAIN

<table>
<thead>
<tr>
<th></th>
<th>XTANDI (N = 183)</th>
<th>Bicalutamide (N = 189)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>12.0</td>
<td>8.5</td>
</tr>
<tr>
<td><strong>Reproductive System and Breast Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>3.4</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>Grade 3-4 Adverse Reactions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32.0</td>
<td>16.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>21.6</td>
<td>16.1</td>
</tr>
<tr>
<td><strong>Infections and Infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15.0</td>
<td>11.0</td>
</tr>
<tr>
<td><strong>Metabolism and Nutrition Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>9.4</td>
<td>39.0</td>
</tr>
</tbody>
</table>

PROSPER (NCT02083924): 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 events. The reasons for death with ≥ 2 patients included coronary artery disorders (n = 7), sudden death (n = 2), cardiac arrhythmias (n = 2), general physical health deterioration (n = 2), stroke (n = 2), and secondary malignancy (n = 5; one each of acute myeloid leukemia, brain neoplasm, mesothelioma, small cell lung cancer, and malignant neoplasm of unknown primary site). Three patients (0.6%) receiving placebo died from adverse events of cardiac arrest (n = 1), left ventricular failure (n = 1), and pancreatic carcinoma (n = 1). Grade 3 or higher adverse reactions were reported among 31% of XTANDI-treated patients and 23% of placebo-treated patients. Discontinuations with an adverse event as the primary reason were reported for 24% of XTANDI-treated patients and 6.0% of placebo-treated patients. Of these, the most common adverse event leading to treatment discontinuation was fatigue, which occurred in 1.8% of the XTANDI-treated patients compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.
### Table 5. Adverse Reactions in PROSPER

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XTANDI (N = 572)</th>
<th>Placebo (N = 574)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>4.9</td>
<td>6.2</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/asthenia</td>
<td>2.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flash</td>
<td>13.8</td>
<td>7.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>12.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>11.3</td>
<td>8.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>9.1</td>
<td>6.9</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aesthetic Conditions</td>
<td>40.4</td>
<td>40.9</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Decreased</td>
<td>5.9</td>
<td>0.2</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>11.8</td>
<td>4.1</td>
</tr>
<tr>
<td>Fractures</td>
<td>9.8</td>
<td>4.9</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.8</td>
<td>0.4</td>
</tr>
</tbody>
</table>

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

### Table 6. Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>XTANDI (N = 3173)</th>
<th>Placebo (N = 2282)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td></td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20.0</td>
<td>0.9</td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>17.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>83.3</td>
<td>3.2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>16.6</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>13.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>6.8</td>
<td>0.1</td>
</tr>
</tbody>
</table>

### Hypertension

In the combined data from four randomized placebo-controlled clinical trials, hypertension was reported in 12% of patients receiving XTANDI and 5% 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 were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

#### Gastrointestinal Disorders:

- vomiting
- Immune System Disorders: hyperreactivity (adrenalin, neurone, lip, or pharyngeal)

#### 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

#### Drugs that Inhibit CYP2C8

Co-administration of a strong CYP2C8 inhibitor (gemfibrozil) increased the composite area under the plasma concentration-time curve (AUC) of enzalutamide plus N-desmethyl enzalutamide by 2.2-fold. Co-administration of XTANDI with strong CYP2C8 inhibitors should be avoided if possible.

#### Drugs that Induce CYP3A4

Co-administration of rifampin (strong CYP3A4 inhibitor and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inducers (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifapentine) with XTANDI should be avoided if possible. St John’s wort may decrease enzalutamide exposure and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, reduce the dose of XTANDI.

### Effect of XTANDI on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inhibitor in humans. At steady-state, XTANDI induced the plasma exposure to midazolam (CYP3A4 substrate), warfarin (CYP2C9 substrate), and omeprazole (CYP2C19 substrate). Concomitant use of XTANDI with narrow therapeutic index drugs that are metabolized by CYP3A4 (e.g., alfentanil, cyclosporine, dihydrolotiamine, argonate, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephentoin, clopidogrel) should be avoided, as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, conduct additional INR monitoring.

### 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).
OVERDOSAGE

In the event of an overdose, 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 overdose.

Patients with Renal Impairment

A dedicated renal impairment trial for XTANDI has not been conducted. Based on the population pharmacokinetic analysis using data from clinical trials in patients with metastatic CRPC and healthy volunteers, no significant difference in enzalutamide clearance was observed in patients with pre-existing mild to moderate renal impairment (30 mL/min ≤ creatinine clearance [CrCL] < 89 mL/min) compared to patients and volunteers with baseline normal renal function (CrCL ≥ 90 mL/min). No initial dosage adjustment is necessary for patients with mild to moderate renal impairment. Severe renal impairment (CrCL < 30 mL/min) and end-stage renal disease have not been assessed.

Patients with Hepatic Impairment

Dedicated hepatic impairment trials compared the composite systemic exposure of enzalutamide plus N-desmethyl enzalutamide in volunteers with baseline mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C, respectively) versus healthy controls with normal hepatic function. The composite AUC of enzalutamide plus N-desmethyl enzalutamide was similar in volunteers with mild, moderate, or severe baseline hepatic impairment compared to volunteers with normal hepatic function. No initial dosage adjustment is necessary for patients with baseline mild, moderate, or severe hepatic impairment.

Patients with Seizure Risk

Patients may be at increased risk of seizure following an overdose.

OVERDOSAGE

In the event of an overdose, 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 overdose.

Patients with Seizure Risk

Patients may be at increased risk of seizure following an overdose.

OVERDOSAGE

In the event of an overdose, 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 overdose.
2021 urology pipeline report

BLADDER CANCER
7 Clinical Updates | IL15 superagonist N-803 shows clinical activity

OVERACTIVE BLADDER
8 Clinical Updates | Biomarker emerges for Botox response in patients with overactive bladder

SEXUAL DYSFUNCTION
9 Question & Answer | Higher T dosing may be required for patients with a higher BMI

KIDNEY CANCER
14 Clinical Updates | Radiation therapy as monotherapy is effective in oligometastatic RCC

PROSTATE CANCER
19 Rapid Readout | Real-world effectiveness with apalutamide in nmCRPC
20 Journal Article of the Month | Transrectal vs transperineal biopsy: Outcomes and QOL
21 Clinical Updates | Transitional zone sampling may be unnecessary in some men
22 Olaparib plus bipolar androgen therapy shows promise in prostate cancer
23 Darolutamide maintenance holds potential in pretreated mCRPC
29 PSMA/PET-derived risk stratification tool performs strongly in study

BENIGN PROSTATIC HYPERPLASIA
30 Question & Answer | Investigators examine effect of statins on LUTS secondary to BPH

INFECTION
32 Clinical Updates | Novel vaccine MV140 is effective at treating recurrent UTIs

INFECTION
36 Coding and Reimbursement | How the 2022 CMS final rule will affect urologists

COLUMNS/DEPARTMENTS
4 Publisher’s Note | Capping a year filled with innovation
6 UroPipeline | Trial of novel copper-based PSMA theranostics for mCRPC hits early enrollment goal
35 Speak Out | What are your thoughts on proposals that physicians should communicate with their patients by text?
39 Practice Matters | Practical ways to address burnout in your urology practice
41 Money Matters | Financial tasks you should complete by the end of the year
44 Medical Economics® | COVID-19 misinformation remains widespread, report indicates
45 Malpractice Consult | Good records can save you in a malpractice suit

© 2021 MultiMedia Healthcare LLC. All rights reserved. Reproduction or translation in any form or by any means, electronic or mechanical including by photography, recording, or informa-
tion storage and retrieval without written permission is prohibited. The unauthorized use, distribution or reproduction of this publication is illegal. 

Library Access
14 Money Matters | Financial tasks you should complete by the end of the year
21 Clinical Updates | Transitional zone sampling may be unnecessary in some men
22 Olaparib plus bipolar androgen therapy shows promise in prostate cancer
23 Darolutamide maintenance holds potential in pretreated mCRPC
29 PSMA/PET-derived risk stratification tool performs strongly in study

EDITORIAL ADVISORY BOARD

EDITORS IN CHIEF
Gopal H. Badlani, MD
Professor of Urology | Wake Forest Baptist Medical Center, Winston-Salem, NC
Michael Cookson, MD
Professor and Chair of Urology | University of Oklahoma Health Sciences Center, Oklahoma City

EMERITUS EDITORIAL CONSULTANTS
Philip M. Hanno, MD, MPH
Clinical Professor of Urology | Stanford University School of Medicine, Stanford, CA

Stephen Y. Nakada, MD
Professor and Chairman | Department of Urology
University of Wisconsin, Madison

J. Brantley Thrasher, MD
Executive Director | American Board of Urology
Charlottesville, VA

EDITORIAL COUNCIL
Experts in 11 key subspecialties of urology who direct in-depth coverage of their field

MEN’S HEALTH/BPH
Steven A. Kaplan, MD
Professor of Urology | Ichan School of Medicine at Mount Sinai, New York

MEN’S HEALTH/PROSTATE CANCER
Stacy Loeb, MD, MSc
Professor of Urology | New York University School of Medicine, New York

CLINICAL EPIDEMIOLOGY
Peter C. Albertsen, MD
Chief of Urology | University of Connecticut Health Center, Farmington

SEXUAL DYSFUNCTION
Arthur L. Burnett, II, MD, MBA
Professor of Urology
Johns Hopkins University School of Medicine, Baltimore

FEMALE UROLOGY
Priya Padmanabhan, MD, MPH
Professor of Urology
Oakland University William Beaumont School of Medicine, Royal Oak, MI

MEN’S HEALTH/INFERTILITY
James M. Hotzaling, MD, MS
Assistant Professor of Surgery (Urology)
University of Utah, Salt Lake City

PEDIATRIC UROLOGY
Barry A. Kogan, MD
Chief of Urology | Albany Medical College, Albany, NY

STONES/ENDOUROLOGY
Brian R. Matlaga, MD, MPH
Professor of Urology
Johns Hopkins University School of Medicine, Baltimore

TRAUMA/RECONSTRUCTION
Bradley A. Erickson, MD, MS
Associate Professor of Urology | University of Iowa, Iowa City

UROLOGIC CANCER
Leonard G. Gomella, MD
Professor and Chairman of Urology
Thomas Jefferson University, Philadelphia

QUALITY AND PATIENT SAFETY
J. Stuart Wolf, MD
Professor of Urology | Dell Medical School at The University of Texas, Austin

CLINICAL PRACTICE BOARD
Urologists who inform the editors of issues facing physicians “in the trenches”

Sheila K. Gemar, MD
Willmar, MN

Michael E. Herzog, MD
Orland Park, IL

Daniel M. Kaplon, MD
Owings Mills, MD

Sivaprasad D. Madduri, MD
Poplar Bluff, MO

Henry M. Rosevear, MD
Colorado Springs, CO

Barry R. Rossman, MD
Princeton, NJ

Michael Cookson, MD
Professor and Chair of Urology | University of Oklahoma Health Sciences Center, Oklahoma City

PRINTED IN U.S.A. • BPA International
UrologyTimes.com

Library Access
To access current and back issues of UrologyTimes.com, please call toll-free 888-527-7008. Outside the U.S. call 218-740-6477.
Editorial

Kristie L. Kahl, Vice President, Content
kkahl@mjhlifesciences.com

Jason M. Broderick, Associate Editorial Director
609-716-7777; jbroderick@mjhlifesciences.com

Benjamin P. Saylor, Content Managing Editor
440-626-2870; bsaylor@mjhlifesciences.com

Janelle Hart, Assistant Editor
609-716-7777; jhart@mjhlifesciences.com

Jonathan Rubenstein, MD, Mark Painter
Coding/Reimbursement Columnists

Jennifer Potash, Copy Chief

Paul Silverman, Copy Supervisor

Marie-Louise Best, Kelly King
Senior Copy Editors

Cheney Baltz, Georgina Carson, Kirsty Mackay, Ron Panzorotti, Yasmeen Qahwash
Copy Editors

Design & Production

Robert Mcgarr, Creative Director

Kristen Morabito, Art Director

Rachel Keatley, Senior Graphic Designer

Publishing & Sales

John Hydrusko, Vice President, Sales

Paul Barchitta, National Account Manager

Juliana Rice, National Account Associate

Eric Temple-Morris, Reprint, Permissions, Licensing

Mike Hennessy Jr, President and CEO

Jack Lepping, Vice Chairman

Neil Glasser, CPA/CFO

Joe Petroziello, Executive Vice President

Silas Inman, Senior Vice President

Michael Ball, Senior Vice President, Operations

Shari Lindenbergh, Vice President, Human Resources & Administration

Chris Hennessy, Vice President, Mergers & Acquisitions

Jeff Brown, Executive Creative Director, Creative Services

Corporate

Mike Hennessy Jr, President and CEO

Jack Lepping, Vice Chairman

Neil Glasser, CPA/CFO

Joe Petroziello, Executive Vice President

Silas Inman, Senior Vice President

Michael Ball, Senior Vice President, Operations

Shari Lindenbergh, Vice President, Human Resources & Administration

Chris Hennessy, Vice President, Mergers & Acquisitions

Jeff Brown, Executive Creative Director, Creative Services

Founder

Mike Hennessy Sr
1960-2021

Mission

Urologists and allied health professionals rely on Urology Times® for analysis, perspective, and practical advice about current health policy, clinical, and business challenges. As a top-read publication in the field and a leading online resource, our goal is to keep practitioners up to date while helping them practice more efficiently.

Publisher’s Note

Capping a year filled with innovation

At the LUGPA annual meeting held in Chicago, Illinois, in November, urologist Jason M. Hafron, MD, commented on the bright future for urologic oncology treatments.

“The future in bladder cancer and prostate cancer is really exploding. The therapies are coming faster than we ever thought,” Hafron said in an interview with Urology Times®. Hafron’s observation is certainly reflected in Associate Editorial Director Jason M. Broderick’s comprehensive look back on urology-related FDA approvals in 2021.

Our clinical coverage this month covers the usual range of topics; in prostate cancer, highlights include Q&A interviews on opioid use after prostatectomy and the use of bipol lar androgen therapy and olaparib (Lynparza) in patients with metastatic castration-resistant prostate cancer. Also look for the latest Journal Article of the Month column from Badar M. Mian, MD, in which he evaluates a paper comparing transrectal and transperineal approaches to prostate biopsy.¹

Other clinical articles this month include coverage of a biomarker for onabotulinumtoxinA response, the bladder cancer IL-15 superagonist N-803, the effect of nutraceuticals on erectile function, the use of statins for lower urinary tract symptoms secondary to benign prostatic hyperplasia, and more.

Although it’s certainly worthwhile to reflect on what has happened over the course of the year, it is also prudent to turn our eye to what will come in the year ahead, as Jonathan Rubenstein, MD, and Mark Painter do in their Coding and Reimbursement column. For their latest article, they break down the key components of the Medicare Physician Fee Schedule and the Hospital Outpatient Prospective Payment System and Ambulatory Surgical Center Payment System for urologists. They write, “Although there are efforts to avert the [conversion factor] cut, we are hopeful but not convinced that Congress will take the action necessary to truly adjust the Medicare budgeting process to avoid the projected decreases in reimbursement as physician groups face increasing costs and administrative burdens.”

Physician burnout is a major issue and one from which urologists are not immune. In this month’s Practice Matters column, Robert A. Dowling, MD, applies a practical approach to the problem, outlining ways urologists can alleviate burnout in their practices. As Dowling writes, “Targeted review of your documentation habits, your schedule, your [electronic health record], and your benchmarked expenses may provide an opportunity to improve your professional satisfaction, extend your career, and optimize your ‘professional efficacy.’”

For Money Matters, Jeff Wirtz, CFP, outlines key year-end financial tasks that should be on your “to do” list.

In Speak Out, Karen Nash queries 3 urologists on whether patients should be able to communicate with their physicians via text. Said one urologist in response, “Patients... don’t understand that urologists are actually surgeons. They expect an almost immediate response to texts, but we’re in the [operating room] for hours on end. Without any real data [showing] that this improves anything, it just makes us too accessible.”

Finally, we wrap up the last issue of 2021 with Malpractice Consult. In the column, Amanda K. Wager, Esq, emphasizes the importance of maintaining complete, clear documentation to bolster credibility in the event of a lawsuit. Thank you, stay safe, and best wishes for a terrific holiday season. We’ll see you in 2022. +

Mike Hennessy Jr
Mike Hennessy Jr is president and CEO of MJH Life Sciences®, publishers of Urology Times®.

Reference

UrologyTimes.com
Trial of novel copper-based PSMA theranostics for mCRPC hits early enrollment goal

The phase 1/2a SECURe trial exploring 2 novel SAR-bisPSMA Targeted Copper Theranostics (TCT) in patients with metastatic castration-resistant prostate cancer (mCRPC) has completed recruitment for the initial dosimetry phase, according to Clarity Pharmaceuticals, the company developing the investigational agents.1

The open-label, single-arm, dose-escalation SECURe trial (NCT04868604) is exploring the prostate-specific membrane antigen (PSMA) PET imaging product 64Cu-SAR-bisPSMA and the PSMA targeted therapy 67Cu-SAR-bisPSMA.2 The basic design of the trial is that 64Cu-SAR-bisPSMA will be used for the selection of patients to receive treatment with 67Cu-SAR-bis-PSMA.

To enroll, patients must have mCRPC that has progressed despite being treated with androgen-deprivation therapy and at least 1 second-generation androgen receptor pathway inhibitor, such as abiraterone acetate (Zytiga) or enzalutamide (Xtandi). Patients are required to have an ECOG performance status of 0 to 2, and a castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L). Individuals with brain metastases are not eligible to enroll.

Across all phases of the study, the total enrollment goal is 44 patients. The study is being conducted at 7 locations in the United States.

Phase 3 study of savolitinib/durvalumab combo in papillary renal cell carcinoma launches

The first patient has been treated in the global phase 3 SAMETA trial evaluating the combination of the investigational MET inhibitor savolitinib and PD-L1 inhibitor durvalumab (Imfinzi) in patients with MET-driven advanced papillary renal cell carcinoma (PRCC).1

The open-label, multicenter study (NCT05043090) is randomizing patients in a 2:1.1 ratio to the MET/PD-L1 inhibitor combination, monotherapy with the tyrosine kinase inhibitor (TKI) sunitinib (Sutent), or single-agent durvalumab.2

“Savolitinib is an oral, potent, and highly selective MET TKI that has demonstrated clinical activity in advanced solid tumors. It blocks atypical activation of the MET receptor tyrosine kinase pathway that occurs because of mutations (such as exon 14 skipping alterations or other point mutations) or gene amplification,” wrote HUTCHMED, the codeveloper of savolitinib, in a recent news release.1 Patients are eligible to enroll in the SAMETA trial if they have confirmed MET-driven PRCC that is both unresectable and either locally advanced or metastatic. They are unable to enroll if they were previously treated in the metastatic setting or were exposed to a MET inhibitor, durvalumab, or sunitinib in any setting.

The trials taking place in many countries, including Argentina, Australia, Brazil, Czech Republic, France, Italy, the Republic of Korea, Mexico, Poland, Spain, Taiwan, Turkey, and the United Kingdom. Global enrollment for this study continues. The investigators plan to evaluate approximately 200 patients.

Patients in the experimental arm will receive 600 mg of savolitinib orally once a day plus 1500 mg of durvalumab intravenously every 4 weeks. In the sunitinib control arm, treatment will consist of 50 mg of sunitinib orally once a day for 4 consecutive weeks along with a 2-week sunitinib-free interval (ie, 6-week cycles). In the immunotherapy control arm, patients will receive 1500 mg of durvalumab monotherapy intravenously every 4 weeks.

Patients will continue with treatment until radiological progression (PD; RECIST 1.1), unacceptable toxicity, or withdrawal of consent. Cross over to the combination arm is allowed for patients with radiological PD in the durvalumab control arm.

The estimated primary completion date is March 8, 2024.

Enrollment is completed in trial of novel nanoparticle-based focal ablation therapy

Patient enrollment has been completed for a pivotal trial of the novel nanoparticle-based focal ablation therapy AuroLase for patients with prostate cancer, according to Nanospectra Biosciences, developer of the treatment.1

AuroLase involves the intravenous delivery of nanoshells that flow through the bloodstream and amass in the prostate tumor. The clinician uses targeted MRI ultrasound fusion technology to identify the lesion and position an optical fiber probe. The prostate tissue is then ablated via the emission of near-infrared energy from an FDA-cleared laser. The precision of the technology spares surrounding healthy tissue from harm.

The pivotal open-label, single-treatment trial of AuroLase has now enrolled 60 patients at 9 clinical locations in the United States. This study was preceded by a positive first-in-human feasibility study that included 46 patients who were treated at 3 US clinical sites.

The efficacy of AuroLase is being evaluated at 6 months using MRI-ultrasound guided target biopsy. One year after focal ablation, investigators will assess the procedure using both targeted biopsy and standard systematic biopsy. As per standard of care, follow-up will continue after the 1-year visit; however, the results of these visits are beyond the scope of the trial.

Nanospectra anticipates that the initial 6-month study results will be available in mid-2022, with the complete results likely to be available by the end of 2022. The company also expects to file for FDA regulatory clearance by the end of next year, with the submitted data package to include both the feasibility and pivotal study data sets.

REFERENCES
IL-15 superagonist N-803 shows clinical activity

Treatment enabled 85% of patients to avoid cystectomy

“Anktiva has demonstrated strong disease control in CIS, and based on the latest data from our study, it is showing the same effect in papillary tumors.”

PATRICK SOON-SHIONG, MD

reported results for cohort A included data for 81 patients. Results presented for cohort A during the 2021 American Urological Association Annual Meeting showed that BCG plus N-803 reached a CR rate of 72% and a 58.6% probability of maintaining a CR for at least 12 months. Additionally, at a median follow-up of 20.4 months, the median duration of CR was 19.9 months.

A combined safety analysis of cohorts A and B (n = 154) showed no immune-related or treatment-related severe adverse events in any patients.

In December 2019, the FDA granted N-803 a breakthrough therapy designation for use in combination with BCG in patients with BCG-unresponsive NMIBC and CIS.

ImmunityBio plans to share full efficacy and safety data for cohorts A and B at the American Society of Clinical Oncology Genitourinary Cancers Symposium in February 2022.

REFERENCES


JASON M. BRODERICK
Associate Editorial Director, Urology Times®
Biomarker emerges for Botox response in patients with overactive bladder

Drop in urinary ATP levels after injections corresponds to improvements in symptoms

JASON M. BRODERICK, Associate Editorial Director, Urology Times®

Urinary adenosine triphosphate (ATP) levels have emerged as a biomarker of response to treatment with onabotulinumtoxinA (BTX-A; Botox) in patients with overactive bladder (OAB), according to findings from a prospective pilot study presented during the 2021 American Urological Association Annual Meeting.1

Specifically, a decrease in urinary ATP levels following BTX-A injections corresponds to clinical improvements in OAB symptoms, Samantha Freeman, a fourth-year medical student at the Albert Einstein College of Medicine in Bronx, New York, said in her presentation. “ATP is released by the urothelium and used as a key signaling molecule. It has been shown to be involved in the proper regulation of both bladder sensory and motor functions. Studies have found that ATP levels are higher in patients with OAB. Animal studies have been able to go a step further and show that BTX-A injections decrease stress-induced ATP release. However, little is known about the effect of these injections on human ATP levels,” Freeman said, who worked on the study with Sylvia O. Suadicani, PhD, and colleagues.

Accordingly, Freeman and her coinvestigators sought to demonstrate this effect in humans by assessing ATP levels and OAB-V8 questionnaire symptom scores to quantify and compare changes in voided urine ATP levels in women with OAB treated with BTX-A.

The study enrolled women 18 years or older. Patients were excluded from enrollment if they had neurogenic OAB, positive urine cultures, genitourinary cancer, or concomitant bladder stones, or if they were pregnant, bed-bound, unable to complete the surveys, or went into retention following injections.

The investigators collected urine samples prior to BTX-A injection and post BTX-A injection visits. “Urine samples were frozen on dry ice until urine ATP levels could be quantified using the luciferin–luciferase bioluminescence assay,” Freeman said. OAB-V8 questionnaires were used to assess symptom severity in patients at the time of urine collection.

Overall, 24 women were recruited to the study. Six women had to be excluded from the study population, mostly because they had a positive urine culture. Of the 18 remaining patients, there were 12 responders to the BTX-A treatment and 6 nonresponders.

“Patients who have improvements in their OAB symptoms following BTX-A injection also have a significant decrease in their urine ATP levels.”

SAMANTHA FREEMAN

The investigators collected a total of 42 urine samples from the 18 patients. Seventeen samples were collected prior to injection of therapy and 25 were collected after the treatment.

“All patients showed up to their first follow-up visit within 2 to 3 weeks of their BTX-A injection. However, second and third follow-up visit times were variable, with some patients not returning for follow-up visits and others coming at varying time points,” said Freeman.

The results of the analysis of urine ATP levels showed that patient responders at all follow-up time points had a negative percentage change in their ATP level, “meaning ATP levels are lower after injection.” Patients who did not respond to treatment had a positive percentage change, “meaning their ATP levels either remained high or even increased after treatment,” Freeman said.

When comparing the 2 groups head-to-head, responders had significantly lower median ATP levels at the 2-week post–BTX-A injection follow-up compared with nonresponders (P =.0268), according to Freeman.

Then the investigators used the OAB-V8 questionnaire scores to determine the correlation between changes in urine ATP levels and the degree to which patients responded symptomatically. They established response categories based on how much OAB-V8 scores improved: nonresponder (<8 points); mild responder (8-16 points); moderate responder (17-24 points); marked responder (>24 points).

The results showed there was a significant difference in percentage ATP change among the categories, with greater improvement in OAB-V8 symptom scores correlating with a decrease in ATP level. The most significant difference occurred between the marked responders and the nonresponders (P =.029).

“Patients who have improvements in their OAB symptoms following BTX-A injection also have a significant decrease in their urine ATP levels,” Freeman said.

In her summary remarks, Freeman concluded, “The results suggest that BTX-A is working on the urothelium and posing either a direct effect or indirect effect of BTX-A on mechanisms of urothelial ATP release and signaling. Therefore, quantification of urinary ATP may provide a valuable tool to assess treatment response and guide further management.”

REFERENCE
Individuals with a higher body mass index (BMI) are associated with a higher incidence of testosterone deficiency. However, current dosing standards for testosterone therapy do not account for the possibility of obese patients (BMI ≥ 30 kg/m²) needing higher doses as a result of their high BMI. In a recent study presented at the 2021 Sexual Medicine Society of North America Fall Scientific Meeting, Martin M. Miner, MD, and coauthors investigated the effect of BMI on the pharmacokinetic profile or dosing of testosterone therapies in men with testosterone deficiency. Miner is the founder of the Men’s Health Center at Miriam Hospital and is a clinical professor of family medicine and urology at the Warren Alpert Medical School of Brown University in Providence, Rhode Island.

Q. Can you discuss the background for this study?
A. This study is a post hoc analysis that I initiated. I was one of the original investigators of Xyosted in their phase 3 trial in pharmacokinetics. My question was: In men with a larger BMI, would they have data to support the use of a larger dose of their weekly testosterone injection? This is part of men receiving testosterone therapy for hypogonadism or low testosterone levels associated with clinical signs and symptoms of testosterone deficiency. In this post hoc analysis, we looked at the effect of BMI on men receiving pharmacokinetic dosing of testosterone and the association between BMI and serum total testosterone levels. The primary end point was the percentage of patients who received more than 1 dose of subcutaneous testosterone enanthate to achieve adequate serum testosterone levels over a 7-day dosing of the Xyosted. This included about 142 patients, and we looked at all the pharmacokinetic parameters, including the trough levels, the area under the curve, the C average, and the Cₘₐₓ.

Q. What were some of the notable findings? Were any of them surprising to you and your coauthors?
A. We found that men who were classified in 3 tertiles based on BMI had levels that were indeed low. Prior to achieving any dosage adjustments, men who were in the upper percentile in terms of BMI required a larger dose of testosterone to achieve eugonadal levels, which means levels between 300 and 1100. The initial levels were inversely related to BMI, so men who are the largest or had the largest BMI have the lowest testosterone levels. That’s what you would expect with obese men. The greater the amount of obesity, the lower their endogenous levels would be. Men would require the largest dose adjustment if they had a larger BMI. In conclusion, we found that men who were larger or had larger BMIs would require larger dosing. It’s an intuitive assumption that never has been found to be the case before.

Q. How do these findings build on previous research into testosterone enanthate?
A. They supported the idea that, for men who are obese, the greater the obesity, the lower their endogenous levels or baseline levels of testosterone. We know there’s an inverse relationship there and that the supposition or the premise that men who are larger would require larger amounts of testosterone to maintain normal or eugonadal levels.

Q. What is the take-home message for the practicing urologist?
A. The take-home message is that when you’re planning to begin repletion of testosterone, you’re likely going to have to consider a man’s BMI and/or waist circumference in doing so. Also, that men who have a larger amount of visceral adiposity, or a larger BMI, may require adjustments in dosing to achieve eugonadal levels and to achieve levels that replete and resolve their clinical symptomatology.

Q. Is there anything else you feel our audience should know about the findings?
A. What’s most important is that 1 dose does not fit all, and people have to be individualized. In terms of testosterone therapy, dosing for men needs to be repleted at an individual level.

REFERENCE
ORGOVYX achieved sustained testosterone suppression¹

- 97% of men achieved and maintained testosterone suppression to <50 ng/dL from Day 29 through Week 48 with ORGOVYX

**MAJOR EFFICACY OUTCOME MEASURE: SUSTAINED TESTOSTERONE SUPPRESSION RATE (TESTOSTERONE LEVELS <50 ng/dL FROM DAY 29 THROUGH WEEK 48)¹**

<table>
<thead>
<tr>
<th>Sustained testosterone suppression rate*</th>
<th>ORGOVYX</th>
<th>Leuprolide</th>
</tr>
</thead>
<tbody>
<tr>
<td>100%</td>
<td>96.7%</td>
<td>88.8%</td>
</tr>
<tr>
<td>80%</td>
<td>(95% CI: 94.9-97.9)</td>
<td>(95% CI: 84.6-91.8)¹</td>
</tr>
<tr>
<td>60%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CI=confidence interval.

¹Kaplan-Meier estimates within each group.

²The testosterone suppression rate of the subgroup of patients receiving leuprolide 22.5 mg [n=264] was 88.0% (95% CI: 83.4-91.4).

³Two patients in each arm did not receive the study treatment and were not included.

⁴11.25 mg is a dosage regimen that is not recommended for this indication in the United States.

**INDICATION**

ORGOVYX is a gonadotropin-releasing hormone (GnRH) receptor antagonist indicated for the treatment of adult patients with advanced prostate cancer.

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**

**QT/QTc Interval Prolongation:** Androgen deprivation therapy, such as ORGOVYX may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congenital long QT syndrome, congestive heart failure, or frequent electrolyte abnormalities and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

**Embryo-Fetal Toxicity:** The safety and efficacy of ORGOVYX have not been established in females. Based on findings in animals and mechanism of action, ORGOVYX 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 and for 2 weeks after the last dose of ORGOVYX.

**Laboratory Testing:** Therapy with ORGOVYX results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotrophic and gonadal functions conducted during and after ORGOVYX may be affected. The therapeutic effect of ORGOVYX should be monitored by measuring serum concentrations of prostate-specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.
ORGOVYX offers an injection-free option for testosterone control\(^1\)\(^-\)\(^3\)

- **RAPID TESTOSTERONE SUPPRESSION WITHOUT A SURGE:** 56% of men treated with ORGOVYX achieved testosterone suppression to <50 ng/dL on Day 4
  - 0% of men treated with leuprolide had testosterone levels <50 ng/dL on Day 4

- **PROFOUND TESTOSTERONE SUPPRESSION:** 95% of men treated with ORGOVYX achieved profound testosterone suppression to <20 ng/dL on Day 29
  - 57% of men treated with leuprolide had testosterone levels <20 ng/dL on Day 29

- **90-DAY TESTOSTERONE RECOVERY:** in a substudy, 55% of the 137 men treated with ORGOVYX had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after treatment discontinuation\(^6\)
  - 3% of 47 men treated with leuprolide had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after discontinuation

---

**IMPORTANT SAFETY INFORMATION (cont’d)**

**Adverse Reactions**

**Serious adverse reactions** occurred in 12% of patients receiving ORGOVYX. Serious adverse reactions in ≥0.5% of patients included myocardial infarction (0.8%), acute kidney injury (0.6%), arrhythmia (0.6%), hemorrhage (0.6%), and urinary tract infection (0.5%). Fatal adverse reactions occurred in 0.8% of patients receiving ORGOVYX including metastatic lung cancer (0.3%), myocardial infarction (0.3%), and acute kidney injury (0.2%). Fatal and non-fatal myocardial infarction and stroke were reported in 2.7% of patients receiving ORGOVYX.

**Most common adverse reactions (≥10%) and laboratory abnormalities (≥15%)** in patients receiving ORGOVYX were hot flush (54%), glucose increased (44%), triglycerides increased (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), alanine aminotransferase increased (27%), fatigue (26%), aspartate aminotransferase increased (18%), constipation (12%), and diarrhea (12%).

**Drug Interactions**

**Co-administration of ORGOVYX with a P-gp inhibitor** increases the area under the curve (AUC) and maximum concentration (C\(\text{max}\)) of ORGOVYX, which may increase the risk of adverse reactions associated with ORGOVYX. Avoid co-administration of ORGOVYX with oral P-gp inhibitors. If co-administration is unavoidable, take ORGOVYX first, separate dosing by at least 6 hours, and monitor patients more frequently for adverse reactions. Treatment with ORGOVYX may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors. If treatment with ORGOVYX is interrupted for more than 7 days, resume administration of ORGOVYX with a 360 mg loading dose on the first day, followed by 120 mg once daily.

**Co-administration of ORGOVYX with a combined P-gp and strong CYP3A inducer** decreases the AUC and C\(\text{max}\) of ORGOVYX, which may reduce the effects of ORGOVYX. Avoid co-administration of ORGOVYX with combined P-gp and strong CYP3A inducers. If co-administration is unavoidable, increase the ORGOVYX dose to 240 mg once daily. After discontinuation of the combined P-gp and strong CYP3A inducer, resume the recommended ORGOVYX dose of 120 mg once daily.

Please see Brief Summary of Prescribing Information for ORGOVYX on adjacent pages.

**References:**

ORGOVYX\(^\text{TM}\) and its associated logo are trademarks of Myovant Sciences GmbH.
©2021 Myovant Sciences GmbH and Pfizer Inc. All rights reserved. PP-US-REL-2100225 05/21
BRIEF SUMMARY

ORGOVYX™ (relugolix) tablets, for oral use

The following is a brief summary of the full prescribing information for ORGOVYX™ (relugolix). Please see the full prescribing information for complete product information.

1 INDICATIONS AND USAGE

ORGOVYX is indicated for the treatment of adult patients with advanced prostate cancer.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 QT/QTc Interval Prolongation

Androgen deprivation therapy, such as ORGOVYX may prolong the QT/QTc interval. Providers should consider whether the benefits of androgen deprivation therapy outweigh the potential risks in patients with congestive long QT syndrome, congestive heart failure, or frequent electrolyte abnormalities and in patients taking drugs known to prolong the QT interval. Electrolyte abnormalities should be corrected. Consider periodic monitoring of electrocardiograms and electrolytes.

5.2 Embryo-Fetal Toxicity

The safety and efficacy of ORGOVYX have not been established in females. Based on findings in animals and mechanism of action, ORGOVYX can cause fetal harm and loss of pregnancy when administered to a pregnant female. In an animal reproduction study, oral administration of relugolix to pregnant rabbits during the period of organogenesis caused embryo-fetal lethality at maternal exposures that were 0.3 times the human exposure at the recommended dose of 120 mg daily based on area under the curve (AUC). Advise males with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

5.3 Laboratory Testing

Therapy with ORGOVYX results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropin and gonadal functions conducted during and after ORGOVYX may be affected. The therapeutic effect of ORGOVYX should be monitored by measuring serum concentrations of prostate specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

• QT/QTc Interval Prolongation.

6.1 Clinical Trials 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 safety of ORGOVYX was evaluated in HERO, a randomized (2:1), open-label, parallel-group study of 611 adult men with advanced prostate cancer. Patients received orally administered ORGOVYX as a loading dose of 360 mg on the first day followed by 120 mg taken orally once daily (n = 622) or received leuprolide acetate administered by depot injection at doses of 22.5 mg (n = 264) or 11.25 mg (n = 44) per local guidelines every 12 weeks (n = 308). Leuprolide acetate 11.25 mg is a dosage regimen that is not recommended for this indication in the US. Among patients who received ORGOVYX, 91% were exposed for at least 48 weeks. Ninety-nine (16%) patients received concomitant radiotherapy and 17 (3%) patients received concomitant enzalutamide with ORGOVYX.

Serious adverse reactions occurred in 12% of patients receiving ORGOVYX. Serious adverse reactions in ≥ 0.5% of patients included myocardial infarction (0.8%), acute kidney injury (0.6%), arrhythmia (0.6%), hemorrhage (0.6%), and urinary tract infection (0.5%). Fatal adverse reactions occurred in 0.8% of patients receiving ORGOVYX including metastatic lung cancer (0.3%), myocardial infarction (0.3%), and acute kidney injury (0.2%). Fatal and non-fatal myocardial infarction and stroke were reported in 2.7% of patients receiving ORGOVYX.

Permanent discontinuation of ORGOVYX due to an adverse reaction occurred in 3.5% of patients. Adverse reactions which resulted in permanent discontinuation of ORGOVYX in ≥ 0.3 % of patients included atroventricular block (0.3%), cardiac failure (0.3%), hemorrhage (0.3%), increased transaminases (0.3%), abdominal pain (0.3%), and pneumonia (0.3%).

Dose interruptions of ORGOVYX due to an adverse reaction occurred in 2.7% of patients. Adverse reactions which required dosage interruption in ≥ 0.3% of patients included fracture (0.3%).

The most common adverse reactions (≥ 10%) and laboratory abnormalities (≥ 15%), were hot flush (54%), glucose increased (44%), triglycerides increased (35%), musculoskeletal pain (30%), hemoglobin decreased (28%), alanine aminotransferase increased (ALT) (27%), fatigue (26%), aspartate aminotransferase increased (AST) (18%), constipation (15%), and diarrhea (12%).

Table 1 summarizes the adverse reactions in HERO.

Table 1: Adverse Reactions (≥ 10%) of Patients with Advanced Prostate Cancer Who Received ORGOVYX in HERO

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ORGOVYX</th>
<th>Leuprolide Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>54</td>
<td>0.6</td>
</tr>
<tr>
<td>52</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>30</td>
<td>1.1</td>
</tr>
<tr>
<td>29</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>28</td>
<td>0.3</td>
</tr>
<tr>
<td>24</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Includes arthralgia, back pain, pain in extremity, musculoskeletal pain, myalgia, bone pain, neck pain, arthritis, musculoskeletal stiffness, non-cardiac chest pain, musculoskeletal chest pain, spinal pain, and musculoskeletal discomfort.

The most common adverse reactions associated with ORGOVYX were hot flush, flushing of the skin, increased weight, insomnia, gynecomastia, hyperhidrosis, depression, and decreased libido.

Table 2 summarizes the laboratory abnormalities in HERO.

Table 2: Select Laboratory Abnormalities (≥ 15%) That Worsened from Baseline in Patients with Advanced Prostate Cancer Who Received ORGOVYX in HERO

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>ORGOVYX</th>
<th>Leuprolide Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>44</td>
<td>2.9</td>
</tr>
<tr>
<td>54</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Triglycerides increased</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>36</td>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>ALT increased</td>
<td>27</td>
<td>0.3</td>
</tr>
<tr>
<td>28</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>AST increased</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>19</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>28</td>
<td>0.5</td>
</tr>
<tr>
<td>29</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

* The denominator used to calculate the rate varied from 611 to 619 in the ORGOVYX arm and from 301 to 306 in the leuprolide arm based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ORGOVYX

P-gp Inhibitors

Co-administration of ORGOVYX with a P-gp inhibitor increases the AUC and the maximum concentration (Cmax) of relugolix, which may increase the risk of adverse reactions associated with ORGOVYX. Avoid co-administration of ORGOVYX with oral P-gp inhibitors.

If co-administration is unavoidable, take ORGOVYX first, separate dosing by at least 6 hours, and monitor patients more frequently for adverse reactions.

Treatment with ORGOVYX may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors.

If treatment with ORGOVYX is interrupted for more than 7 days, resume administration of ORGOVYX with a 360 mg loading dose on the first day, followed by 120 mg once daily.

Combined P-gp and Strong CYP3A Inducers

Co-administration of ORGOVYX with a combined P-gp and a strong CYP3A inducer decreases the AUC and Cmax of relugolix, which may reduce the effects of ORGOVYX. Avoid co-administration of ORGOVYX with combined P-gp and strong CYP3A inducers.
If co-administration is unavoidable, increase the ORGOVYX dose. After discontinuation of the combined P-gp and strong CYP3A inducer, resume the recommended dose of ORGOVYX once daily.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of ORGOVYX have not been established in females.

Based on findings in animals and mechanism of action, ORGOVYX can cause fetal harm and loss of pregnancy when administered to a pregnant female. There are no human data on the use of ORGOVYX in pregnant females to inform the drug-associated risk.

In an animal reproduction study, oral administration of relugolix to pregnant rabbits during organogenesis caused embryo-fetal lethality at maternal exposures that were 0.3 times the human exposure at the recommended dose of 120 mg daily based on AUC (see Data). Advise patients of the potential risk to the fetus.

Data

Animal Data

In an embryo-fetal development study, oral administration of relugolix to pregnant rabbits during the period of organogenesis resulted in abortion, total litter loss, or decreased number of live fetuses at a dose of 9 mg/kg/day (approximately 0.3 times the human exposure at the recommended dose of 120 mg daily based on AUC). (see Data).

8.2 Lactation

Risk Summary

The safety and efficacy of ORGOVYX at the recommended dose of 120 mg daily have not been established in females. There are no data on the presence of relugolix in human milk, the effects on the breastfeeding child, or the effects on milk production.

Relugolix and/or its metabolites were present in milk of lactating rats (see Data).

Data

Animal Data

In lactating rats administered a single oral dose of 30 mg/kg radioisobaled relugolix on post-partum day 14, relugolix and/or its metabolites were present in milk at concentrations up to 10-fold higher than in plasma at 2 hours post-dose.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on findings in animals and mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

Infertility

Males

Based on findings in animals and mechanism of action, ORGOVYX may impair fertility in males of reproductive potential.

8.4 Pediatric Use

The safety and efficacy of ORGOVYX in pediatric patients have not been established.

8.5 Geriatric Use

Of the 622 patients who received ORGOVYX in the HERO study, 81% were 65 years of age or older, while 35% were 75 years of age or older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. There was no clinically relevant impact of age on the pharmacokinetics of ORGOVYX or testosterone response based on population pharmacokinetic and pharmacokinetic/pharmacodynamic analyses in men 45 to 91 years of age.

12.3 Pharmacokinetics

Specific Populations

No clinically meaningful differences in the pharmacokinetics of relugolix were observed based on age (45 to 91 years), race/ethnicity (Asian [19%], White [71%], Black/African American [8%]), body weight (41 to 193 kg), mild to severe renal impairment (creatinine clearance [CLcr] 15 to 89 mL/min, as estimated by the Cockcroft-Gault equation), or mild to moderate hepatic impairment (Child-Pugh A or B). The effect of end-stage renal disease with or without hemodialysis or severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of relugolix has not been evaluated.

Drug Interactions Studies

Clinical Studies

Combined P-gp and Moderate CYP3A Inhibitor: Co-administration with erythromycin (P-gp and moderate CYP3A inhibitor) increased the AUC and Cmax of relugolix by 6.2-fold.

Combined P-gp and Strong CYP3A Inhibitor: Co-administration with rifampin (P-gp and strong CYP3A inhibitor) decreased the AUC and Cmax of relugolix by 55% and 23%, respectively.

Other Drugs: No clinically significant differences in the pharmacokinetics of relugolix were observed when co-administered with voriconazole (strong CYP3A inhibitor), atorvastatin, enalaprilatme, or acid-reducing agents. No clinically significant differences in the pharmacokinetics of midazolam (sensitive CYP3A substrate) or rosuvastatin (CYP2B6 substrate) were observed upon co-administration with relugolix.

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Relugolix is a substrate of CYP3A and CYP2C8. Relugolix is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4. Relugolix is an inducer of CYP3A and CYP2B6, but not an inducer of CYP1A2.

Transporter Systems: Relugolix is a substrate of P-gp, but not a substrate of BCRP.

Relugolix is an inhibitor of BCRP and P-gp, but not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OAT2, MATE1, MATE2-K, or BSEP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Two-year carcinogenicity studies were conducted in mice at oral relugolix doses up to 100 mg/kg/day and in rats at doses up to 600 mg/kg/day. Relugolix was not carcinogenic in mice or rats at exposures up to approximately 75 or 224 times, respectively, the human exposure at the recommended dose of 120 mg daily based on AUC.

Relugolix was not mutagenic in the in vitro bacterial reverse mutation ( Ames) assay or clastogenic in the in vitro chromosomal aberration assay in Chinese hamster lung cells or the in vivo rat bone marrow micronucleus assay.

In human GnRH-receptor knock-in mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses ≥ 3 mg/kg twice daily for 28 days. The effects of relugolix were reversible, except for testis weight, which did not fully recover within 28 days after drug withdrawal. In a 39-week repeat-dose toxicity study in monkeys, there were no significant effects on male reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human exposure at the recommended dose of 120 mg daily based on AUC).

13.2 Animal Toxicology and/or Pharmacology

Phospholipidosis (intracellular phospholipid accumulation) was observed in multiple organs and tissues (e.g., liver, pancreas, spleen, kidney, lymph nodes, lung, bone marrow, gastrointestinal tract or testes) after repeated oral administration of relugolix in rats and monkeys. In a rat 26-week toxicity study, phospholipidosis was observed at doses ≥ 100 mg/kg (approximately 18 times the human exposure at the recommended dose based on AUC). In a monkey 39-week toxicity study, this effect was observed at doses ≥ 1.5 mg/kg (approximately 0.6 times the human exposure at the recommended dose based on AUC) and demonstrated evidence of reversibility after cessation of treatment. The significance of this finding in humans is unknown.

17 PATIENT COUNSELING INFORMATION

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

QT/QTc Interval Prolongation

• Advise patients that androgen deprivation therapy treatment with ORGOVYX may prolong the QT interval. Inform patients of the signs and symptoms of QT prolongation. Advise patients to contact their healthcare provider immediately for signs or symptoms of QT prolongation.

Androgen Deprivation

• Inform patients about adverse reactions related to androgen deprivation therapy with ORGOVYX, including hot flashes, flushing of the skin, increased weight, decreased sex drive, and difficulties with erectile function.

Embryo-Fetal Toxicity

• Inform patients that ORGOVYX can be harmful to a developing fetus and can cause loss of pregnancy.

• Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

Infertility

• Inform patients that ORGOVYX may cause infertility.

Manufactured by Bushu Pharmaceuticals, Ltd, Kawagoe, Saitama, Japan

Manufactured for Myovant Sciences, Inc., Brisbane, CA 94005

Issued: December 2020

214621-MS-000

ORGOVYX™ and its associated logo are trademarks of Myovant Sciences GmbH.

©2021 Myovant Sciences GmbH and Pfizer Inc. All rights reserved.

PP-US-REL-2000227 01/21
Radiation therapy as monotherapy is effective in oligometastatic RCC

Use of the modality resulted in median progression-free survival of 22.7 months

BENJAMIN P. SAYLOR
Managing Editor, Urology Times®

Radiation therapy as monotherapy may be a safe and effective treatment for patients with oligometastatic renal cell carcinoma (RCC), according to findings from a phase 2 study published in Lancet Oncology.1

Use of the modality resulted in median progression-free survival (PFS) of 22.7 months in patients with RCC, according to a news release about the study.

“These findings are exciting because we’re challenging the dogma in radiation oncology that RCC is biologically radioresistant. Our strategy to iteratively radiate tumors as they grow and appear has demonstrated promising results. This adds to a growing body of evidence suggesting/indicating radiation therapy could offer an alternative treatment beyond systemic therapy for patients with this disease,” said lead author Chad Tang, MD, an assistant professor in the Department of Radiation Oncology at The University of Texas MD Anderson Cancer Center in Houston.2

The study (NCT03575611) evaluated patients 18 years or older who had 5 or fewer metastatic lesions, an ECOG performance status of 0 to 2, and no more than 1 previous systemic therapy without limitations on RCC histology. Patients received stereotactic body radiotherapy consisting of 5 or fewer fractions with at least 7 Gy per fraction directed at all lesions and maintained off systemic therapy.

The coprimary end points were feasibility and progression-free survival. The study also included a second cohort, in whom investigators will evaluate the feasibility of sequential stereotactic body radiotherapy alone in patients with low-volume metastatic disease. That cohort will be reported separately, according to the investigators.

A total of 30 patients were enrolled in the study, all of whom had clear cell histology and underwent nephrectomy prior to enrollment. The trial had 20 White (67%), 7 Hispanic (23%), 2 Black (7%), and 1 Native American (3%) participants. Median age was 65 years, and 24 (80%) of the patients were men. The entire cohort completed at least 1 round of radiotherapy with fewer than 7 days of unplanned breaks. “At a median follow-up of 17.5 months, median PFS was 22.7 months (1-year PFS 64%),” the investigators wrote.

At 3 months after treatment, biopsies confirmed the efficacy of radiation therapy for eliminating viable tumor cells or significantly reducing their proliferation. At first follow-up, investigators conducted CT-guided biopsy on 14 patients, of whom 6 tested negative for viable malignancy. In the remaining patients tested, a meaningful reduction in tumor cell proliferation (15% before radiation therapy, 6% after treatment) was observed. A total of 23 patients remained off systemic therapy at the end of the study period.

Two patients experienced a grade 3 adverse event (AE; back pain or muscle weakness), and 1 patient experienced a grade 4 AE (hyperglycemia). No treatment-related deaths were reported. “Given these results, I’m encouraged that serial radiation therapy for oligometastatic RCC has the potential to be practice changing,” Tang said. “We are giving patients another option for treatment that minimizes the burden of toxicity on the body while extending survival and maximizing their quality of life. We plan to continue studying this strategy on patients with slightly larger burdens of disease and to analyze biomarkers from these treated patients to improve our ability to select patients who benefit from this treatment.”

REFERENCES


Stewart discusses study of neoadjuvant axitinib in renal cell carcinoma

In this video, Grant Stewart, MD, discusses the background and findings of the study, “NAXIVA – a phase II neoadjuvant study of axitinib for reducing extent of venous tumor thrombus in clear cell renal cell carcinoma with venous invasion: translational results.” Stewart is a professor of surgical oncology and honorary consultant urological surgeon at the University of Cambridge, England.
2021 was another busy year in the urology space, with multiple drugs and devices receiving FDA approval. In this article, we look back on the notable developments in treatment and diagnostics within the specialty.

**January**

Relugolix launches in US prostate cancer market

The prostate cancer drug relugolix (Orgovyx) is now available in the United States through authorized specialty distributors. The gonadotropin-releasing hormone receptor antagonist was approved in December 2020 for the treatment of patients with advanced prostate cancer. The approval was based on data from the phase 3 HERO study (NCT03085095), which showed that 96.7% of patients randomized to relugolix maintained castration through 48 weeks, compared with 88.8% of patients receiving leuprolide (P<.001). The benefit with relugolix was sustained across all major secondary end points (P<.001). Relugolix was also associated with a 54% lower risk of major adverse cardiovascular events compared with leuprolide (HR, 0.46).

**Label update is approved for darolutamide in nonmetastatic CRPC**

The FDA updated the label for darolutamide (Nubeqa) in nonmetastatic castration-resistant prostate cancer (CRPC) to include overall survival (OS) data from the pivotal phase 3 ARAMIS trial. In the ARAMIS trial (NCT0200614), adding darolutamide to androgen-deprivation therapy (ADT) reduced the risk of death by 31% compared with ADT plus placebo in men with nonmetastatic CRPC (HR, 0.69; P=.003). At a median follow-up of 29 months, the 3-year OS rates were 83% and 77% in the darolutamide and placebo arms, respectively. This OS benefit was reached even though over half (55%) of the patients in the control arm received darolutamide or other subsequent treatments after the study was unblinded.

**Nivolumab/cabozantinib combo is approved for frontline kidney cancer**

The combination of nivolumab (Opdivo) and cabozantinib (Cabometyx) was approved by the FDA as a frontline treatment for patients with advanced renal cell carcinoma (RCC). The approval was based on findings from the phase 3 CheckMate 9ER trial (NCT0141177), which showed that the combination reduced the risk of disease progression or death by 49% vs sunitinib (Sutent) in treatment-naive patients with advanced RCC, with a median progression-free survival (PFS) of 16.6 months vs 8.3 months, respectively (HR, 0.51; P<.0001). Additional findings showed that at a median follow-up of 18.1 months, the median OS was not reached in either arm, and there was a 40% reduction in the risk of death with the combination (HR, 0.60; P=.001).

**February**

MRI labeling is expanded for InterStim SNM bladder and bowel control devices

The FDA approved expanded MRI labeling for the InterStim II and InterStim Micro sacral neuromodulation systems that use SureScan MRI leads. The devices are used to treat patients with bladder and bowel control conditions. Medtronic, the developer of the devices, reported in a news release that the updated MRI guidelines in the label expand the range of MRI scan parameters and allow a briefer waiting period between MRI scans.

**Durvalumab indication for bladder cancer voluntarily withdrawn**

AstraZeneca voluntarily withdrew the FDA indication for the PD-L1 inhibitor durvalumab (Imfinzi) for use in previously treated patients with locally advanced or metastatic bladder cancer. Durvalumab received an accelerated approval from the FDA for

---

**2021 UROLOGY PIPELINE REPORT**

**2021 FDA ACTIVITY IN UROLOGY**

**January**

- Relugolix (Orgovyx) launches in US prostate cancer market
- Label update is approved for darolutamide (Nubeqa) in nonmetastatic CRPC
- Nivolumab (Opdivo)/cabozantinib (Cabometyx) is approved for frontline kidney cancer

**February**

- MRI labeling is expanded for InterStim SNM bladder and bowel control devices
- Durvalumab (Imfinzi) indication for pretreated bladder cancer is voluntarily withdrawn
- Updated version is approved for neurostimulator device

**March**

- Atezolizumab (Tecentriq) indication for pretreated bladder cancer is voluntarily withdrawn
- Tivozanib (Fotivda) is approved for kidney cancer

**April**

- Vibegron launches in US OAB market
- Sacituzumab govitecan (Trodelvy) is approved for bladder cancer

**May**

- FDA grants clearance to novel single-use cystoscope
- PSMA-PET imaging agent piulfuolastat F 18 (Pylarify) is approved for prostate cancer
- New subcutaneous formulation of leuprolide mesylate (Camcevi) is approved for prostate cancer
FDA approves tivozanib for kidney cancer
The FDA approved tivozanib (Fotivda) for the treatment of adult patients with relapsed or refractory advanced RCC who have received 2 or more prior systemic therapies. The approval was based on data from the phase 3 TIVO-3 trial (NCT02627963), in which the VEGF tyrosine kinase inhibitor tivozanib demonstrated a significant improvement in PFS compared with sorafenib (Nexavar), with similar OS in patients with highly relapsed/refractory metastatic RCC.6

APRIL
Vibegron launches in US OAB market
The β3-adrenoceptor agonist vibegron (Gemtesa) was made commercially available in the United States for the treatment of adult patients with overactive bladder with symptoms of urge urinary incontinence (UUI), urgency, and urinary frequency. The FDA approved vibegron on December 23, 2020, for use in this setting based on the phase 3 EMPOWUR trial (NCT03492281). In the primary study analysis, at 12 weeks, vibegron showed a mean change from baseline in the average daily number of micturitions of –1.8 compared with –1.3 for placebo and –1.6 for tolerodine (P < .001).9 The mean change from baseline in UUI episodes was –2.0, –1.4, and –1.8, respectively.

Sacituzumab govitecan is approved for bladder cancer
The FDA granted an accelerated approval to sacituzumab govitecan (Trodelvy) for the treatment of patients with locally advanced or mUC previously treated with platinum-based chemotherapy. Atezolizumab received an accelerated approval from the FDA for this indication in May 2016 based on cohort data from the phase 2 IMvigor210 study (NCT02108652). However, an FDA accelerated approval is contingent upon the results of a confirmatory trial and in May 2017, Roche reported that the phase 3 IMvigor211 study (NCT02302807) exploring atezolizumab in the second-line setting for patients with locally advanced or mUC missed its primary end point of improving OS.7

FDA approves updated version of neurostimulator device
The FDA approved the third-generation version of Axogen’s NeuroModulation Technologies’ rechargeable implantable neurostimulator (INS) for the treatment of adult patients with urinary and bladder dysfunction.5 The INS device was launched commercially in the United States in November 2019. A second-generation version approved in April 2020 prolonged the device’s recharge interval. The third-generation model upgrades the software embedded in the device and enhances the functionality of the remote control, used by patients to monitor their stimulation level and the need to recharge the stimulator.

MARCH
Atezolizumab indication for pretreated bladder cancer is voluntarily withdrawn
Roche (Genentech) voluntarily withdrew the FDA indication for the PD-L1 inhibitor atezolizumab (Tecentriq) for use in patients with locally advanced or metastatic urothelial carcinoma (mUC) previously treated with platinum-based chemotherapy. Atezolizumab received an accelerated approval from the FDA for this indication in May 2016 based on cohort data from the phase 2 IMvigor210 study (NCT02108652). However, an FDA accelerated approval is contingent upon the results of a confirmatory trial and in May 2017, Roche reported that the phase 3 IMvigor211 study (NCT02302807) exploring atezolizumab in the second-line setting for patients with locally advanced or mUC missed its primary end point of improving OS.7

PSMA-PET imaging agent piflufolastat F 18 approved for prostate cancer
The FDA approved the PSMA-PET imaging agent piflufolastat F 18 (Pylarify) for identifying suspected metastasis or recurrence of prostate cancer. The approval was based on findings from the CONDOR7 (NCT01739684) and OSPREY (NCT02981368) studies. In the CONDOR study, 63.9% of men with biochemically recurrent prostate cancer who had no evidence of disease on standard-of-care imaging had a change in intended management after their piflufolastat F 18 scan.

New subcutaneous formulation of leuprolide mesylate is approved for prostate cancer
The FDA approved a ready-to-use 6-month subcutaneous depot formulation of leuprolide mesylate (Camcevi 42 mg) for the treatment of patients with advanced prostate cancer. The approval was based on findings from a phase 3 trial (NCT02234115) in which the primary efficacy end points were the percentage of subjects with suppression of serum testosterone (≤ 50 ng/dL) by day 28 and from day 28 to day 336.10 These primary end points were successfully achieved; 97% of subjects had a serum testosterone level ≤ 50 ng/dL by day 28 and from day 28 to day 336, consistent with active suppression of the androgen axis. The approval was based on findings demonstrating the noninferiority of this subcutaneous formulation compared with the current FDA-approved intramuscular formulation of leuprolide (Lupron Depot) for the treatment of advanced prostate cancer who had no evidence of disease on standard-of-care imaging.11

JULY
- Enfortumab vedotin (Padcev) receives regular approval for bladder cancer
- Soft-tissue 3D printing technology is granted FDA clearance for GU conditions

AUGUST
- Frontline pembrolizumab (Keytruda)/lenvatinib (Lenvima) is approved for kidney cancer
- Belzutifan (Welireg) is approved for VHL-associated kidney cancer
- Dostarlicmb (Jemperli) receives tumor-agnostic approval
- Adjuvant nivolumab is approved for bladder cancer
- FDA updates pembrolizumab indication in frontline bladder cancer

SEPTEMBER
- FDA authorizes AI-based software for prostate cancer detection
- Adjuvant pembrolizumab is approved for renal cell carcinoma

OCTOBER
- FDA approves tivozanib for kidney cancer
- Atezolizumab indication for pretreated bladder cancer is voluntarily withdrawn

NOVEMBER
- FDA approves updated version of neurostimulator device
- Atezolizumab indication for pretreated bladder cancer is voluntarily withdrawn

DECEMBER 2021 | 21

UrologyTimes.com
therapy in patients with heavily pretreated locally advanced or metastatic urothelial carcinoma. The approval was based on findings from the phase 2 Study 004 (NCT03401788), which enrolled patients with VHL-associated RCC, as well as nonrenal lesions. Belzutifan induced an overall response rate of 49% (n=30) among 61 patients with VHL-associated RCC.

Dostarlimab receives tumor-agnostic approval

The FDA granted an accelerated approval to the PD-1 inhibitor dostarlimab-gxly (Jemperli) for the treatment of adult patients with mismatch repair-deficient recurrent or advanced solid tumors, as determined by an FDA-approved test. The approval was supported by results from the ongoing phase 1 GARNET trial (NCT02715284). Across 209 evaluable patients with solid tumors, the PD-1 inhibitor induced an objective response rate of 41.6%. The objective response rate was composed of a complete response rate of 9.1% and a partial response rate of 32.5%. The median duration of response was 34.7 months (range, 2.6-35.5+).

Adjuvant nivolumab is approved for bladder cancer

The FDA approved nivolumab (Opdivo) for the adjuvant treatment of patients with urothelial carcinoma who are at high risk of recurrence after undergoing radical resection, regardless of prior neoadjuvant chemotherapy, nodal involvement, or PD-L1 status. The approval was based on the randomized, double-blind, phase 3 CheckMate 274 trial (NCT02632409), which evaluated nivolumab in 353 patients vs 356 patients receiving placebo. Patients who received nivolumab had a median disease-free survival (DFS) of 20.8 months vs 10.8 months in the placebo arm. Additional findings from the study indicated that 74.5% of patients in the nivolumab arm who had a PD-L1 expression equal to or greater than 1% were alive and disease-free at 6 months vs 55.7% of those in the placebo (HR, 0.55; P<.001). The approval was supported by results from the ongoing phase 3 KEYNOTE-564 trial (NCT03142334), which showed that at a median follow-up of approximately 24 months, the median DFS was not reached with either adjuvant nivolumab vs placebo (HR, 0.68; P<.001).22 Previously, the PD-1 inhibitor was indicated for patients with locally advanced or mUC who were not eligible for cisplatin-containing chemotherapy who had PD-L1-positive tumors, or in patients who were not eligible for any platinum-containing chemotherapy, regardless of PD-L1 status; however, in the confirmatory KEYNOTE-361 trial (NCT02853305), which explored frontline pembrolizumab as a single agent and combined with chemotherapy in patients with advanced or mUC who were eligible for platinum-containing chemotherapy, the dual primary end points of OS and PFS vs standard chemotherapy were not met.

FDA updates pembrolizumab indication in frontline bladder cancer

The FDA converted the accelerated approval of frontline pembrolizumab in advanced bladder cancer to a full approval and revised the indication to cover the treatment of patients with locally advanced or mUC who are not eligible for any platinum-containing chemotherapy. Previously, pembrolizumab was approved for patients with advanced RCC who have previously received a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy; or patients who are ineligible for cisplatin-containing chemotherapy and have previously received 1 or more prior lines of therapy. The approval was based on findings from the EV-301 (NCT03474107) and EV-201 (NCT03219333) trials. In the phase 3 EV-301 trial, enfortumab vedotin reduced the risk of death by 30% vs chemotherapy in patients with heavily pretreated locally advanced or metastatic urothelial carcinoma. The FDA approved pembrolizumab (Keytruda) for the first-line treatment of adult patients with advanced RCC. The approval was based on findings from the phase 3 KEYNOTE-581/CLEAR trial (NCT02811861), which showed that at a median follow-up of approximately 24 months, the median OS was not reached with pembrolizumab vs placebo (HR, 0.55; P<.001).20 The approval was supported by results from the ongoing phase 3 KEYNOTE-361 trial (NCT02853305), which showed that at a median follow-up of approximately 24 months, the median DFS was not reached with pembrolizumab vs placebo (HR, 0.68; P<.001).

Soft-tissue 3D printing technology is granted FDA clearance for GU conditions

The FDA granted 510(k) clearance to Lazarus 3D for its PRE-SURE 3D printing technology for use across all genitourinary conditions. The technology produces synthetic, soft-tissue models with a lifelike quality—including bleeding—that allows clinicians to map out and simulate surgeries in preparation for operating on their actual patients. The PRE-SURE system creates the realistic models directly from patient MRI/CT data. Urology areas covered for this FDA clearance include conditions of the prostate, bladder, kidneys, and genitalia.

Adjuvant pembrolizumab approved for RCC

The FDA approved pembrolizumab (Keytruda) plus lenvatinib (Lenvima) for the first-line treatment of adult patients with advanced RCC. The approval was based on findings from the phase 3 KEYNOTE-811/CLEAR trial (NCT02811861) (Study 307), which showed that frontline therapy with the combination reduced the risk of death by 34% vs sunitinib in patients with advanced RCC. Belzutifan is approved for VHL-associated kidney cancer

The FDA approved belzutifan (Welireg) for adult patients with von Hippel-Lindau (VHL) disease who require therapy for associated RCC, central nervous system hemangioblastomas, or pancreatic neuroendocrine tumors not requiring immediate surgery. The approval was based on data from the phase 2 Study 004 (NCT03401788), which enrolled patients with VHL-associated RCC, as well as nonrenal lesions. Belzutifan induced an overall response rate of 49% (n=30) among 61 patients with VHL-associated RCC.

FDA authorizes artificial intelligence–based software for prostate cancer detection

The FDA authorized the marketing of Paige Prostate, an artificial intelligence–based software platform to help pathologists identify prostate cancer when they review slide images from prostate biopsies. The standard biopsy review process involves the pathologist examining digitally scanned slide images from prostate biopsies to find areas that are suspicious for cancer. Paige Prostate provides a supplementary assessment of the image and locates the area with the highest probability of harboring cancer. The pathologist can then examine this specific area further if it was not identified on initial assessment.

Prostate, an artificial intelligence–based software for prostate cancer detection

The FDA approved pembrolizumab for the adjuvant treatment of patients with RCC at intermediate-high or high risk of recurrence following nephrectomy, or following nephrectomy and resection of metastatic lesions. The approval was based on data from the phase 3 KEYNOTE-564 trial (NCT03142334), which showed that at a median follow-up of approximately 24 months, the median DFS was not reached with either adjuvant pembrolizumab (n = 496) or placebo (n = 498) as per investigator assessment; however, the HR for DFS showed that pembrolizumab induced a 32% reduction in the risk of disease recurrence or death compared with placebo (HR, 0.68; P=.0010).22
Real-world effectiveness with apalutamide in nmCRPC

BENJAMIN P. SAYLOR
Managing Editor, Urology Times

In the Rapid Readouts video series, produced by Urology Times, leading experts present slides and posters from annual oncology conferences, symposiums, and meetings, highlighting the ever-changing landscape of treatment choices. In this installment, based on study results presented at the 2021 American Urological Association Annual Meeting in September, real-world data point to excellent prostate-specific antigen (PSA) response and treatment adherence to apalutamide (Erleada) in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC).1

“Research regarding the clinical effectiveness of apalutamide in real-world practice is limited,” Judd W. Moul, MD, a urologic oncologist at Duke University in Durham, North Carolina, said during his review in the Rapid Readouts video. For the study, investigators sought to describe PSA response and treatment adherence among patients with nmCRPC treated with apalutamide. Investigators used electronic medical records data collected as part of routine care for 95 large practices. Data collected included patient demographics, diagnoses, procedures, prescriptions, and laboratory test results (PSA, testosterone). Sixty-three practices had additional data on next-generation androgen receptor inhibitor medications dispensed.

The study utilized a retrospective longitudinal cohort design, with the index date (February 14, 2018) defined as the first apalutamide dispensation among patients with nmCRPC. The investigators evaluated baseline characteristics in 12 months preceding the index date. PSA response and treatment patterns were evaluated from the index date to earliest of end-of-data availability (October 4, 2019), a switch to another first- or second-generation androgen or death.

Study outcomes were PSA response (PSA50) on apalutamide and adherence and persistence to apalutamide. PSA response was assessed among patients who had a baseline PSA level and at least 1 follow-up PSA level. Response was defined as at least a 50% decline from the baseline PSA (including index date) to any PSA measurement during the first 6 months or 12 months of the follow-up period. The investigators assessed adherence using the medication possession ratio, defined as the number of days of supply within the entire exposure to therapy. Persistence was assessed as the proportion of patients who did not have a specific gap in treatment within a fixed period of time following the index date.

The cohort included 193 patients: 33 Black patients, 138 non-Black patients, and 22 patients with an unknown racial background. A majority (76%) were between 71 and 90 years of age. Nearly the entire cohort (98.4%) had prior use of androgen deprivation therapy. Year of apalutamide initiation (index date) was 2018 in 124 patients (64.2%) and 2019 in 69 patients (35.8%). Baseline PSA level was 7.0 plus or minus 11.8 ng/mL (median, 3.2 ng/mL) for the overall cohort, 10.5 plus or minus 14.4 ng/mL (median, 6.4 ng/mL) in Black patients, and 5.6 plus or minus 9.0 ng/mL (median, 2.8 ng/mL) in non-Black patients. PSA doubling time was 10.8 plus or minus 9.6 months (median, 9.5 months) in the overall cohort, 10.2 plus or minus 10.8 months (median, 7.3 months) in Black patients, and 10.1 plus or minus 7.7 months (median, 8.4 months) in non-Black patients.

The investigators reported that during the first 6 months after initiating treatment with apalutamide, 83.5% of patients with nmCRPC achieved PSA50; by 12 months, 86.0% had achieved PSA50. Responses were similar between Black and non-Black patients. Moul also compared the paper’s findings with the phase 3 SPARTAN trial (NCT01946204), which was the official registration trial that led to apalutamide’s FDA approval.

“The real-world data, as far as PSA response, are very similar to the SPARTAN trial,” Moul said. Regarding adherence during exposure to apalutamide, a mean proportion of 93.6% of days were covered with prescription fills. Adherence was similar in Black and non-Black patients. Adherence rates were quite excellent,” Moul said.

Persistence rates were also positive; at 6 months, 79.7% of patients did not have a greater than 45-day gap in treatment; this percentage was 62.7% at 12 months. In addition, the investigators found that a numerically higher proportion of Black patients with nmCRPC were persistent at 12 months.

“These real-world PSA responses were robust and consistent with response rates observed in the SPARTAN trial,” which reported a PSA50 of 89.7%,” Moul said. Discussing the study’s implications, Moul said the research “shows in real-world practice that apalutamide lowers the PSA effectively and patients are adherent to the medication.”

REFERENCES

UrologyTimes.com
Transrectal vs transperineal biopsy: Outcomes and QOL

Transrectal ultrasound–guided prostate needle (TR) biopsy has been the gold standard for the diagnosis of prostate cancer for nearly 3 decades. More recently, transperineal prostate (TP) biopsy has been gaining popularity because of possible improvement in postbiopsy complications. However, studies have reported variable results that largely suggest that both biopsy techniques are quite comparable in their diagnostic and complications outcomes, except for pain during the procedure, which is often worse during the in-office TP biopsy. However, other short-term effects on quality of life related to these procedures (or tests) have not been studied in detail between the TR and TP procedures.

To measure the differences in the test-related quality of life between the 2 biopsy procedures, Shankar et al conducted postbiopsy surveys of men undergoing ultrasound-guided TR or TP biopsy.1 They included men undergoing an in-office, ultrasound-guided prostate biopsy, without MRI guidance or MR-ultrasound fusion, and without any history of Gleason score 7 or higher cancer. Over 77% of patients were biopsy-naïve.

Patients were recruited for participation in the study before the biopsy at 7 clinics, and 161 patients agreed to be contacted for the postbiopsy survey. Of these, 120 (60 TR, 60 TP) patients eventually completed the survey whereas the remainder either declined to complete the survey or could not be contacted. Biopsies were performed by 7 urologists, including some performing only the TR or the TP procedure. Average age of patients was 64.5 years, 81% were white, and 62% had a college degree. Most patients were biopsy-naïve, including 80% in the TR and 75% in the TP cohort.

The authors used 2 main survey instruments during the phone interview, including Testing Morbidities Index (TMI) and Short-Form 12 version 2 (SF-12). The TMI includes several domains including pain and anxiety before and during the procedure, embarrassment during the procedure, and any mental or physical impact the procedure. The mean baseline self-reported physical health, as determined by the SF-12 physical component score, was similar for both groups (TR: 50.6 [SD ± 9.8]; TP: 52.3 [SD ± 8.5]). Similarly, there was no difference in the mean baseline self-reported mental component scores between the TR and TP cohorts.

The mean summary testing-related health utility score (scale: 0-1, where 1=perfect baseline health) was 0.86 (95% CI, 0.84-0.88) for TR biopsy and 0.81 (95% CI, 0.81-0.85) for TP biopsy (P=0.08). The only significant difference in the individual domain-level scores (scale: 1-5, with 1 = no health impact, 5 = extreme health impact), was related to more pain during TP biopsy (TR 2.3, 95% CI, 2.1-2.4; TP 2.9, 95% CI, 2.6-3.1; P=0.0002). There were no significant test-related differences in other domains during the biopsy procedure. The overall cancer detection (52% and 53%) and high-grade cancer detection rates (23% and 20%) appeared similar between the TR and TP procedures, respectively. The complications rates, including hospitalizations and infections, were also similar between the TR and TP cohorts.

The temporary testing-related health impact between TR (86% of “perfect” health) and TP biopsy (83% of “perfect” health) were clinically and statistically similar, except for pain during the procedure, which was more painful for those undergoing TP biopsy.

It is not clear why the authors excluded patients undergoing MRI-US fusion biopsy and patients with prior biopsy with Gleason score higher than 6. The goal of the study was to evaluate procedure-related effect on short-term quality of life, which is not likely to be affected by the histology. Conversely, the image fusion targeted biopsy procedures take longer to complete than TRUS biopsy and thus, could have affected the patient experience during the procedure.

The study had a relatively small sample size and patients were not randomly assigned to TR or TP biopsy procedures. It’s possible that patients may have elected or favored 1 procedure over the other, and thus were more accepting of the procedure-related adverse experience. Similarly, the urologists with expertise and/or experience with exclusively performing TP biopsies could have mitigated any potential difference in patient experience between the 2 procedures.

It appears that the TR and TP biopsy procedures are essentially comparable in various aspects of the procedure. If the cancer detection rates, and complications including infection rates, and procedure-related-effect on quality of life are similar, how does a clinician recommend one procedure over the other to the patients? Despite our best efforts, the non-randomized study design can introduce a number of confounders that can affect the results. There are ongoing randomized control trials that should provide us with essential, high-quality data to inform the discussion regarding TR vs TP prostate biopsy.

REFERENCE

Transitional zone sampling may be unnecessary in some men

Zone-dependent approach may reduce biopsy-related morbidity, investigators say

**Liset Hilton**

Urology Times® Correspondent

Transitional zone sampling may not be necessary for prostate cancer detection in men with exclusively peripheral prostate cancer–suspicious lesions found on multiparametric MRI (mpMRI) who undergo targeted and systematic prostate biopsies, according to a study published in *Journal of Urology*.¹

The study of 863 men found peripheral targeted and systematic prostate biopsies without transitional zone sampling yielded similar cancer detection to the sampling protocol with transitional zone sampling. And the zone-dependent approach may reduce biopsy-related morbidity, the authors wrote.

Investigators in Germany and Australia studied men who underwent extended systematic biopsies and transitional zone sampling in addition to mpMRI/ultrasound fusion targeting of at least 1 mpMRI-categorized suspicious lesion in the peripheral zone. The men had no suspicious lesions on mpMRI in the transitional zone. The authors defined clinically significant prostate cancer as a Gleason score of 3 + 4 or greater. They retrospectively compared clinically significant prostate cancer detection rates between 2 biopsy protocols. One was a combination of peripheral mpMRI targeted and extended systematic prostate biopsy, including transitional zone sampling. The other was peripheral mpMRI targeted plus systematic prostate biopsy without transitional zone sampling.

Investigators found:

- The extended protocol yielded prostate cancer detection for clinically significant prostate cancer at 48% versus 47% among those who did not have transitional zone sampling.
- Gleason score 3 + 3 in the extended protocol group was 21% versus 20%, with omission of systematic transitional zone sampling.
- Transitional zone systematic prostate cancer sampling detected an additional 2.0% of cancer.

“This zone-dependent biopsy strategy warrants prospective evaluation to optimize the extent of systematic biopsies in presence of suspicious mpMRI lesions,” the authors wrote.

Michael S. Cookson, MD, MMHC, professor and chairman of the Department of Urology at the University of Oklahoma Health Sciences Center in Oklahoma City and coeditor in chief of *Urology Times*, said in an interview that there is debate about how extensive and how many biopsies need to be obtained in the era of mpMRI.

“When lesions are easily visible on MRI, adds to the potential morbidity of the procedure, including bleeding infection and urinary retention, according to Cookson. “The transition zone is an area that is particularly susceptible to urinary bleeding and outlet obstruction, so avoidance of this at least has the potential to reduce the risk of this postbiopsy complication. In addition, transition zone–only tumors are relatively rare and in the absence of any demonstrable suspicion on mpMRI could probably be avoided,” Cookson said.

Although not addressed in this paper, future analyses should look at the potential for reducing complications by avoiding transition zone biopsies in this setting, Cookson noted.●

REFERENCE


**How plant-based diets are lowering the risk of aggressive prostate cancer**

In this video, Stacy Loeb, MD, PhD, MSc, discusses the background, findings, and takeaways of the American Journal of Clinical Nutrition study “Association of plant-based diet index with prostate cancer risk.” Loeb is a professor in the departments of urology and population health at the NYU Grossman School of Medicine, New York, New York.

Using your phone’s camera, hover over the QR code and scan.
Almost half of patients had a PSA50 response, phase 2 data indicate that combining the PARP inhibitor olaparib (Lynparza) with bipolar androgen therapy (BAT) demonstrated promising clinical activity in patients with castration-resistant prostate cancer (CRPC), according to findings from a phase 2 study presented during the European Society for Medical Oncology Congress 2021.1

Almost half (47%) of patients had a prostate-specific antigen (PSA)50 response, defined as a 50% or greater decline in PSA level, at a median follow-up of 22.7 months, the median progression-free survival (PFS) was 12.6 months.

“BAT plus olaparib is associated with high response rates and long PFS. Clinical benefit was observed regardless of homologous recombination repair (HRR) gene mutational status.”

MICHAEL SCHWEIZER, MD

“BAT plus olaparib is associated with high response rates and long PFS. Clinical benefit was observed regardless of homologous recombination repair (HRR) gene mutational status. Treatment was well tolerated, although caution should be taken in using this in men with a history of cardiovascular disease. Larger studies evaluating this regimen are warranted,” lead study author Michael Schweizer, MD, assistant professor, Division of Medical Oncology, University of Washington School of Medicine; associate professor, Clinical Research Division, Fred Hutchinson Cancer Research Center; and physician, Seattle Cancer Care Alliance, and coinvestigators wrote in their abstract’s conclusion.

The single-center (Fred Hutch) phase 2 study (NCT03516812), which officially launched on August 29, 2018, enrolled 36 patients (median age, 70 years; range, 51-88) with CRPC, as shown by PSA progression (Prostate Cancer Clinical Trials Working Group 3 criteria) and castrate serum testosterone level (≤ 50 mg/dL).2 Patients also had to have a PSA level that was 1 ng/mL or lower and rising on 2 sequential measurements occurring 2 or more weeks apart. Prior abiraterone acetate (Zytiga) and/or enzalutamide (Xtandi) was required. Among 30 evaluable patients, 13 had prior abiraterone, 7 had prior enzalutamide, and 10 had received both.

Docetaxel in the hormone-sensitive prostate cancer setting was allowed; however, enrollment was prohibited for patients who received docetaxel for metastatic CRPC. Patients with cancer-related pain were also excluded from enrollment.

All patients received olaparib at 300 mg orally twice daily plus BAT. The BAT consisted of 400 mg of testosterone enanthate or testosterone cypionate every 28 days while continuing androgen deprivation to suppress endogenous testosterone. The treatment cycles repeated every 28 days unless there was disease progression or unacceptable toxicity.

The primary end points were safety and the PSA50 response rate at a maximum of 12 weeks after starting treatment. The investigators officially measured the PSA50 end point in the entire study population; however, they also conducted an exploratory analysis of outcomes in patients stratified by HRR gene mutational status. The study required that at least half of the enrolled patients had at least 1 HRR gene alteration. Secondary outcome measures included radiographic response rate, PSA progression rate, overall survival, radiographic PFS, and quality of life.

Among 30 evaluable patients, 14 (47%) reached a PSA50 response, including 7 of 15 patients harboring an HRR mutation and 7 of 15 patients without an HRR mutation. Of note, the median PFS was higher in the group without HRR mutations vs the group with HRR mutations, at 14.8 months vs 7.5 months (P=.015), respectively.

Regarding safety, 6 patients discontinued treatment early for a variety of reasons including progression (n = 2), nausea (n = 2), stroke (n = 1), and myocardial infarction (n = 1). There were 5 patients with grade 3 or higher treatment-related adverse events (AEs). Among these AEs were 1 grade 4 stroke and 1 death of myocardial infarction. The study was eventually amended to exclude patients with a history of myocardial infarction; after that point, no further cardiovascular AEs were reported.

Olaparib was approved by the FDA in May 2020 for use as a single agent in adult patients with deleterious or suspected deleterious germline or somatic HRR-mutated metastatic CRPC who progressed following prior treatment with enzalutamide or abiraterone.

REFERENCES
Darolutamide maintenance holds potential in pretreated mCRPC

NICHOLE TUCKER
Senior Editor, Targeted Oncology™

Findings from the phase 2 SAKK 08/16 trial (NCT02933801) shared during the European Society for Medical Oncology (ESMO) Congress 2021 showed that maintenance therapy with darolutamide (Nubeqa) led to a statistically significant but clinically modest radiographic progression-free survival (rPFS) and event-free survival (EFS) benefit in pretreated patients with metastatic castration-resistant prostate cancer (mCRPC).

Patients had received at least 1 novel hormonal agent and had nonprogressive disease after subsequent treatment with taxane-based therapy. The study met its primary end point and 1 secondary end point. The treatment was also found to be tolerable in patients.

Based on the signal of efficacy with new hormonal agents (NHAs), and the survival observed with darolutamide in 2 prior studies, investigators hypothesized that progression of disease might be delayed with an immediate switch to darolutamide in patients with disease stabilization under chemotherapy following pretreatment with another NHA.

“We have heard a lot about the changing treatment landscape in mCRPC in the past years and so many different agents have been introduced; however, the optimal treatment sequence remains unclear. Darolutamide is an androgen receptor antagonist [that] has a distinct structure with potentially fewer [adverse effects (AEs)] due to decreased blood-brain barrier penetration,” said Richard Cathomas, PD, DrMed, deputy head of oncology/hematology at Kantonsspital Graubünden in Chur, Switzerland, during the ESMO presentation.

In the randomized, placebo-controlled, double-blind SAKK 08/16 trial, 92 patients were included and randomized 1:1 at 26 centers across Switzerland, Italy, Spain, and France to receive darolutamide 600 mg twice daily or matching placebo starting 2 to 8 weeks after the end of taxane-based therapy. Patients were stratified by country, World Health Organization (WHO) performance status, prior therapy, site of metastases, and planned start of study treatment following taxane-based therapy.

At baseline, the darolutamide arm had a median age of 71 years (range, 56-81). The WHO performance score in the group was 0 in 100% of patients. Sites of metastasis included bone (87%), lymph node (51%), liver (2%), and lung (2%). The majority of the darolutamide arm (53%) had a Gleason score between 8 and 10. Finally, the time from the end of taxane to the start of darolutamide was 35 days or more in 51% of patients.

In the placebo arm, the median age was 72 years (range, 55-87). Ninety-eight percent of patients in the control arm had a WHO performance score of 0. Metastatic sites were the same as the darolutamide arm, with 89% of patients having bone metastases, 51% having lymph node metastases, and 2% and 4% having liver or lung metastases, respectively. Also, mirroring the darolutamide arm, 53% of patients in the placebo arm had a Gleason score between 8 and 10. Following taxane-based therapy, 53% of patients in the control arm started placebo after 35 days or more.

Looking at prior NHA therapy in the darolutamide arm compared with the placebo arm, 60% of patients in each group received prior abiraterone (Zytiga) and 31% received enzalutamide (Xtandi). Also, 9% of patients in each arm received both. Response to previous treatment largely included partial responses including in 24% of the experimental arm vs 33% of the placebo arm. In addition, 36% of patients in the darolutamide arm vs 38% of the placebo arm achieved stable disease (SD) on their prior therapy.

In addition to assessing rPFS at 12 weeks, the study’s secondary end points included rPFS, EFS, overall survival (OS), prostrate-specific antigen response of 50% (PSA50), and safety determined by AEs. The study was 80% powered to detect improvement in rPFS at 12 weeks with darolutamide. At a median follow-up of 18 months, the 12-month rPFS with darolutamide was 64.7% (95% CI, 47.6%-77.5%) compared with 52.2% (95% CI, 36.1%-66.1%) in the placebo arm (P=.127). The result was 0.15 below the significance threshold.

Median rPFS in the darolutamide arm was 5.5 months compared with 4.5 months in the placebo arm (HR, 0.54; 95% CI, 0.32-0.91; log-rank P=.017). In terms of EFS, the median observed in the darolutamide arm was 5.4 months vs 2.9 months with placebo (HR, 0.46; 95% CI, 0.29-0.73; log-rank P=.001). Median OS was 24.0 months with darolutamide compared with 21.3 months in the placebo arm (HR, 0.62; 95% CI, 0.33-1.26; log-rank P=.181).

Further efficacy results from SAKK 08/16 showed PSA50 responses were achieved in 22% of the patients treated with darolutamide vs 4% of those treated with placebo (P=.014). The median duration of PSA response observed with darolutamide was 7.7 months compared with 2.8 months in the placebo arm.

The safety analysis showed that treatment-related AEs were mild and occurred were similar between the 2 treatment arms. In the darolutamide arm, 26% of the events were grade 1 compared with 22% in the placebo arm. The most common treatment-related AEs were grade 1 fatigue and anorexia, which occurred in 11% of the darolutamide arm vs 20% in the placebo arm and 2% vs 4%, respectively.

Results from SAKK 08/16 provide proof of concept for immediate switch to darolutamide maintenance following taxane-based therapy with at least 1 NHA. Further, the data signal that response to NHA may be predictive of benefit from maintenance after NHA and taxane-based therapy in patients with mCRPC. According to Cathomas, the results are hypothesis-generating for a phase 3 clinical trial.

REFERENCE
INDICATIONS
ERLEADA® (apalutamide) is an androgen receptor inhibitor indicated for the treatment of patients with:
• Metastatic castration-sensitive prostate cancer (mCSPC)
• Metastatic castration-resistant prostate cancer (nmCRPC)

IMPORTANT SAFETY INFORMATION WARNINGS AND PRECAUTIONS
Cerebrovascular and Ischemic Cardiovascular Events — In a randomized study (SPARTAN) of patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 5 patients (0.3%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within 6 months of randomization were excluded from the SPARTAN and TITAN studies.
In the SPARTAN study, cerebrovascular events occurred in 4.7% of patients treated with ERLEADA® and 0.8% of patients treated with placebo. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA® and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from a cerebrovascular event. Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA®.

TITAN final analysis data are not currently reported in the ERLEADA® Prescribing Information. The following TITAN primary analysis results are included in the ERLEADA® Prescribing Information: Median OS: NE vs NE; HR=0.67; 95% CI: 0.51, 0.89; P=0.0053.

As soon as you diagnose mCSPC or nmCRPC...

ADVERSE REACTIONS
Adverse Reactions — The most common adverse reactions (≥10%) that occurred more frequently in the ERLEADA®-treated patients (≥2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Laboratory Abnormalities — All Grades (Grade 3-4)
• Hematology — In the TITAN study, white blood cell decreased ERLEADA® 7% (0.4%), placebo 7.8% (0.6%). In the TITAN study, anemia ERLEADA® 70% (0.4%), placebo 69% (0.5%). In the SPARTAN study, anemia ERLEADA® 29% (0.3%), placebo 30% (0.5%). Leukopenia ERLEADA® 45% (2.5%), placebo 21% (2.5%).
• Chemistry — In the TITAN study, hyperglycemia ERLEADA® 17% (3%), placebo 12% (2%). In the SPARTAN study, hypercholesterolemia ERLEADA® 70% (0.1%), placebo 68% (0.6%). Hyperuricemia ERLEADA® 70% (2%), placebo 59% (1%).

Embryo-Fetal Toxicity — The safety and efficacy of ERLEADA® have not been established in females. Based on its mechanism of action, ERLEADA® 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 and for 3 months after the last dose of ERLEADA® [see Use in Specific Populations (8.1, 8.3)].

Pharmacokinetic interactions — The effect of ERLEADA® on the pharmacokinetics of other drugs was not studied. Drugs with a high potential for drug-drug interactions should be used with caution.

F:7.5 "  B:10.5 "  S:14.5 "

© Janssen Biotech, Inc. 2021 03/21 cp-145567v6
In the SPARTAN study, cerebrovascular events occurred in 4.7% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the TITAN study*, patients treated with ERLEADA® and 3% of patients treated with placebo died from a cerebrovascular event. (nmCRPC)

**INDICATIONS**

- Treatment of patients with:
  - Castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study [published online April 29, 2021].
  - Castration-resistant prostate cancer; NR = not reached; OS = overall survival;

**WARNINGS AND PRECAUTIONS**

**IMPORTANT SAFETY INFORMATION**

- In a randomized study (SPARTAN) of patients with castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study [published online April 29, 2021].

**Adverse Reactions**

- Rash — In 2 randomized studies (SPARTAN and TITAN), rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 36% with ERLEADA® vs 8% with placebo. Grade 3 rash (defined as covering >20% body surface area [BSA]) were reported with ERLEADA® treatment (0.6%) vs placebo (0.5%). The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively.

**Hypothyroidism** — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA® and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

**Drug Interactions**

- Co-administration of a strong CYP3A4 or CYP2D6 inhibitor is predicted to increase the steady-state exposure of the active metabolites. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability (see Dosage and Administration) [2.5].

**Effect of ERLEADA® on Other Drugs**

- CYP3A4, CYP2C9, and UGT Substrates — ERLEADA® is a strong inducer of CYP3A4 and CYP2C9, and a weak inducer of CYP3A7. Concomitant use of ERLEADA® with medications that are primarily metabolized by CYP3A4, CYP2C9, or CYP3A7 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UDP-glucuronosyltransferase (UGT) can result in increased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

**Laboratory Abnormalities**

- All Grades (Grade 3-4)

**References:**

1. PSA = prostate-specific antigen; mPSA = multiplex prostate-specific free survival; nmPSA = Selective Prostate Androgen Receptor Targeting with ARN-509; TITAN = Targeted Investigational Treatment Analysis of Novel Androgening.

**Study Design:** TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with nmCRPC (n=1,022). Patients had newly diagnosed nmCRPC or relapsed metastatic disease after an initial diagnosis of localized disease. Patients with visceral (i.e., bone or lung) metastases to the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concomitant GnRH analog or had a prior bilateral orchiectomy. The dual primary endpoints were overall survival and PFS. 11 All patients who enrolled in the TITAN study started ADT for mCRPC at 6 months prior to randomization.

**Study Design:** TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with nmCRPC (n=1,022). Patients had a PSA doubling time <10 months and serum testosterone level <50 ng/dL. All patients enrolled were confirmed to be non-metastatic by blinded central imaging review. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN study received a concomitant GnRH analog or had a bilateral orchietomy. The primary endpoint was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of blinded independent central review-confirmed distant metastases, defined as new bone or soft tissue lesions or enlarged lymph nodes >20 mm above the baseline, or death due to any cause, whichever occurred first. Secondary endpoints were time to metastasis, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of opioid or chemotherapy.

**Visit erleadahep.com**
Brief Summary of Prescribing Information for ERLEADA® (apalutamide) tablets, for oral use
See package insert for Full Prescribing Information

INDICATIONS AND USAGE
ERLEADA is indicated for the treatment of patients with:
- Metastatic castration-sensitive prostate cancer (mCSPC)
- Non-metastatic castration-resistant prostate cancer (nmCRPC)

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Cerebrovascular and Ischemic Cardiovascular Events
Cerebrovascular and ischemic cardiovascular events, including events leading to death, occurred in patients receiving ERLEADA. Monitor for signs and symptoms of ischemic heart disease and cerebrovascular disorders. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA for Grade 3 and 4 events.

In a randomized study (SPARTAN) of patients with nmCRPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 3% of patients treated with placebo. In a randomized study (TITAN) in patients with mCSPC, ischemic cardiovascular events occurred in 4% of patients treated with ERLEADA and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 5 patients (0.5%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event.

In the SPARTAN study, cerebrovascular events occurred in 4.7% of patients treated with ERLEADA and 0.8% of patients treated with placebo [see Clinical Trials Experience]. In the TITAN study, cerebrovascular events occurred in 1.9% of patients treated with ERLEADA and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

Patients with history of unstable angina, myocardial infarction, congestive heart failure, stroke, or transient ischemic attack within six months of randomization were excluded from the SPARTAN and TITAN studies.

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

In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 2%. The median time to onset of fracture was 314 days (range: 20 to 583 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 9% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 2%. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

Falls
Falls occurred in patients receiving ERLEADA with increased frequency in the elderly [see Use in Specific Populations]. Evaluate patients for fall risk.

In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure.

Seizure
Seizure occurred in patients receiving ERLEADA. Permanently discontinue ERLEADA in patients who develop a seizure during treatment. It is unknown whether anti-epileptic medications will prevent seizures with ERLEADA. Avoid patients of the risk of developing a seizure while receiving ERLEADA and of engaging in any activity where sudden loss of consciousness could cause harm to themselves or others.

In two randomized studies (SPARTAN and TITAN), five patients (0.4%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 450 days after initiation of ERLEADA. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

Embryo-Fetal Toxicity
The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetal abnormalities and embryo-fetal lethality at maternal exposures ≥ 2 times the human clinical exposure (AUC) at the recommended dose. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA [see Use in Specific Populations and Clinical Pharmacology (12.1) in Full Prescribing Information].

ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:
- Cerebrovascular and Ischemic Cardiovascular Events [see Warnings and Precautions].
- Fractures [see Warnings and Precautions].
- Falls [see Warnings and Precautions].
- Seizure [see Warnings and Precautions].

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 most common adverse reactions (> 10%) that occurred more frequently in the ERLEADA-treated patients (> 2% over placebo) from the randomized placebo-controlled clinical trials (TITAN and SPARTAN) were fatigue, arthralgia, rash, decreased appetite, fall, weight decreased, hypertension, hot flush, diarrhea, and fracture.

Metastatic Castration-sensitive Prostate Cancer (mCSPC)
ERLEADA, a randomised (1:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had mCSPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or placebo. All patients in the TITAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had prior bilateral orchiectomy. The median duration of exposure was 20 months (range: 0 to 34 months) in patients who received ERLEADA and 18 months (range: 0.1 to 34 months) in patients who received placebo.

Ten patients (2%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardiopulmonary arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (>1%) were rash, fatigue, and hypertension.

Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

Table 1 shows adverse reactions occurring in >10% on the ERLEADA arm in TITAN that occurred with a ≥2% absolute increase in frequency compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

Table 1: Adverse Reactions in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>17</td>
<td>0.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>28</td>
<td>6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>18</td>
<td>8</td>
</tr>
</tbody>
</table>

* Per the Common Terminology Criteria for Adverse Reactions (CTCAE), the highest severity for these events is Grade 3

Clinical Pharmacology (12.3) in Full Prescribing Information

Laboratory Abnormalities Occurring in ≥ 15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in TITAN (mCSPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>Grade 3-4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White blood cell decreased</td>
<td>27</td>
<td>0.4</td>
</tr>
<tr>
<td>Chemistries</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

* Does not reflect fasting values
ERLEADA® (apalutamide) tablets

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized [2:1], double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchectomy. The median duration of exposure was 30 months (range: 0.1 to 76 months) in patients who received ERLEADA and 11 months (range: 0.1 to 37 months) in patients who received placebo.

Twenty-four patients (3%) who were treated with ERLEADA died from adverse reactions. The reasons for death with ≥ 2 patients included infection (n=7), myocardial infarction (n=3), cerebrovascular event (n=2), and unknown reason (n=3). ERLEADA was discontinued due to adverse reactions in 11% of patients, most commonly from rash (3%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 33% of patients; the most common (>1%) were rash, diarrhea, fatigue, nausea, vomiting, hypertension, and hematuria. Serious adverse reactions occurred in 25% of ERLEADA-treated patients and 23% in patients receiving placebo. The most frequent serious adverse reactions (>2%) were fracture (5%) in the ERLEADA arm and urinary retention (4%) in the placebo arm.

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with a ≥2.0 absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (>5%) in the ERLEADA arm compared to placebo.

### Table 3: Adverse Reactions in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse Reaction</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>Placebo N=398</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue</td>
<td>39</td>
<td>1</td>
<td>28</td>
<td>0.3</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>16</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>25</td>
<td>5</td>
<td>6</td>
<td>0.3</td>
</tr>
<tr>
<td>Metabolism and nutritional disorders</td>
<td>Decreased appetite</td>
<td>12</td>
<td>0.1</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Fall</td>
<td>16</td>
<td>2</td>
<td>9</td>
<td>0.8</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Fracture</td>
<td>12</td>
<td>3</td>
<td>7</td>
<td>0.8</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>20</td>
<td>1</td>
<td>15</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Additional clinically significant adverse reactions occurring in ≥2% or more of patients treated with ERLEADA included hypothyroidism (8% versus 2% on placebo), pruritus (8% versus 2% on placebo), and heart failure (2% versus 1% on placebo).

### Table 4: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference >5 All Grades) in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades %</td>
<td>Grade 3-4 %</td>
<td>All Grades %</td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70</td>
<td>0.4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyphosphatemia</td>
<td>76</td>
<td>0.1</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>67</td>
<td>2</td>
</tr>
<tr>
<td>Hykapnea</td>
<td>32</td>
<td>2</td>
</tr>
</tbody>
</table>

* Does not reflect fasting values

** Rash**
In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 5% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted (see Drug Interactions).

** Hypothyroidism**
In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, hypothyroidism was reported for 8% of patients treated with ERLEADA and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy was initiated in 5% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted (see Drug Interactions).

** Effect of Other Drugs on ERLEADA**
Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties (sum of unbound apalutamide plus the potency-adjusted unbound N-desmethyl-apalutamide). No initial dose adjustment is necessary however, reduce the ERLEADA dose based on tolerability (see Dosage and Administration (2.2) in Full Prescribing Information). Mild or moderate inhibitors of CYP2C8 or CYP3A4 are not expected to affect the exposure of apalutamide.

** Effect of ERLEADA on Other Drugs**
ERLEADA is a strong inducer of CYP3A4 and CYP2C19, and a weak inducer of CYP2C9 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP3A4, CYP2C19, or CYP2C9 can result in lower exposure to these medications. Substitution for these medications is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA with medications that are substrates of UDP-glucuronosyl transferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA and evaluate for loss of activity (see Clinical Pharmacology (12.3) in Full Prescribing Information).
ERLEADA® (apalutamide) tablets

Dosage and Administration

Patients should take ERLEADA as a single 120 mg tablet each morning after an empty stomach and at least 1 hour before or 2 hours after a meal. ERLEADA tablets should not be split, crushed, chewed, or sublingually administered. ERLEADA should be swallowed whole.

Geriatric Use

Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were less than 65 years, 41% of patients were 65 to 74 years, and 40% were 75 years and over. No overall differences in effectiveness were observed between older and younger patients. Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse reactions occurred in 35% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older. No overall differences in effectiveness were observed between older and younger patients. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

OVERDOSAGE

There is no known specific antidote for apalutamide overdose. In the event of an overdose, stop ERLEADA, undertake general supportive measures until clinical toxicity has been diminished or resolved.

PATIENT COUNSELING INFORMATION

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

Cerebrovascular and Ischemic Cardiovascular Events

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

 Rash

• Inform patients that ERLEADA is associated with rashes and to inform their healthcare provider if they develop a rash (see Adverse Reactions).

Embryo-Fetal Toxicity

• Inform patients that ERLEADA can be harmful to a developing fetus. Advise female patients of the importance of effective contraception during treatment and for 3 months after the last dose of ERLEADA. Advise male patients to use a condom if having sex with a pregnant woman (see Warnings and Precautions).

Infertility

• Advise male patients that ERLEADA may impair fertility and not to donate sperm during therapy and for 3 months following the last dose of ERLEADA (see Use in Specific Populations).

Manufactured by:
Janssen Ortho LLC
Gurabo, PR 00778
Manufactured for:
Janssen Products, LP
Horsham, PA 19044
© 2019 Janssen Pharmaceutical Companies
cp-5059v6
PSMA/PET-derived risk stratification tool performs strongly in study

Nomogram was found to be superior to other established risk stratification tools

JASON M. BRODERICK
Associate Editorial Director, Urology Times®

At the 2021 American Society for Radiation Oncology Annual Meeting, investigators shared positive outcomes of a study exploring a nomogram designed to predict the probability of nodal and metastatic disease detected by prostate-specific membrane antigen (PSMA) PET/CT imaging in patients with newly diagnosed cN0M0 high-risk prostate cancer.1

Presenting author Martin Ma, MD, PhD, said the nomogram was “significantly prognostic” of key clinical end points and achieved outcomes comparable with staging collaboration for cancer of the prostate (STAR-CAP) and was superior to other established risk stratification tools.

“The model has an area under the curve of 0.75, and 90% of patients who had a nomogram-estimated risk below cutoff for overall upstaging could have been spared PSMA PET/CT, as our model correctly predicted no upstaging. In other words, our model missed only about 10% of patients who would have benefited from PSMA PET imaging,” said Ma, a resident physician in the Department of Radiation Oncology at the University of California, Los Angeles.

Ma said there are several items factored into the nomogram, including a patient’s initial prostate-specific antigen level, the percentage of positive cores on systematic biopsy, Gleason grade group, and cT stage. The nomogram combines these factors to calculate an estimate of nodal and distant metastatic upstaging probabilities.

The study assessed the prognostic capability of the nomogram at predicting the following clinical outcomes: biochemical recurrence (BCR), distant metastasis (DM), prostate cancer–specific mortality (PCSM), and overall survival (OS).

The study included 3 cohorts. There were OS and PCSM data available for these patients, but BCR and DM data were not available. The final cohort was a National Cancer Database (NCDB) cohort with 88,909 patients with high- and very high-risk prostate cancer treated between 2010 and 2016. There were only OS data available for this cohort.

“In the multi-institutional cohort, the PSMA nomogram was significantly predictive of all clinical end points. The C-index was 0.63 for BCR, 0.69 for DM, 0.71 for PCSM, and 0.60 for OS. These results were upheld across various subgroups categorized by treatment types, including radical prostatectomy, external beam radiation therapy (EBRT), and EBRT plus brachytherapy,” Ma said. “Performance was slightly lower for the EBRT plus brachytherapy subgroup [compared with the other subgroups].”

The finding that the nomogram was predictive of clinical end points was validated by the results from the SEER and NCDB cohorts. For the SEER cohort, the C-index was 0.71 for PCSM and 0.61 for OS. In the NCDB cohort, the C-index for OS was 0.62.

Ma further explained that in the multi-institutional cohort, C-index data showed that the “PSMA nomogram outperformed the STAR-CAP, Cancer of the Prostate Risk Assessment, and Memorial Sloan Kettering Cancer Center nomograms for all end points (P < 0.01), except performance was similar to STAR-CAP for PCSM (P = .11).” Similar results were observed for the SEER and NCDB cohorts.

In his concluding remarks, Ma said, “The PSMA nomogram predicted the risk of upstaging on PSMA PET/CT and is linked with long-term clinical outcomes. The nomogram also showed improved risk stratification, outperforming other models for all end points.”

After his discussion, Ma was asked about the use of this nomogram for risk stratification in light of ongoing breakthroughs with genomic tests for risk stratification, such as Decipher. “As a scientist at heart, I believe genomic risk stratification will be the future. However, for now, when Decipher is not widely available…using something based on traditional clinical pathological risk factors does make sense,” Ma said.

The PSMA nomogram is currently available from UCLA online at https://www.uclahealth.org/radonc/psma-risk-calculate.

REFERENCE
Prior studies have shown that statins, drugs typically used to lower cholesterol, are associated with a mild reduction in prostate growth over time. Newer studies are investigating the effect of these drugs on patients with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH).

In a recent *Journal of Urology* study, Jordan J. Kramer, MD, and coauthors examined whether statins impact LUTS incidence in asymptomatic men and progression in symptomatic men with BPH. Kramer is a PGY4 urology resident at Cedars-Sinai Medical Center, Los Angeles, California.

Q. Could you discuss the background for this study?

A. This study looks a lot at BPH and associated LUTS, BPH being benign prostatic hyperplasia, which involves increased proliferation of stromal epithelial cells in the region of the prostate called the transitional zone located around the urethra. Because of that location, this tissue bulges in and can actually decrease the patient’s ability to urinate and can lead to lower urinary tract symptoms. LUTS can be very annoying to the patient, interrupt their day-to-day activities, and interrupt their sleep, waking them up multiple times during the night. Also, when those symptoms progress, they can lead to urinary retention, catheterization, as well as UTIs and bladder stones, all of which require endoscopic management of some sort. Not only do these symptoms progress, but they’re also seen in a large proportion of patients.

There was an autopsy study that looked at men in their 50s and saw that 50% of them had histologic evidence of BPH on the tissue pathology and that prevalence only increases with age. Preventive management strategies are widely appreciated on an individual basis, and the condition affects a large patient population, so there needs to be more work looking into preventative strategies.

How does this tie in with cholesterol and statin use? Picking statins sounds like, “Pick the medication that lots of people are taking, so we can see if it has anything to do with BPH LUTS.” But it’s really tied in there pretty well because for sex steroid biosynthesis, one of the starting points is cholesterol. Because statins are HMG coA reductase inhibitors, we thought that if you caught the pathway that early, perhaps less cholesterol and fewer of its products will reach the point of becoming testosterone and dihydrotestosterone (DHT), which are the fuels for prostatic growth. There have been some prior studies on this, a few of which came from our group. One of them looked at statin use and its ability to slow prostate size growth, in which we saw a little bit of an effect. It was about 10 times smaller than the effects seen by dutasteride or finasteride [Proscar]. But still, it was a little bit of effect. We thought maybe that’s a possible way into the study of this. And then another study looked at the effects of cholesterol on the development of LUTS, and that one showed that a higher ratio of cholesterol to HDL was predictive of LUTS progression, and that high HDL was a protective factor for LUTS progression. So with all of those things combined, we thought maybe there’s something here worth looking at for a possible preventive measure.

Q. What were some of the notable findings? Were any of them surprising to you and your coauthors?

A. We based our study on the data set from the REDUCE trial [NCT00056407], which was done in 2010. This study looked at men aged 50 to 75 years who had a prior negative prostate biopsy but an elevated [prostate-specific antigen level]. The REDUCE trial randomized them, testing dutasteride vs placebo to see whether that would affect their prostate cancer risk. Now, of course, we didn’t look at prostate cancer results in our study, but that age range of 50 to 75 years is the perfect range to look at LUTS and BPH, since any man who is going to develop LUTS would develop it within that time frame. Some already have LUTS by the time they enter that time range as well.

We had 2 groups in our study. One was termed “asymptomatic,” where they had an International Prostate Symptom
Benign Prostatic Hyperplasia

Score (IPSS) of less than 8, which is officially in the “mildly symptomatic” category based on the questionnaire. Or, we had “symptomatic” patients who had an IPSS score of greater than 8 already. We looked at whether statin use, or nonuse, was related to a development of new onset of LUTS or a progression of LUTS. We defined those based on an increase in their IPSS score, need for BPH medications, or BPH endoscopic or surgical treatments. We saw that there actually was no difference, unfortunately, in the group where they already had LUTS to begin with, and we didn’t see any change in the onset to new LUTS. In the group that already had LUTS, we didn’t see any change in the time for progression of their LUTS.

Q. What is the significance of these data for patients with LUTS?
A. Our results are a little disappointing, but it’s still important knowledge to have because these are drugs that are widely taken by older people and although there are lots of treatments for BPH and associated LUTS, it’d be great to prevent having those treatments in the first place. Any medication has its own risks and benefits, any surgery has its own risks and benefits, and no intervention is completely innocuous. So is the result of our study surprising to us? It is a little bit for a few reasons, one of which was that cholesterol fits into that pathway of sex steroid production and you would think that if we’re able to cut it off further down the pathway with 5α reductase inhibitors, cutting it off early would maybe have an effect. And the results from prior studies made it seem like it might be possible as well.

Q. What is the take-home message for the practicing urologist?
A. I’d say there’s probably 2 take-home messages, the first of which would be that any prescription of statin use for patients should just be left up to the primary care doctor or cardiologist, purely for the cardiovascular benefits. Currently, there is no role for statins in management of LUTS. Any possible benefits seem to be subclinical and would not be appreciated by the patient, so why risk the potential side effects of any drug if they won’t even see the benefit?

And then the other take-home message is that more research does need to be put into preventive measures for LUTS and BPH because, currently, there aren’t really any good options for that. There’s no, at least, pharmaceutical option that’s good. The biggest drugs at our disposal right now are blockers and 5α reductase inhibitors. You wouldn’t start a patient on a blocker preemptively in their 30s or 40s. It’s not going to prevent progression, and certainly there’s a 15% chance of having retrograde ejaculation and many young men are not going to tolerate that for symptoms that they don’t even have yet. So that wouldn’t work.

“More research does need to be put into preventive measures for LUTS and BPH because, currently, there aren’t really any good options for that.”
JORDAN J. KRAMER, MD

And then, of course, you wouldn’t want to start a 5α reductase inhibitor preemptively either, also for its potential adverse effects. There’s no pharmaceutical option that’s good for us. All we can really offer preemptively is lifestyle changes, which are pretty much the same across the board for almost any disease you’re trying to prevent. It’s exercise increase, weight loss, eating more fruits and vegetables, and there was even one study that looked at small daily alcohol consumption that actually slowed the progression of BPH as well. But you can’t really rely on that for this kind of disease.

Q. Is there anything else you feel our audience should know about the findings?
A. In all likelihood, any future drug that would be used in preventing BPH with LUTS onset and progression would probably have to do with something in the sex steroid biosynthesis pathway. Clearly, intervening too early on that pathway doesn’t make a difference. Intervening later in the pathway between the conversion of testosterone into DHT would not be useful preemptively either. Maybe there’s something in between there that we just haven’t seen yet. So there for sure needs to be more research into possible pharmaceutical intervention, since nothing is taking its place right now.

An interesting proof of the hormone reliance of BPH development, however, is seen in transgender patients. When they are going through their male to female gender-affirming surgery, they undergo bilateral orchietomy, which drops their testosterone level to run below 20 ng/dL. If these procedures are done early in life, they actually do not go on to develop BPH at all, even though the procedure leaves their prostate intact. The only instances in the literature of BPH with LUTS in a male-to-female transgender patient happened in those who underwent their transition much later in life after having decades of testosterone and DHT affecting their prostate growth. So I think, ultimately, the next drug that’s going to be effective in prevention is going to have to do with that hormone pathway in some respect. We just need to do more research on it.

REFERENCE

Advantages of Aquablation system for patients with BPH

In this video, Kevin Zorn, MD, FRSCC, FACS, discusses the advantages of the novel Aquablation therapy, including the preservation of antegrade ejaculation. Zorn is an associate professor of urology at the University of Montreal, Canada.

Using your phone’s camera, hover over the QR code and scan to watch.
Women who suffer from recurrent urinary tract infections (rUTIs) are typically treated with antibiotics. However, these treatment regimens are associated with high rates of morbidity as the world faces rising antibiotic resistance. A recent study presented during the American Urological Association’s (AUA) 2021 Annual Meeting found that the novel MV140 (Uromune) vaccine is a safe and effective strategy for treating rUTI in women.1

MV140 is a polybacterial sublingual vaccine, consisting of Escherichia coli, Klebsiella pneumoniae, Enterococcus faecalis, and Proteus vulgaris, which induces a T cell–specific adaptive and immune response at the genitourinary tract, according to lead investigator J. Curtis Nickel, MD, FRCSC, a professor in the Department of Urology at Queen’s University and a urologist at Kingston and Hotel Dieu General Hospitals, Ontario, Canada.

The findings shared at the AUA meeting included results from early uncontrolled studies, the first phase 3 multicenter, double-blind, placebo-controlled randomized controlled trial (RCT), ongoing safety monitoring from special access programs (SAPs; 2014-2020), and the first North American clinical experience evaluating MV140 for the prevention of rUTI in women.1

Across 5 uncontrolled studies, results showed that 1408 women treated with MV140 had significantly higher UTI-free rates (35%-90%) compared with 499 women treated with antibiotics (0%-9%). Additionally, the RCT revealed UTI-free rates of 55.7% at 3 months and 58.0% at 6 months, whereas the placebo group exhibited a rate of 25%. The median number of UTIs in MV140-treated patients within this study was 0.0 (IQR, 0.0-1.0) compared with 3.0 for patients on placebo (IQR, 0.5-6.0).

Regarding the ongoing SAP study, 1.7% of over 20,500 patients reported adverse reactions. And in the North America study, patients experienced a 48% UTI-free rate with an overall 82% reduction in UTI episodes. One patient had 2 mild vaccine-related adverse reactions in this study.

In an interview with Urology Times®, Nickel discussed why the vaccine is a game changer and next steps.

Q. Please provide the background for this study.
A. rUTIs in women are a major health care issue. It’s not really associated with mortality; it’s associated with a lot of morbidity. With more than half of women having a UTI sometime in their life, about 40% of them will be classified as having rUTIs. That’s more than 3 per year, and for many that can be, on average, about 6 a year. So 3 of 100 women every year are classified as having recurrent urinary tract infections.

The way we manage those is by using things like cranberry extract, probiotics, and certainly intravaginal estrogen for perimenopausal and postmenopausal women. But the only treatment that’s really effective is antibiotics—either episodic antibiotics or long-term prophylactic antibiotics that are taken for weeks and months. The antibiotics themselves are problematic. There is cost to patient and society, and there...
is the detrimental effect of antibiotics on the patient with adverse events, sometimes being quite serious and even irreversible. Antibiotics work only as long as the patient is taking the antibiotic. And then we have the rising spectra of national and international antibiotic resistance, which is becoming a huge international medical issue.

Q. The abstract describes the vaccine as “game changing.” Can you explain why?
A. Right now, there is a huge unmet need in women’s health for some way to prevent recurrent urinary tract infections. I mentioned the methods that we have, and the only one that really works well is interval estrogen in peri- and postmenopausal women, but it doesn’t work in all. We discussed the problems associated with antibiotics. What we’re looking for is some safe and effective intervention that will completely change the way we manage recurrent urinary tract infections in women. I and others have always believed that the answer would be a vaccine. Over the past 20 years, we’ve looked at vaccines, and there are vaccines available with some efficacy but not enough to change the game from antibiotics to something safer and more effective. That’s why I think this vaccine, with its effectiveness and safety, will be a major game changer.

“I know the vaccine works. This study met and exceeded the end point in reducing the risk and preventing urinary tract infections.”
J. CURTIS NICKEL, MD, FRCSC

Q. Were you or your coinvestigators surprised by any of the study findings?
A. I am always surprised when a large, well-planned, randomized, placebo-controlled trial is positive or even more positive than we thought with early observational, uncontrolled studies. And we do have evidence from at least 5 studies that this sublingual vaccine is effective and safe. I have the only early clinical experience in North America, having had over 65 patients vaccinated and having followed them, some for over a year. I know the vaccine works. This study met and exceeded the end point in reducing the risk and preventing urinary tract infections.

Q. What is the next step? What will future research on MV140 focus on?
A. In this study, we were able to show that there was a very clinically significant decrease in the rate of UTIs in the vaccinated group, preventing UTIs in almost 60% of vaccinated patients. We found that if patients did get a UTI, and there was a significant median time to UTI that was many times greater in the vaccinated group, it was usually mild and self-limited. The study went for 9 months. Based on real-world experience with this vaccine in special access programs outside North America, we believe that the vaccine efficacy may wear out after a year or 2. So future studies are going to have to look at revaccinating patients who revert to their recurrent urinary tract infection state.

Further, there is some evidence in observational studies that’s effective and complicated, showing outcomes for UTIs in the frail and older population, in children, and in men. We’re going to have to look at all those groups. This could be a game changer for rUTIs in children who rely on antibiotics. It could be a game changer in the frail and older population, particularly those in long-term care homes, where UTIs are a significant problem, even causing mortality and antibiotic overutilization. We’d also like to see it used in complicated UTIs in men. All of these are going to have to be studied, and that’s why it’s so exciting. This vaccine has legs to run on.

Q. Is there a take-home message for the practicing urologist?
A. The take-home message for international urologists is that this vaccine is available on named patient programs or special access programs. Unfortunately, that’s not the case for North America. Health Canada realizes the huge unmet need and is going to be looking at regulatory approval on an expedited basis based on the observation studies, the special access program safety audit on over 20,000 patients have already received this, the Canadian early experienced trial that we’re doing, and the RCT. We may have approval in Canada for this vaccine for Canadian women with rUTIs sometime next year. The FDA is going to probably look at these data and advise whether further studies will be required in the United States before it’s widely available in the country, either under special access programs or across the board.

Q. Is there anything else you feel our audience should know?
A. It’s exciting research. The randomized, placebo-controlled study has replicated all the previous studies, looking at rUTIs and this vaccine. The other thing they should realize is that it is a vaccine that is self-administered by the patient sublingually over 3 months. That is why it appears to be so safe. It’s not an injected vaccine. The immunity builds up very slowly over 3 months, and it persists for 9 months. We’ll see how long that durability effect is over the long term, but keep your eyes and ears open because, as I said, this vaccine will be a game changer for women’s health in the future.

REFERENCE
What are your thoughts on proposals that physicians should communicate with their patients by text?

Administrators can improve the patient experience, but we have to make sure it also improves the physician experience. Does it lead to better patient care? This job doesn’t really leave you 24/7, so this could help fuel burnout and make it more difficult for us to get our work done.

Patients also don’t understand that urologists are actually surgeons. They expect an almost immediate response to texts, but we’re in the OR [operating room] for hours on end. Without any real data [showing] that this improves anything, it just makes us too accessible.

Texting appointment reminders is fine, but what can you safely send? You have to make sure your messaging service is HIPAA [Health Insurance Portability and Accountability Act] compliant. Someone changes their phone number, hasn’t updated it, and you send out health information. How can you confirm the right person gets the message?

It’s another push by outside players to make physicians more accessible, as opposed to a physician-driven component to improve patient care.

I just got a MyChart message saying, ‘Now texting your physician’s office is as easy as texting your friends.’ Currently, that means texting my nursing staff, but with the worker shortages even that could create an overload from excess communication. Other questions: Billing-wise, where does this leave us? What other business allows this much access in terms of being able to text a professional directly? I think our medical portal probably meets the need.

I don’t know the benefit is.”

Joshua Broghammer, MD
Kansas City, Kansas

It hasn’t been propagated at my hospital. I don’t know any providers at my hospital who text with patients, although I know other urologists who do.

It seems intrusive for the provider. That would be my impression if I were asked to do it. Of course, the patient would have to agree to it and be interested in opening that line of communication.

The hospital texts patients with appointment confimations and reminders, so that’s commonplace. As for provider and patient communication, it would be intrusive, at least with my practice, because I’m essentially a solo provider. I have a partner, but we don’t share calls or patient responsibilities so there’s no one covering for me. Even though I don’t take calls for my hospital, my hospital calls me all the time. The [emergency department] calls if a patient ends up there with urological issues because I’m the urologist who works there. That’s the nature of my practice. So since I’m sort of always available, making myself more available isn’t something I’d be interested in.

If I were in a practice with 30 urologists, I would understand the expectation to respond to patient text messages. It’s reasonable in that sort of practice. So it’s practice specific is my answer. I’m not afraid of being inundated during working hours. I’ve been working at my hospital for 6 years, so I understand the nature of the area. I don’t work in a large population center where you’ll see more volume. I know my volume and the amount of inquiries my patients have. So I wouldn’t be worried.”

David Sisul, MD
Blackfoot, Idaho

I’m in a unique situation because I work part-time at 2 different institutions. There’s no institutional policy I am aware of for physicians to text patients. I have developed communication patterns over the years, determining what meets the patient’s needs with safe and effective care without miscommunication that can result in mistakes.

Personally, I don’t text with patients, yet there are a number of patients, particularly those at higher risk, to whom I give my cell phone number and tell them to call me if they have issues. I never suggest texting.

If somebody has a problem, I want to know about it. Going through my staff is always better. With so much information coming through, you’ll get numb to it. You’ll start getting texts about someone heard on the news or asking whether they should keep an appointment. I want those to be screened by my staff. Patients can’t tell what’s important or not. I want to be immediately available for the important things. My office staff can call me anytime, anywhere for anything that’s important. They know that.

Trying to figure out over the years how to lessen the chance of problems while serving the patient’s needs is a fine line.

You’re talking to somebody who’s never been on Facebook, Instagram, or TikTok. I hope to use technology for my benefit, to make sure patients have access to help, but that shouldn’t be directly from me most of the time.”

Robert Fleischer, MD
Cooperstown, New York
How the 2022 CMS final rule will affect urologists

Urology as a specialty will see a 3.71% decrease in overall payments

In July 2021, the Centers for Medicare & Medicaid Services (CMS) released its proposed rules for the Medicare Physician Fee Schedule (MPFS) and for the Hospital Outpatient Prospective Payment System and Ambulatory Surgical Center (OPPS/ASC) Payment System. We had discussed this and our thoughts on these proposed rules in our August 2021 column.1 Societies and interested parties were able to provide their thoughts on the proposed rules to CMS during the comment period. The biggest impacts on urology involved the proposed reduction in the conversion factor (CF) and the effect of updated clinical labor rates on nonfacility-based procedures. On November 2, 2021, CMS released its final rules for the MPFS and OPPS/ASC Payment System outlining the policies to be implemented on January 1, 2022. Despite comments from interested parties hoping for changes, CMS adopted much of what had been proposed in July.

FINANCIAL IMPACT
The CF for 2022 is scheduled to be $33.5983, a decrease of 3.71% from the current $34.8931. This decrease is primarily due to the expiration of a 1-time contribution from the trust fund as directed by one part of the of the Consolidated Appropriations Act of December 2020, which raised the CF by 3.75% for the 2021 calendar year only. This reduction will directly affect payment for work performed by providers for patients covered by Medicare and Medicare Advantage plans. The relative value unit (RVU) changes overall are projected as a 0.0% impact based on the full volume of services for the specialty code payments. Taken in combination, this means that urology as a specialty will see a 3.71% decrease in overall payments in 2022 despite providing the same volume of services. The impact will not be equal for all urologists based upon their practice patterns and case mix.

As noted in our August 2021 article, clinical labor rates had not been updated in nearly 2 decades but were proposed to be updated for 2022. The concern was that these rates would dramatically increase due to being nearly 2 decades behind and, when plugged into a budget-neutral system, would lead to significant shifts in the reimbursement for practice expenses. The net effect of a significant shift would benefit services with high clinical labor rates but would adversely affect the reimbursement for services with low clinical labor yet high expenses, such as nonfacility-based surgical procedures, especially those with high device or nonlabor practice expenses.

Because of this, there was a push by many to have CMS delay the implementation of this change for at least 1 year while the true effects could be further studied, and/or to implement a device offset for the device-intensive procedures. Unfortunately, neither of these asks were accepted by CMS in the final rule. However, the final rule did allow a 4-year phase-in of the updated clinical labor rates, which would let practices adjust to this change. In addition, CMS will use the median Bureau of Labor Statistics (BLS) wage data instead of the mean wage data, and the 2021 BLS fringe benefits multiplier of 1.296 as opposed to the 2002 BLS fringe benefits multiplier of 1.366. These changes will help mitigate the sudden and significant change to urology practices, at least in the short run. Practices will need to evaluate how this affects them both for 2022 and for years to come.

For the OPPS and ASC Payment System, CMS is increasing payment by a factor of 2.3%.

As noted above, the RVU changes for 2022 when adjusted for volume across all urologists are projected to be 0%. The global look at RVU changes does not tell the entire story and will not apply equally to all urologists. The codes listed in the Table demonstrate the changes in RVU that will affect in-office (nonfacility) payments, noting also that the affected codes are also reduced by the CF decrease of 3.71%. For this table, we have also included the codes that will be increased enough to offset the CF decrease. Only 11 codes with modifiers remained unchanged in total values for the Urology CPT section. Taking all RVU adjustments into account, most CPT codes in the Urology CPT section have slightly increased. The high volume of the negatively adjusted CPT codes offset the small increases for those positive RVU adjustments. Physician payments in the facility setting did not see many RVU changes. Codes with a negative fee impact between 0 and 3.71% are not included in the table.

Many urology practices also must contend with decreases in fees associated with radiology and radiation oncology decreases due to RVU decreases on top of the CF decrease. For those
groups with ambulatory surgical centers, the changes in code payment structure were limited and the overall payment was increased by approximately 2.0% for most services.

For the OPPS and ASC Payment System, CMS is increasing payment by a factor of 2.1%. Hospitals and ASCs that fail to meet their respective quality reporting program requirements are subject to a 2.0% reduction in the calendar year 2022 fee schedule increase factor, in continuation of existing policy.

QUALITY PAYMENT PROGRAM CHANGES
For calendar year 2022, CMS will require clinicians to meet a higher performance threshold to be eligible for incentives following threshold requirements established for the Quality Payment Program’s Merit-based Incentive Payment System (MIPS) under the Medicare Access and CHIP Reauthorization Act of 2015. 2022 is the last performance year in which CMS will provide additional funds for exceptional performance; CMS will in future years only use penalties to fund bonus payments for exceptional performance. The threshold score for 2022 performance will be 75 with 30% of the score assigned to Quality and Cost categories, 25% to Promoting Interoperability, and 15% for Improvement Activities.

EVALUATION AND MANAGEMENT CHANGES
Split/shared visits are those where the service is provided in part by both the physician and nonphysician practitioner (NPP) of the same group. Although prior guidance was interpreted as limiting split/shared billing to established patients and not allowing critical care services to be split/shared, in 2022 CMS will change its policy and permit physicians and NPPs to bill for split/shared visits for both new and established patients and also for critical care services. Historically, the billing provider could be the physician if performing a “substantive portion” of the visit. CMS had proposed to allow billing by the practitioner who performed more than 50% of the time of the service and would allow split/shared billing based upon time. In the final rule, there will be a 1-year transition period for this to take place, so during 2022 split/shared billing can be based upon time or medical decision-making using 1 of 3 key components of the visit (history, exam or medical decision-making) to qualify as the “substantive portion” of the visit. If performing a key component of the visit is utilized, the practitioner who bills the visit must perform and document the performance of that component in its entirety. For critical care services, which are time-based codes already, the physician or NPP must provide more than half of the total time in order to bill for the visit.

In the office setting, shared/split visits will not be allowed. CMS will continue to recognize “incident to” rules to determine how to classify services provided in the office setting. No changes were made to the “incident to” rules. We have seen many practices struggle with “incident to” billing for advanced practice providers (APPs). It is worth reviewing these guidelines and your practice’s policies every year. CMS also stated that Medicare will not recognize modifier -52 with E/M codes.

### TABLE. Percentage Change to Medicare Fees for Common Urology Code for Calendar Year 2022 Compared With Calendar Year 2021

<table>
<thead>
<tr>
<th>Code</th>
<th>Modifier</th>
<th>In-office % Medicare fee change</th>
<th>Code</th>
<th>Modifier</th>
<th>In-office % Medicare fee change</th>
</tr>
</thead>
<tbody>
<tr>
<td>50200</td>
<td>—</td>
<td>-5.90%</td>
<td>51784</td>
<td>—</td>
<td>-5.21%</td>
</tr>
<tr>
<td>50382</td>
<td>—</td>
<td>-3.79%</td>
<td>51792</td>
<td>26</td>
<td>-4.32%</td>
</tr>
<tr>
<td>50384</td>
<td>—</td>
<td>-5.83%</td>
<td>51797</td>
<td>TC</td>
<td>-4.64%</td>
</tr>
<tr>
<td>50385</td>
<td>—</td>
<td>-7.47%</td>
<td>52007</td>
<td>—</td>
<td>-6.63%</td>
</tr>
<tr>
<td>50386</td>
<td>—</td>
<td>-4.04%</td>
<td>52010</td>
<td>—</td>
<td>-5.98%</td>
</tr>
<tr>
<td>50391</td>
<td>—</td>
<td>-3.97%</td>
<td>52204</td>
<td>—</td>
<td>-5.03%</td>
</tr>
<tr>
<td>50431</td>
<td>—</td>
<td>5.97%</td>
<td>52265</td>
<td>—</td>
<td>-8.71%</td>
</tr>
<tr>
<td>50433</td>
<td>—</td>
<td>-4.53%</td>
<td>52332</td>
<td>—</td>
<td>-10.04%</td>
</tr>
<tr>
<td>50434</td>
<td>—</td>
<td>-4.15%</td>
<td>52441</td>
<td>—</td>
<td>-8.00%</td>
</tr>
<tr>
<td>50551</td>
<td>—</td>
<td>-3.80%</td>
<td>52442</td>
<td>—</td>
<td>-11.21%</td>
</tr>
<tr>
<td>50555</td>
<td>—</td>
<td>-3.79%</td>
<td>52647</td>
<td>—</td>
<td>-6.08%</td>
</tr>
<tr>
<td>50557</td>
<td>—</td>
<td>-3.79%</td>
<td>52648</td>
<td>—</td>
<td>-6.08%</td>
</tr>
<tr>
<td>50561</td>
<td>—</td>
<td>-3.78%</td>
<td>53850</td>
<td>—</td>
<td>-9.23%</td>
</tr>
<tr>
<td>50592</td>
<td>—</td>
<td>-9.57%</td>
<td>53852</td>
<td>—</td>
<td>-8.86%</td>
</tr>
<tr>
<td>50593</td>
<td>—</td>
<td>-9.96%</td>
<td>53854</td>
<td>—</td>
<td>-8.23%</td>
</tr>
<tr>
<td>50606</td>
<td>—</td>
<td>-18.25%</td>
<td>53855</td>
<td>—</td>
<td>-10.54%</td>
</tr>
<tr>
<td>50693</td>
<td>—</td>
<td>-5.91%</td>
<td>54150</td>
<td>—</td>
<td>-5.21%</td>
</tr>
<tr>
<td>50694</td>
<td>—</td>
<td>-5.36%</td>
<td>54160</td>
<td>—</td>
<td>-4.15%</td>
</tr>
<tr>
<td>50695</td>
<td>—</td>
<td>-5.76%</td>
<td>54162</td>
<td>—</td>
<td>-4.09%</td>
</tr>
<tr>
<td>50705</td>
<td>—</td>
<td>-4.91%</td>
<td>54235</td>
<td>—</td>
<td>-4.08%</td>
</tr>
<tr>
<td>50706</td>
<td>—</td>
<td>-8.87%</td>
<td>54450</td>
<td>—</td>
<td>-4.19%</td>
</tr>
<tr>
<td>50951</td>
<td>—</td>
<td>-3.97%</td>
<td>55200</td>
<td>—</td>
<td>-6.96%</td>
</tr>
<tr>
<td>50953</td>
<td>—</td>
<td>-3.79%</td>
<td>55250</td>
<td>—</td>
<td>-7.50%</td>
</tr>
<tr>
<td>50957</td>
<td>—</td>
<td>-3.86%</td>
<td>55700</td>
<td>—</td>
<td>-5.41%</td>
</tr>
<tr>
<td>51700</td>
<td>—</td>
<td>-4.96%</td>
<td>55873</td>
<td>—</td>
<td>-8.20%</td>
</tr>
<tr>
<td>51701</td>
<td>—</td>
<td>-4.43%</td>
<td>55874</td>
<td>—</td>
<td>-8.42%</td>
</tr>
<tr>
<td>51702</td>
<td>—</td>
<td>-4.74%</td>
<td>56420</td>
<td>—</td>
<td>4.44%</td>
</tr>
<tr>
<td>51720</td>
<td>—</td>
<td>-4.45%</td>
<td>56501</td>
<td>—</td>
<td>3.96%</td>
</tr>
<tr>
<td>51725</td>
<td>26</td>
<td>-4.15%</td>
<td>57061</td>
<td>—</td>
<td>4.07%</td>
</tr>
<tr>
<td>51726</td>
<td>26</td>
<td>-4.10%</td>
<td>57465</td>
<td>—</td>
<td>-7.19%</td>
</tr>
<tr>
<td>51729</td>
<td>26</td>
<td>-3.97%</td>
<td>64561</td>
<td>—</td>
<td>-4.8%</td>
</tr>
<tr>
<td>51784</td>
<td>TC</td>
<td>-8.24%</td>
<td>64566</td>
<td>—</td>
<td>-7.8%</td>
</tr>
</tbody>
</table>
CHANGES TO THE ASC COVERED PROCEDURES LIST

Similar to the IPO list, in the 2021 final rule CMS added 267 surgical procedures to the ASC Covered Procedures List (CPL) beginning in 2021. However, CMS is restoring criteria for adding procedures to the ASC CPL if they meet Medicare’s criteria. Three codes were proposed initially for removal and are being retained, including 2 urology CPT codes: 0499T (cystourethroscopy, with mechanical dilation and urethral therapeutic drug delivery for urethral stricture or stenosis, including fluoroscopy, when performed) and 54650 (orchiopexy, abdominal approach, for intra-abdominal testis [eg. Fowler-Stephens]). Also in the works is adoption of a nomination process, to begin in March 2022, to let external parties nominate surgical procedures to be added to the ASC CPL.

APPROPRIATE USE CRITERIA PROGRAM PUSHED BACK AGAIN

The somewhat controversial Appropriate Use Criteria program has been postponed again. Previously, the payment penalty phase of the program was to begin January 1, 2022. However, CMS now will not begin that phase until at least January 1, 2023, or the January 1 following the declared end of the PHE for COVID-19. This flexible effective date is intended to consider the impact that the PHE for COVID-19 has on practitioners, providers, and beneficiaries.

CONCLUSIONS

Based on the current path of Medicare and the MIPS/MACRA program revisions, it is hard not to feel déjà vu to the days of the sustainable growth rate when yearly patches were provided to maintain physician payment. Although there are efforts to avert the CF cut, we are hopeful but not convinced that Congress will take the action necessary to truly adjust the Medicare budgeting process to avoid the projected decreases in reimbursement as physician groups face increasing costs and administrative burdens. It will take the collective support of physicians and patients to initiate change to this now-outdated approach.

REFERENCES


QUESTIONS?

Send coding and reimbursement questions to Jonathan Rubenstein, MD, and Mark Painter c/o Urology Times®, at UTeditors@mjhlifesciences.com. Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative, and every effort has been made to ensure its accuracy at the time it was written. However, readers are encouraged to check with their individual carrier or private payers for updates and to confirm that this information conforms to their specific rules.

CHANGES TO THE INPATIENT ONLY LIST

CMS created and maintained an Inpatient Only (IPO) list, which includes services Medicare will only pay for when performed in an inpatient setting because of their medical complexity. In the final rule for 2021, CMS decided to eliminate the IPO list over a 3-year period, with 298 services to be removed initially. However, CMS received numerous stakeholder comments opposing elimination of the IPO list mainly over patient safety issues. In the final rule for 2022, CMS halted the elimination of the IPO list and restored to the list the services removed in 2021, except for a few orthopedic codes. Procedures can still be removed from the IPO list if deemed appropriate based on Medicare criteria.
Practical ways to address burnout in your urology practice

The World Health Organization defines burnout as “a syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed. It is characterized by 3 dimensions: feelings of energy depletion or exhaustion; increased mental distance from one’s job or feelings of negativism or cynicism related to one’s job; and reduced professional efficacy.” The contributions to burnout identified by physicians include bureaucratic tasks, time pressure, lack of respect, insufficient compensation, lack of control and autonomy, increased computerization, and government regulation. Much of the energy on this subject is directed at recognizing the symptoms, learning coping skills, and accepting the inevitability of these contributing workplace stresses. In this article, I will take a slightly different approach by challenging the inevitability of some factors and offering a few practical suggestions that may help manage burnout by addressing the root cause.

BUREAUCRATIC TASKS

When physicians complain about bureaucratic tasks, they are probably thinking about processes imposed by government and private insurance companies. Prior authorizations, requests for medical records, drug formulary substitutions, and appeals of denials are examples of the systemic dysfunction in our fee-for-service reimbursement environment that may push work to the physician. Some of these bureaucratic tasks can be prevented, or prevented from requiring physician involvement. For example, most contemporary electronic health records include drug formulary checking as part of the core functionality. It may require a subscription, configuration, or training. A small investment of time on the front end prevents time-consuming tasks later—like answering a call from a pharmacist or patient about a routine substitution.

Prior authorizations and requests from insurance companies for medical records are generally predictable. Most urology practices have 20 common patient types, 20 common surgical procedures, and less than 20 common insurance companies. Your practice can easily track this activity for a month and learn to recognize which combination of activities/companies/diagnoses are generating these requests; armed with that intelligence, you can prevent requests by authorizing or submitting records proactively. Report abuses to your state board of insurance. As a last resort, consider terminating contracts with companies whose bureaucracies are not worth the contribution to your bottom line—and your burnout.

Another type of bureaucratic task that may contribute to physician burnout is low-value documentation to support compliance with coding, reimbursement, or value-based care models. A prime example of this is documenting the review of systems for a routine office encounter, or citing extraneous information to document medical decision-making. There is usually no good reason to cite a review of systems for an established patient; reimbursement is almost always based on history, medical decision-making, and/or time spent with the patient.

Keeping current with arcane and complex coding rules is in itself a contribution to burnout. Instead of trying to master every possible coding scenario, or coding every single encounter one at a time, simplify: Identify your 20 common visit types that constitute 80% of your encounters and code them the same way every time. Override or turn off the coding engine in your electronic health record (EHR) for these common visits. Be sure your note templates are working for you, not against you, by including only the necessary sections or choices.

Documenting for the Merit-Based Incentive Payment System (MIPS) deserves special mention as a potential contributing factor to burnout. There is widespread frustration with the effort required for MIPS participation, the modest rewards, and the perceived lack of benefit to patient care. However, there is no need for most physicians to understand the complexities of the model, the scoring paradigms, or the fee schedule adjustments. Simplification, delegation, repetition, and discipline will relieve the pressure from these bureaucratic tasks. Recent MIPS data reveal that urologists are submitting data for quality measures that are driven entirely by nonphysician documentation. In most practices, if the clinical staff take vital signs, update the current medication list, and perform a urinalysis at each visit, they will have optimized performance on quality measures—all with no direct physician documentation. There is a real cost to MIPS: It may contribute to staff burnout, and it may extend the length of patient intake by a few minutes—but it involves bureaucratic tasks that are arguably already being done for other reasons or can be delegated and simplified. If you think MIPS is a cause of your burnout, take a look at your processes and see whether they can be simplified.

Burnout is often recognized when the amount or pace of work exceeds the available capacity. There is a finite number of hours in a work week, and once the limit is reached, the only management strategy to relieve time pressure is to work more efficiently, ie, do more work in the same or fewer hours. The first step in addressing this contribution to burnout is to believe that it is possible to be more efficient and understand it...
will take some work to get there. The next step is to keep a journal of a day in your life. To the extent possible, track everything you do: hospital rounds, travel time, clinic hours (copy a list of your appointments, including patient type), meals, surgeries, consults, phone calls, document review and sign-off, on-call activities, drug rep visits, sleep, etc. Your EHR may have an audit report that can simplify this record, especially for visits and phone calls. If you have a scribe, they can keep your journal.

Next, give your journal to a staff or manager who can transcribe your diary into rows on a spreadsheet with these columns: category (patient care, admin, personal), task, time spent, required physician (Y/N), notes. You should fill out the column on whether a task required a physician or could have been delegated. A high-level analysis of this journal should tell you how much time is being spent on each category, and what activities do and do not require your involvement. Urologists and practice owners are understandably proud of the ability to “do it yourself”; relieving time pressure requires a fresh look at trade-offs and delegation.

Drilling down into your clinic schedule should identify possible opportunities for scheduling efficiency. Get specific: Is your schedule full of routine visits and going through the motions? Can your scheduling template be refined to prevent high-pressure situations like cancer conferences back to back? Do you have a workable list of patients available to fill empty slots on short notice? Do you program work in spots or pauses in your schedule? If you have been in practice for years, there should be a predictable pattern of patient types (demand) and schedule openings (supply). Rearranging a schedule may return time previously spent on travel, waiting, or switching from clinical to nonclinical activities. Many urologists have come to recognize that doing 4 surgeries on a Friday is far less reasonable and necessary. The major expense categories are recurring and fixed: rent, salaries, insurance, etc. Drugs and supplies are examples of variable expenses. Your accounting software or accountant should be able to provide you with a summary of expenses by category. The next step is to benchmark these expenses to other urology or physician practices. Benchmarks are published by professional associations, private companies and, in some cases, the Centers for Medicare & Medicaid Services. If your expenses are higher than benchmarks in 1 or more categories, it’s time to roll up your sleeves and look at every expense. Finally, consider participation in group purchasing organizations to reduce the cost of supplies or even professional services.

**INCREASED COMPUTERIZATION**

I have some bad news: Computers are here to stay and demand to use them may increase. Resistance is not productive. Contemporary surveys identifying computers as the source of burnout could be reflecting several correctable problems. First, physicians may be using outdated software or systems. First- and second-generation EHRs were typically deployed on local servers that require upgrades and maintenance and were often plagued by performance issues, design flaws, and bugs. Modern systems are deployed in the cloud, are more reliable, and have a better (faster) user experience. If you are still on an early system, consider changing to address your burnout. (Warning: Changing EHRs is stressful, too!)

Second, almost all small and medium practices underinvest in initial training and completely ignore ongoing training. The inevitable result is an undertrained physician user who forges a path of least resistance and hardens inefficient or redundant workflows. This is completely preventable and a correctable contribution to burnout; users do not know what they don’t know. The contemporary EHR is typically upgraded and enhanced several times a year, resulting in new features, many of them time-saving. Retraining requires a small investment of time; it will return huge dividends. This may be the single most treatable contribution to physician burnout.

Third and related: Many physicians do not use order sets, macros, favorites, or other time-saving features of almost all EHRs; they may not believe there is a better or faster way, especially if they have been using the system for years. Open your mind to the possibility that there may be a faster way of doing computer tasks, and that you may need training to even understand the possibilities. Finally, if you truly blame the computer or your EHR for your burnout, take another look at a scribe. The evidence is strong that scribes reduce physician burnout* and are a good return on investment.

Bottom line: Burnout is a real and serious phenomenon with multiple contributing causes and significant consequences. Some burned-out physicians may surrender to the idea that there is nothing they can do, leading to depression or more serious outcomes—including “reduced professional efficacy.” I challenge you to instead believe it can be better and to take some simple steps under your control. Targeted review of your documentation habits, your schedule, your EHR, and your benchmarked expenses may provide an opportunity to improve your professional satisfaction, extend your career, and optimize your “professional efficacy.”

**REFERENCES**


Financial tasks you should complete by the end of the year

Q. What are some financial planning tasks I should focus on before year-end?
A. The final months of the year are a good time to determine whether financial planning is on track. Do strategies need adjusting, or accounts require updating? The sooner these items are addressed, the better the position you likely will be in for 2022.

Is your emergency fund where it should be? If you tapped into your emergency fund for any reason this year, make sure the account is replenished. It is always a good idea to review your budget and see whether necessary spending has increased or decreased and then review your emergency fund level. The general rule of thumb for an emergency fund is to have 3 months of your necessary expenses saved in cash for a dual-income household or 6 months for a single-income household or if one individual earns significantly more and that income is relied upon to maintain your family’s standard of living.

Have you maxed out your retirement accounts or are they on track to max out by year’s end? Contributions to 401(k) and 403(b) accounts must be made by December 31, 2021. The 2021 limit for employee contributions is $19,500. Individual retirement account (IRA) contributions can be made until the tax filing deadline in April 2022. The 2021 contribution limit for IRAs is $6000. If you are older than 50, catch-up contributions may be available.

Have you used all the money remaining in your dependent care or health care flexible spending accounts (FSAs)? Most FSAs are use-it-or-lose-it accounts, meaning money left over at the end of the year is forfeited back to the plan, not to you. Some employers do offer a grace period into next spring or a $500 carryover from one year to the next for health care FSAs, but most do not.

Have you made contributions to your children’s 529 accounts? These accounts offer excellent tax advantages if saving for college or other post-high school educational opportunities. Many states offer a state income tax deduction for contributing to a 529 account. Sometimes these tax savings can be substantial. Contributions must be made before December 31, 2021, to receive a 2021 tax deduction.

Have you designated all the gifts you planned to give this year? For 2021, the annual gift tax exclusion amount is $15,000 per individual or $30,000 for a married couple. This means you can give up to these amounts to an unlimited number of individuals without having to worry about gift taxes. Making gifts can be a great way to remove assets from an estate if future estate taxes are a concern. Gifts must be made before December 31, 2021.

Have you made your charitable donations for the year? Check whether you have any appreciated investment assets you could donate instead of cash. Donating appreciated investments allows you to avoid paying capital gains taxes when you sell the investments, and you get to claim a deduction for the full value of the donated asset. The charity can then sell the investment and not have to pay capital gains taxes. However, be aware that with the increased standard deduction under current tax law, you may need to donate a substantial amount to see any tax benefit. Donations must be made by December 31, 2021, to count toward your 2021 taxes.

Have any of your investments lost money this year? If any investments in your taxable accounts are in the red, you could consider selling those investments to harvest the loss. Tax loss harvesting can be used to offset gains elsewhere or potentially lower your 2021 tax bill. If your captured losses exceed your realized gains, you will have a net capital loss. Up to $3000 ($1500 if you are married and file separately) of net capital losses can be deducted against ordinary income, including salary, self-employment income, and interest income. Any excess loss above these amounts can be carried forward to future years to cancel out gains or deduct against income. Sales to capture losses must occur before the end of the year to count toward 2021.

Do you need to update beneficiaries? If there has been a major change in your life, you may need to update the beneficiaries on your retirement accounts and life insurance policies. You may also need to update your will and power of attorney documents. There is no deadline for these changes, but the sooner the better.

There are likely to be other items to check on, but this list should give you a good start on making sure you end the year on strong financial footing.

The information in this column is designed to be authoritative. The publisher is not engaged in rendering legal, investment, or tax advice. If you would like assistance with your individual investment strategy, please email witz@mediqus.com.
The Permanente Medical Group, Inc. (TPMG - Kaiser Permanente Northern California) is one of the largest medical groups in the nation with over 9,000 physicians, 22 medical centers, numerous clinics throughout Northern and Central California and a 75-year tradition of providing quality medical care. We currently have the following opportunities for BE/BC Urologists to join us in the California Central Valley:

**ADULT UROLOGISTS**

Fresno and Manteca, California

*Ask us about our Forgivable Loan and Incentives!*

**EXTRAORDINARY BENEFITS:**

- Competitive compensation and benefits package, including comprehensive medical and dental
- Moving allowance and home loan assistance - up to $200,000 (approval required)
- Malpractice and tail insurance
- Paid holidays, sick leave, education leave
- Shareholder track
- Three retirement plans, including pension

To learn more about these opportunities and to apply, please visit:

You may also email your CV to: Victor Ramirez at Victor.R.Ramirez@kp.org or call: (510) 625-6281.

**CENTRAL CALIFORNIA OFFERS:**

- A short drive to the San Francisco Bay Area, Sierra Nevada Mountains, or the Pacific Coast, as well as close proximity to three national parks, including Yosemite, Kings Canyon and Sequoia
- Mild winters, dry summers, and close to some of our state’s most popular recreation destinations
- Great schools, numerous local parks, vibrant arts scene, local farmer’s markets, and lively theater and music performances
- High quality and attractive lifestyle with a lower cost of living
- A “reverse commute” for those wishing to live in the Bay Area

**A FEW REASONS TO CONSIDER A PRACTICE WITH TPMG:**

- Work-life balance focused practice, including flexible schedules and unmatched practice support.
- We can focus on providing excellent patient care without managing overhead and billing.
- We practice in an environment with patients at the center, deliver culturally responsive and compassionate care to our member populations, and are committed to a culture of equity, inclusion, and diversity.

**CONNECT WITH US:**

We are an EOE/AA/M/F/D/V Employer. VEVRAA Federal Contractor
Central New York

HIRING
BC/BE UROLOGISTS

Associated Medical Professional of New York is seeking BC/BE General and Subspecialized Urologists for Private Equity physician partnership opportunities located in Central New York. New physicians will enjoy partnership with 30 physicians in multiple stages of their career, offering great mentorship. AMP provides quality healthcare at 9 convenient locations and 9 hospitals around CNY. Brand new surgery center, multiple ancillary profit centers, and group call options provide work life balance for physicians. For fellowship trained physicians, there are opportunities to create a niche practice. Qualified candidates will receive a sign on bonus, robust benefits package, competitive salary, transition payment, student loan assistance and moving expenses.

JOIN ONE OF THE FASTEST GROWING GROUPS IN THE COUNTRY!

Central New York is a fantastic place to raise a family and offers all the warmth and charm you can find in the region.

Site visits are being scheduled!

Contact Audrey Barker, Vice President Physician Recruitment
(740) 607-5924 (cell) | abarker@us-uro.com

Associated Medical Professionals

Las Vegas Urology

Urology Times

Are you looking for talent?

Las Vegas Urology would love to welcome you aboard! Living and practicing in the beautiful suburbs of the city, raising a family is hassle free and as pleasant as in any midwestern town. Nevada boasts no state income tax and was recently ranked the #10 city to relocate in the world by money.co.uk.

Las Vegas Urology offers a great starting salary and full benefits package, and our established physicians will welcome you and serve as great mentors. 4-day work weeks and weekend call every fifth week will be offered. If you or someone you know with these qualifications is interested, please inquire with current CV and contact information and we look forward to welcoming you to the team!

EMAIL: Kromero@lasvegasurology.com

Las Vegas Urology

Contact me today to place your ad.

Joanna Shippoli | (440) 891-2615
jshippoli@mjhlifesciences.com

UrologyTimes.com

NEVADA

TexaS

Unique all-cash/no-insurance practice limited to vasectomy, vasectomy reversal, male fertility, low testosterone, and cutting-edge treatment of ED seeks associate leading to partnership. Male fertility and microsurgery fellowship training preferred but willing to train the right candidate. Impeccable interpersonal skills are a must. Located in the North Dallas suburb of Frisco.

Find out more about our practice at www.vasectomyreversalctor.com

Contact Dr. Jeffrey Buch at jbuch0920@gmail.com

Find out more about our practice at www.vasectomyreversalctor.com

Build the team you need

For your recruitment ad needs contact:

Joanna Shippoli
(440) 891-2615
jshippoli@mjhgroup.com
COVID-19 misinformation remains widespread, report indicates

Belief in misinformation is correlated with party affiliation and news source

JEFF BENDIX

Bendix is a senior editor for Medical Economics®.

More than a year and a half into the COVID-19 pandemic, misinformation about the disease and vaccinations remains widespread, and correlated with party affiliation, vaccination status, and where people get their news.

Those are among the results of the latest Kaiser Family Foundation COVID-19 Vaccine Monitor report released earlier in November. It found that 78% of US adults either believe or aren’t certain about at least 1 of 8 false statements regarding the COVID-19 pandemic or vaccines for the disease.

Among unvaccinated adults, 64% either believe or are unsure about at least half of the false statements, compared with 19% of vaccinated adults. Nearly half (46%) of Republicans, and 14% of Democrats, either believe or are unsure about half the statements.

“The findings highlight a major challenge for efforts to accurately communicate the rapidly evolving science about the pandemic when false and ambiguous information and spread quickly, whether inadvertently or deliberately, through social media, polarized news sources, and other outlets,” the authors note.

The most common misconceptions regarding COVID-19 and its vaccines include:

• The government is exaggerating the number of COVID-19 deaths by counting deaths from other factors (38% believe it’s true, 22% aren’t sure).
• Pregnant women shouldn’t get the vaccine (17% believe it, 22% aren’t sure).
• Deaths due to the COVID-19 vaccine are being intentionally hidden by the government (18% believe it, 17% aren’t sure).
• The COVID-19 vaccine causes infertility (8% believe it, 23% aren’t sure).

COVID-19–related misconceptions generally align with which news outlet people find trustworthy for COVID-19 information, the study finds. For example, 46% of those who trust Newsmax, and 37% who trust One America News—both conservative-leaning outlets—believe 4 or more of the false statements, compared with 11% of those who trust CNN, and 12% who trust network news.

In addition, the news outlets people trust for COVID-19–related information line up with party affiliation. Among all those polled, 46% said they had “a great deal” or “a fair amount” of trust in local TV stations, and 45% in network news. But broken down by party, 66% of Democrats and 34% of Republicans say they trust local TV news. For network news, it was 72% and 25%, respectively.

Conversely, 13% overall said they had “a great deal” or “a fair amount” of trust in One America News and Newsmax. Those outlets are watched by 17% and 22%, respectively, of Republicans, but only 10% and 8% of Democrats.

Differences in COVID-19–related misperceptions are particularly stark when it comes to vaccine status and party affiliation. Although 32% of those polled believe 4 or more false statements, the number rises to 64% among the unvaccinated, compared with 19% of those who’ve been vaccinated.

Similarly, 46% of Republicans, and 37% of independents, but only 14% of Democrats, believe 4 or more false statements. A divide also exists according to community type, with 44% of rural respondents, 33% of suburbanites and 26% of urban dwellers believing four or more false statements.

REFERENCE

Good records can save you in a malpractice suit

Complete, clear documentation bolsters your credibility

If it was not charted, it did not happen” may be a cliché, but it sums up the importance of properly and thoroughly charting medical records. Records are vital for providing care; however, once attorneys are involved, medical records also become the basis—and one of the most critical aspects—of medical malpractice defense.

WHY ARE MEDICAL RECORDS IMPORTANT IN CIVIL LITIGATION?

Medical malpractice litigation is built around the patient’s medical records, which provide the only objective documentation of both the plaintiff’s condition and the care provided at a time when there was no conflict or other motivation to conceal or exaggerate the care provided. They also are critical in helping the provider recall events that occurred months or even years ago. Because it is the health care provider’s responsibility to document, medical records become extremely important in providing a defense.

As a result, judges and juries often consider medical records to be one of the most trustworthy and probative pieces of evidence in the case. Therefore, well-documented medical records provide the best defense for providers. The inverse is also true; poorly documented medical records may become strong evidence of an incompetent provider. Although poor records do not automatically show negligence, the patient’s attorney will use it to argue subpar care.

WHAT IF THERE IS MISSING OR INCOMPLETE INFORMATION?

Go back to: “If it was not charted, it did not happen.” The patient’s attorney certainly will use this, or at least keep it in mind, when prosecuting the case. The patient’s attorney will attack the provider’s credibility by showing the incomplete records. During the provider’s deposition, the patient’s attorney may use skilled cross-examination to obtain the health care provider’s testimony of their recollection about the care provided. A few evidently unimportant details now become the focal point of the patient’s allegations and, therefore, the jury deliberations. The patient’s attorney will argue that if the physician or nurse had provided a specific treatment, then the patient’s injuries would not have happened. If the patient’s attorney can show that important information is missing from the records, then it is not a far leap for the jury to find that the missing information supports the patient’s claims.

Although poor records do not automatically show negligence, the patient’s attorney will use it to argue subpar care.

This attack on credibility may occur even if the information is not necessarily missing. For example, many systems for electronic health records have prefilled data. Often, the provider entering the patient’s information will not update or change the prefilled data. It then becomes difficult to argue that certain assessments occurred because the same word-for-word language is used throughout the patient’s record. It should also be noted that when dealing with electronic health records, parties can hire an expert to conduct a metadata audit, which will provide a complete analysis of every keystroke, the timing of the entries, who made the entries, and how long the document was open for review and revision. If it is shown that the medical record was altered, it can expose the provider to punitive damages and a medical board investigation.

Neither patient nor physician wants or expects to get involved in civil litigation arising from the medical care provided. Unfortunately, it happens. When it does, the provider will be grateful that they took care to follow best practices in the record documentation by charting timely, thoroughly, and consistently.

EHR outages and patient safety

“On October 4, 2021, the social media platform Facebook and its subsidiaries Instagram and WhatsApp experienced an unprecedented system outage lasting over 6 hours. Although the computer glitch inconvenienced 18 million users and adversely affected small businesses dependent on the technology for sales, it’s doubtful that anyone died. Unfortunately, the same can’t be said when system outages affect health care facilities,” writes Rebekah Barnard, MD, in an article in Medical Economics®.
THE RIGHT SOLUTION FOR MOST OF YOUR BPH PATIENTS

A low-risk way to make a real difference1,2

• The #1 minimally invasive BPH procedure chosen by urologists3
• Can be performed in-office/outpatient with local anesthesia and rapid recovery4,5
• Preserves6 and possibly improves7 sexual function
• Lowest catheterization rate of leading BPH procedures4,6,8-11
• Effective alternative to drug therapy without heating, cutting or removing prostate tissue2,12
• Proven, durable results as shown by Healthcare Claims and Utilization Analysis1 and L.I.F.T. Study6

These benefits are based on controlled studies and/or real world outcomes.1,11
Treat a broad spectrum of anatomies with confidence

The Prostatic Urethral Lift with the UroLift® System is included in the standard of care in the 2020 AUA BPH Guidelines.

Treats symptoms due to urinary outflow obstruction secondary to BPH, including lateral and median lobe hyperplasia, in men 45 years or older, with prostates < 100 cc.

UroLift.com
Stay informed of the latest data, practice advice, and products & devices

Watch

Scan QR code or visit: www.urologytimes.com/uroview