**Target: Bladder cancer**

Genetic testing, targeted therapies signal a new era of precision medicine

Lisette Hilton / UT Correspondent

The FDA announced in April 2019 that it had approved erdafitinib (Balversa), the first personalized therapy targeting a genetic alteration for treatment of advanced bladder cancer.

“We’re in an era of more personalized or precision medicine, and the ability to target cancer treatment to a patient’s specific genetic mutation or biomarker is becoming the standard,” Richard Pazdur, MD, acting director of the FDA Oncology Center of Excellence, said at the time of the approval.

There are other firsts when it comes to erdafitinib. It is the first fibroblast growth factor receptor 3 (FGFR3) inhibitor and first oral agent approved for the treatment of bladder cancer, according to Arlene Sieker-Radliff, MD, professor of genitourinary medical oncology at The University of Texas MD Anderson Cancer Center, Houston.

Determining if advanced bladder cancer patients are candidates for the FGFR3 inhibitor involves genetically testing bladder cancer tumor tissue for the presence of an FGFR mutation, according to Yair Lotan, MD, professor and chief of urologic oncology at UT Southwestern Medical Center in Dallas.

“For bladder cancer patients who have either metastatic disease or patients with advanced disease who might become metastatic, there is value in knowing whether or not they have FGFR mutations, so one would know whether or not erdafitinib is a treatment option available to them,” Dr. Lotan said.

Tumor genetic testing with a tumor specimen is different than the clinical genetic testing for germline heritable mutations, according to Elizabeth Pimplack, MD, MS, chief of genitourinary medical oncology at Fox Chase Cancer Center, Philadelphia.

See **BLADDER CANCER**, on page 10

**Inside**

- **KIDNEY STONES**
  Novel thulium laser fiber appears to outperform Holmium:YAG laser

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  Trial supports combined behavioral, medical approach to treating OAB

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- **SEXUAL DYSFUNCTION**
  Low-fat diet associated with lower testosterone level

**PROSTATE CANCER**

**Addressing PCa’s racial disparity**

Several decades of data show that Black men are less likely to be screened and treated for prostate cancer than their white counterparts. In this interview, Kelvin A. Moses, MD, PhD, of Vanderbilt University Medical Center, Nashville, TN discusses the reasons for these disparities and how practicing urologists can address them.

For the full interview, turn to page 18

**KEY FDA NEW DRUG APPROVALS IN BLADDER CANCER, 2016-2020**

- **Atezolizumab (TECENTRIQ)**
  Locally advanced or metastatic urothelial carcinoma (UC) in patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1, or are not eligible for any platinum-containing chemotherapy regardless of level of tumor PD-L1 expression

- **Nivolumab (Opdivo)**
  Locally advanced or metastatic UC in patients who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemo

- **Durvalumab (Imfinzi)**
  Locally advanced or metastatic UC in patients who have disease progression during or following platinum-containing chemotherapy or whose disease has progressed within 12 months of receiving platinum-containing chemo before or after surgery

- **Avelumab (BAVENCIO)**
  Locally advanced or metastatic UC in patients who have disease progression during or following platinum-containing chemotherapy or who have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemo

- **Pembrolizumab (KEYTRUDA)**
  Locally advanced or metastatic UC in patients who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1; or in patients who are not eligible for platinum-containing chemo regardless of PD-L1 status

- **Erdafitinib (BALVERSA)**
  For adults with locally advanced or metastatic UC that has susceptible fibroblast growth factor receptor 3 (FGFR3) or FGFR2 genetic alterations and who have progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemo

- **Enfortumab vedotin-ejfv (PADCEV)**
  Locally advanced or metastatic UC in patients who have previously received a PD-1/L1 inhibitor and a platinum-containing chemotherapy before or after surgery or in a locally advanced or metastatic setting

- **Pembrolizumab**
  For patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, nonmuscle-invasive bladder cancer with carcinoma in situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy
The UroLift System procedure is FDA-cleared for the treatment of symptoms due to urinary outflow obstruction secondary to BPH, including lateral and median lobe hyperplasia, in men 45 years of age or older. Results and patient experience may vary. Most common adverse events reported include hematuria, dysuria, micturition urgency, pelvic pain, and urge incontinence. Most symptoms were mild to moderate in severity and resolved within 2 to 4 weeks after the procedure. Consult the Instructions for Use (IFU) for more information.


I went from getting up 3 times a night to sleeping through 6-8 hours! What a difference it has made at work as well. I can now complete longer surgeries without urgency to void.

Philip Butler, M.D., F.A.C.S. Genesis Healthcare Partners and UROLIFT® SYSTEM PATIENT

MAIN REASONS I CHOSE THE UROLIFT® SYSTEM AND RECOMMEND IT TO MY PATIENTS

Patients have a better recovery experience than TURP, with durable results and no new and lasting sexual dysfunction*1-5
Rapid relief and recovery in days, not months
Lowest catheter rate of the leading BPH procedures
The only leading BPH procedure that does not destroy tissue
Proven durability through 5 years
Real world outcomes consistent with randomized controlled data*

To learn more about My Story, visit www.info.UroLift.com/Butler
Check out the data at UroLift.com

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*Dr. Butler is a paid consultant of NeoTract | Teleflex. Results may vary.
**No instances of new, sustained erectile or ejaculatory dysfunction in the FDA pivotal study.

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Chairman’s Letter

Expanding the treatment armamentarium for bladder Ca

MIKE HENNESSY, SR
Mike Hennessy, Sr. is Chairman and founder of Urology Times’ parent company, MJH Life Sciences.

The specialty of urology has a long-standing reputation for innovation as part of a relentless, unending quest to improve the care of patients. One noteworthy example providing the focus for this month’s cover feature is bladder cancer.

The past several years have seen a flurry of activity in the bladder cancer space. Just last month, we highlighted the FDA approvals of enfortumab vedotin-ejfv (PADCEV) as well as a new indication for anti-PD-1 therapy pembrolizumab (KEYTRUDA). We also reported on phase III data evaluating radiolabeled small molecule that binds to prostate-specific membrane antigen, as well as a study of a new indication for anti-PD-1 therapy pembrolizumab (KEYTRUDA).

This month, we look at the emergence of tarcevax (page 12), the latest installment of “Hands On,” in which several experts in the field, also explores bladder cancer tests currently available and in the pipeline. One such test, Cabladder, is also discussed in a report on page 9.

Our February issue contains a plethora of prostate cancer content, leading off with “Journal Article of the Month,” in which Badar M. Mian, MD, analyzes a recent study comparing functional outcomes of localized prostate cancer treatments (page 12). We also report on a phase II trial of a radioabeled small molecule that binds to prostate-specific membrane antigen, as well as a study evaluating chronic opioid use following prostatectomy.

Continuing our prostate cancer coverage this month is the latest installment of “Hands On,” in which Parth Patel, MD, Alex Belshoff, MD, PhD, and Gopal Gupta, MD, present a case for transperineal prostate biopsy (page 16). Urology Times Editorial Consultant J. Brantley Thrasher, MD, provides thoughtful commentary on this article for this month’s “From the Board” editorial (page 5).

The issue of racial disparity in prostate cancer treatment is also explored this month: On page 18, Dr. Thrasher interviews Kelvin A. Moses, MD, PhD, on the subject, while the latest installment of “Speak Out” features discussion of recent studies regarding active surveillance and radiation in African-American men (page 26).

Our clinical coverage continues on page 27 with an article about a promising investigational tool for kidney stone ablation. In the area of overactive bladder, we report on a recent study supporting a combined behavioral/medical therapy approach to treating men with lower urinary tract symptoms of OAB (page 28). For BPH, look for coverage of a retrospective study examining prostate artery embolization for treating urinary retention and gross hematuria in non-index BPH patients (page 29).

We wrap up this month’s clinical content with a report on a recent study examining the association between a low-fat diet and testosterone levels (page 30) as well as an article about a clinical trial of a paclitaxel-coated balloon for the treatment of recurrent bulbar urethral strictures (page 31).

This month’s slate of columns leads off with “Coding and Reimbursement,” in which Jonathan Rubenstein, MD, and Mark Painter outline what you need to know about Category III CPT codes (page 12). For “Practice Matters,” Robert A. Dowling, MD, examines the costs of participation (and non-participation) in the Merit-based Incentive Payment System (page 14). In “Money Matters,” Jeff Witt, CFP, gives an overview of important IRS updates for 2020 (page 38).

In addition to our regular columns, this month’s issue features a helpful breakdown of what urologists should know about non-compete agreements in contracts (page 39). And be sure to read UT Clinical Practice Board Member Henry Rosevear, MD, insightful column on the challenges of recruiting a urologist to his group practice (page 40).

This February issue concludes with “Malpractice Consult,” for which Acacia Brush Perko, Esq., analyzes the case of a pediatric patient suffering from antenatal hydronephrosis that led to a costly settlement (page 42).

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TP-Bx: The answer to rising infectious complications?

J. BRANTLEY THRASHER, MD
Dr. Thrasher, a Urology Times editorial consultant, is executive director of the American Board of Urology, Charlottesville, VA.

The transrectal ultrasound-guided approach to prostate biopsy (TRUS-BX) has been one of the more frequently performed procedures for urologists for almost two decades. For many of us, it presented a significant advance in biopsy, using ultrasonic guidance to more accurately image the prostate in lieu of digital rectal palpation. It also spared countless finger and glove biopsies known to be a significant occupational hazard. However, the use (and misuse) of antibiotics such as fluoroquinolones has resulted in growing concern over fluoroquinolone-resistant (FQR) rectal flora and infectious complications following TRUS-BX.

A variety of strategies have been reported to address this concern. Identifying patients as high risk for quinolone resistance and adding a single dose of 1M gentamicin or a second-generation cephalosporin such as ceftriaxone has been one effective strategy (J Urol 2013; 189:1769–75). More recently, authors have successfully employed povidone-iodine rectal washes as an inexpensive agent to reduce post-biopsy infection and avoid additional antibiotic use (J Vis Exp 2015; [103]:52670). The transperineal approach to prostate biopsy (TP-BX) has seen a resurgence in popularity due to a lower risk of infectious complications (Urology 2013; 81:1142–6; BJU Int 2014; 114:384–8) and a similar prostate cancer detection rate (World J Surg 2019; 17:31). (See this month’s Hands On article, page 16.) However, widespread adoption has been hampered by the perceived problems of the need for general anesthesia to complete the biopsy and the subsequent increase in time and cost versus TRUS-BX.

Recent reports from the UK and Australia have described a more standardized local anesthetic approach to TP-BX that combines locally anesthetized perineal skin with a subcutaneous perineal nerve block combined with a standard periprostatic nerve block (Prostate Cancer Prostatic Dis 2017; 20:311–7; BJU Int 2017; 120:164–7). The authors reported excellent anesthesia, based on a patient-reported visual analog pain score. However, the approach was slightly different in the UK study, which included the addition of oral analgesia along with topical 2% diltiazem ointment and the use of lidocaine-infused gel into the rectum. These differences highlight the most significant impediment to the widespread adoption of TP-BX technique—the lack of a standardized protocol for anesthesia that provides a simple cost- and time-efficient biopsy technique as an alternative to TRUS-BX.

I don’t believe the issue here is that urologists are so firmly entrenched in TRUS-BX that they won’t embrace the need for an innovative strategy to reduce the risk of infectious complications. Urologists have proven to be innovators in a multitude of areas, including early adoption of ESWL, lasers, and robotics. Most see the wisdom of avoiding biopsies through the rectum as the flora continues to adapt to our strategies of adjusting antibiotic prophylaxis. However, a more standardized protocol that is office based, reliable, and reproducible as well as cost- and time-efficient is required to entice more urologists to abandon the TRUS-BX approach.

A more standardized protocol that is office based, reliable, and reproducible as well as cost- and time-efficient is required to entice more urologists to abandon the TRUS-BX approach.

FEEDBACK
Send your comments to Dr. Thrasher c/o Urology Times, at urology_times@mmhgroup.com

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

IMPORTANT SAFETY INFORMATION
WARNINGs AND PRECAUTIONS
Ischemic Cardiovascular 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, 6 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from an ischemic cardiovascular event. Patients with current evidence of unstable angina, myocardial infarction, or congestive heart failure within 6 months of randomization were excluded from the SPARTAN and TITAN studies.

Ischemic cardiac events, including events leading to death, occurred in patients receiving ERLEADA®. Monitor for signs and symptoms of ischemic heart disease. Optimize management of cardiovascular risk factors, such as hypertension, diabetes, or dyslipidemia. Consider discontinuation of ERLEADA® for Grade 3 and 4 events.

Fractures—In a randomized study (SPARTAN) of patients with nmCRPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. 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.

Falls—In a randomized study (SPARTAN), falls occurred in 16% of patients treated with ERLEADA® compared with 9% of patients treated with placebo. Falls were not associated with loss of consciousness or seizure. Falls occurred in patients receiving ERLEADA® with increased frequency in the elderly. Evaluate patients for risk of falls.

Seizure—In 2 randomized studies (SPARTAN and TITAN), 5 patients (0.4%) treated with ERLEADA® and 1 patient treated with placebo (0.1%) experienced a seizure. Permanently discontinue ERLEADA® in patients who develop a seizure.

References:
1. ERLEADA® (Prescribing Information). Horsham, PA: Janssen Biotech, Inc. 2019 8/19 cp-94339v1

NEW INDICATION
Now approved for the treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).

ERLEADA® + ADT reduced the risk of death by 33% vs placebo + ADT†

(Median overall survival was not estimable in either arm: HR=0.67; 95% CI: 0.51, 0.89; P=0.0053)

Hypothyroidism—In 2 randomized studies, hypothyroidism was reported in 1% of patients treated with placebo 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.

DURG 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. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability (see Dosage and Administration (2.2)).

Effect of ERLEADA® on Other Drugs—ERLEADA® is a strong inducer of CYP3A4 and CYP19, and a weak inducer of CYP3A5 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 UGT glycosuronidase 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.

P-gp, BCRP, or OATP1B1 Substrates—Apalutamide is a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1).Clinically. Concomitant use of ERLEADA® with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP, or OATP1B1 must be co-administered with ERLEADA® and evaluate for loss of activity if medication is continued.

Please see Brief Summary of full Prescribing Information for ERLEADA® on subsequent pages.

*All patients who enrolled in the TITAN study started ADT for mCSPC 6 months prior to randomization.

Study Design: TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC (N=1052). Patients had de novo mCSPC or relapsed metastatic disease after initial diagnosis of localized disease. All patients in the TITAN trial received a concomitant GnRH agonist or had a bilateral orchiectomy. Patients with visceral, liver, or lung metastases as the only sites of metastases were excluded. Patients were randomized 1:1 to receive ERLEADA® 240 mg orally once daily + ADT or placebo orally once daily + ADT. The dual primary endpoints were overall survival and radiographic progression-free survival.\[11\]
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), acute respiratory arrest (n=1), sudden unexpected death in sleep (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 4% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption occurred in 23% of patients; the most frequent (≥1%) were rash, fatigue, and hypotension. 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 (nmCRPC). The safety signal of rash is lower when compared to placebo. Table 2 shows laboratory abnormalities that occurred in ≥5% of patients, and more frequently (≥5%) in the ERLEADA arm compared to placebo.

### Table 1: Adverse Reactions in TITAN (nmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
<th>Between Arm Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>24.7%</td>
<td>15.5%</td>
<td>0.1%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6.0%</td>
<td>1.9%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>7.0%</td>
<td>0.6%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>0%</td>
<td>0.2%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

### Table 2: Laboratory Abnormalities Occurring in ≥15% of ERLEADA-Treated Patients and at a Higher Incidence than Placebo (Between Arm Difference > 5% All Grades) in TITAN (nmCRPC)

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=524</th>
<th>Placebo N=527</th>
<th>Between Arm Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>System/Oral Class</th>
<th>ERLEADA N=803</th>
<th>Placebo N=938</th>
<th>Between Arm Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General adverse and administration site conditions</td>
<td>28%</td>
<td>5.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

### 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=938</th>
<th>Between Arm Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

### Table 5: 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=328</th>
<th>Placebo N=398</th>
<th>Between Arm Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hypomagnesemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Hyperuricaemia</td>
<td>0%</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
ERLEADA® (apalutamide) tablets

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

CYP3A, CYP2C19, and UGT Substrates

ERLEADA is a strong inducer of CYP34A and CYP2C19, and a weak inducer of CYP3A4 in humans. Concomitant use of ERLEADA with medications that are primarily metabolized by CYP34A, CYP2C19, or CYP3A4 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].

P-gp, BCRP or OATP1B1 Substrates

Apalutamide was shown to be a weak inducer of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide 1B1 (OATP1B1) clinically. At steady-state, apalutamide reduced the plasma exposure to fexofenadine (a P-gp substrate) and rosuvastatin (a BCRP/OATP1B1 substrate). Concomitant use of ERLEADA with medications that are substrates of P-gp, BCRP, or OATP1B1 can result in lower exposure of these medications. Use caution if substrates of P-gp, BCRP or OATP1B1 must be co-administered with ERLEADA and evaluate for loss of activity if medication is continued [see Clinical Pharmacology (12.3) in full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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 at pregnancy [see Clinical Pharmacology (12.1) in full Prescribing Information]. There are no human data on the use of ERLEADA in pregnant women. ERLEADA is not indicated for use in females, so animal embryo-fetal developmental toxicity studies were not conducted with apalutamide.

Contraception

Females and Males of Reproductive Potential

Males

Contraception

Based on the mechanism of action and findings in an animal reproduction study, advise male patients 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].

Infertility

Based on animal studies, ERLEADA may impair fertility in males of reproductive potential [see Nonclinical Toxicology (13.1) in full Prescribing Information].

Pediatric Use

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

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 years 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 39% 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.

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).

Ischemic Cardiovascular Events

Inform patients that ERLEADA has been associated with ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular event occur [see Warnings and Precautions].

Falls and Fractures

Inform patients that ERLEADA is associated with an increased incidence of falls and fractures [see Warnings and Precautions].

Seizures

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].

Death

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

Dosage and Administration

Inform patients receiving concomitant gonadotropin-releasing hormone (GnRH) analog therapy that they need to maintain this treatment during the course of treatment with ERLEADA.

Inform patients to take their dose at the same time each day (once daily). ERLEADA can be taken with or without food. Each tablet should be swallowed whole.

Inform patients that in the event of a missed daily dose of ERLEADA, they should take their normal dose as soon as possible on the same day with a return to the normal schedule on the following day. The patient should not take extra tablets to make up the missed dose [see Dosage and Administration (2.1) in full Prescribing Information].

Embryo-Fetal Toxicity

Inform patients that ERLEADA can be harmful to a developing fetus. Advise male patients with female partners of reproductive potential to use 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].

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cp-50510v2
Bladder cancer biomarker test accurately adjudicates atypical cytology

Study reaffirms test’s performance in ruling out cancer in patients undergoing hematuria evaluation

Cheryl Guttman Krader
UT Contributing Editor

Findings from a retrospective analysis pooling data from four studies investigating the performance of a urinary bladder cancer biomarker test (Cxbladder) demonstrate that it accurately adjudicated atypical cytology, including in cases that also had equivocal cystoscopy.

The study also reaffirms the biomarker test’s performance for accurately ruling out bladder cancer in both patients undergoing evaluation for hematuria and those being monitored for recurrence of bladder cancer.

“The results of our retrospective study support taking advantage of the Cxbladder test to identify patients who should be further evaluated for cancer and to spare those who likely do not have cancer from an unnecessary workup.”

BADRINATH KONETY, MD, MBA

The research was summarized in a paper published in European Urology (2019; 76:238–43). “Previous studies have only evaluated the accuracy of Cxbladder for ruling out bladder cancer, but they did not analyze its value for atypia adjudication,” lead author Badrinath Konety, MD, MBA, told Urology Times. “Up to 20% to 25% of urine cytology samples may be classified as atypical by local cytology, and the AUA/SUO joint guideline for diagnosis and treatment of nonmuscle-invasive bladder cancer suggests it is reasonable to use a second test to adjudicate equivocal cytology.

“The results of our retrospective study support taking advantage of the Cxbladder test to identify patients who should be further evaluated for cancer and to spare those who likely do not have cancer from an unnecessary workup,” added Dr. Konety, professor of urology and director of the Institute for Prostate and Urologic Cancers, University of Minnesota Medical School, Minneapolis.

Cxbladder is a multiplex mRNA test that measures concentrations of five genes in unfractionated urine. There are three versions of the test that are used in different clinical settings and that incorporate different clinical information in the prediction algorithm that determines the test result.

The retrospective study pooled data from 1,784 patients who participated in three prospective clinical trials and one real-world clinical study investigating the diagnostic performance of the Cxbladder tests. Ultimately, data were analyzed for 852 samples from 775 patients for which there were results from both the urine biomarker test and local cytology.

Of the 852 samples, 436 were from patients being evaluated for hematuria and 416 were from patients previously diagnosed with urothelial cancer (UC). A subgroup of 153 samples from 146 samples had atypical cytology, of which 14 had both atypical cytology and equivocal cystoscopy results.

Slightly higher negative predictive value seen

Analyses comparing the diagnostic performance of Cxbladder with cytology showed that the urinary biomarker test had a slightly higher negative predictive value, 97.4% versus 92.6%. "More noteworthy, however, was the finding that Cxbladder had a much lower false-negative rate than cytology, missing only 8.5% of pathology-confirmed tumors compared with 63% that were missed by cytology.

In the subgroup of 153 samples with atypical cytology, 26 (17%) were confirmed by pathology as positive for UC. Cxbladder correctly identified all 26 tumors, including the two found in the 14 patients who had atypical cytology and equivocal cystoscopy.

"The latter two cases were high-risk tumors and included a high-grade ≥T1 UC and one carcinoma in situ," said Dr. Konety. "Further study is warranted to investigate the value of Cxbladder in cases where cytology is atypical and cystoscopy is indeterminate."

Dr. Konety conducts research for Pacific Edge, several of his co-authors are researchers/consultants for Pacific Edge, and one co-author is an employee of the company.

ROLLING SUBMISSION OF BLA FOR BLADDER CANCER TREATMENT INITIATED

Sesen Bio recently announced that it has initiated the submission of its Biologics License Application (BLA) for Vicinium for the treatment of bacillus Calmette–Guérin-unresponsive nonmuscle-invasive bladder cancer (NMIBC) under Rolling Review to the FDA. Vicinium was granted Fast-Track Designation by the FDA in 2018.

The company reported that it has submitted completed non-clinical and clinical modules, and a partially completed Chemistry, Manufacturing and Controls (CMC) module.

Sesen Bio said it anticipates completing the BLA submission with the finalization of the CMC module in 2020. If the FDA accepts the BLA filing, the company plans to request a Priority Review.

Vicinium is currently in a phase III registration trial for the treatment of high-risk, BCG-unresponsive NMIBC. Vicinium is a locally administered targeted fusion protein composed of an anti-EPCAM antibody fragment tethered to a truncated form of Pseudomonas Exotoxin A for the treatment of high-risk NMIBC.

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“Fortunately, with bladder cancer we often have banked tissue from a patient’s biopsy or surgery,” Dr. Plimack said. “But it’s really the medical oncologist that’s going to order the test and choose which specimen to send because the test result is most relevant at the point of metastases. A patient with localized disease may never be metastatic or be a candidate, in which case they do not require testing. For a patient with metastatic disease who then quickly recurs, based on currently available data, they should go through prior treatment before erdafitinib makes sense. Erdafitinib is not usually a first-line treatment.”

Urologists often see bladder cancer patients whose disease has progressed despite standard treatment that might involve surgery and chemotherapy. Some metastatic patients have had the option of immunotherapy, but if that was ineffective, treatment options were limited, according to urologist Badrinath Kone, MD, MBA, professor of urology at the University of Minnesota, Minneapolis. Now, with erdafitinib, which binds to FGFR1, FGFR2, FGFR3, and FGFR4, many of these patients have a new option for second-line therapy.

“The other option of course is immunotherapy,” Dr. Koney said. “The advantage of erdafitinib is that it’s oral, it seems to be well-tolerated, and it’s based on a receptor that is more widely expressed as opposed to PD-1 or PD-L1, which are not as widely expressed. The FGFR mutation is one of the most common mutations you’ll find in bladder cancer, so more patients may be eligible for this treatment.”

The urologist’s role in erdafitinib treatment could soon expand.

“There are some clinical trials that are looking at FGFR inhibitors in patients with Bacillus Calmette-Guerin (BCG)-unresponsive disease,” Dr. Lotan said. “It wouldn’t be standard of care to test for FGFR in a patient without advanced disease, but that doesn’t mean that in the near future—the next few years—it won’t become something of value.”

Biomarkers, in general, have many potential uses in bladder cancer treatment. In fact, the International Consultation of Urologic Diseases has devoted 2020 to molecular markers and their roles in bladder, prostate, and other urologic cancers, according to Dr. Lotan, who is editor for the ICUD’s bladder section.

The importance of tissue testing

Erdafitinib’s approval and potential impact on response rate and survival highlight why it’s increasingly important for patients to have their tumor tissues tested, according to Dr. Siefker-Radtke.

“In the phase II trial [N Engl J Med 2019; 381:338-48], the response rate was about 40% in patients with FGFR-altered tumors, and overall median survival was about 13.8 months,” said Dr. Siefker-Radtke, who led the phase II trial.

“In a group of patients who have progressed despite chemotherapy, that’s a promising result and provides patients an opportunity for an additional treatment if they have an FGFR3 alteration, Dr. Siefker-Radtke said.

“It’s important to test patients with incurable bladder cancer when they are first diagnosed with stage 4 disease because obtaining the tissue takes time,” Dr. Siefker-Radtke said.

“Knowing the presence of this mutation early allows patients to either participate in clinical trials of oral agents targeting FGFR3 or even consider some combination strategies for targeting FGFR3,” she said.

The bigger picture

FGFR3 is among the early targets identified in bladder cancer. About 60% of patients with low-grade, low-stage bladder cancer are thought to have FGFR3 alterations. And the prevalence of these alterations is estimated to be from 15% to 20% in patients with stage 4 urothelial bladder tumors, Dr. Siefker-Radtke said.

“This may actually be higher in urothelial tumors of the renal pelvis where the presence of these mutations has been reported as high as 35%,” she said.

Patients with upper urinary tract cancer have even fewer treatment options and less definitive data from clinical trials. If the trial data on erdafitinib in patients with upper tract tumors does pan out, “that’s a real need that could be filled by this drug,” Dr. Koney said.

Dr. Siefker-Radtke said testing for FGFR3 mutations in advanced bladder cancer patients is top priority when she is testing for mutations.

“Following that, there is more limited data on the need for additional testing,” she said. “There is some data that if a patient is not eligible for cisplatin and their tumors are PD-L1 high, then they might benefit from a single-agent immune checkpoint inhibitor. So, that would be the second marker that I would consider testing, but only in patients who haven’t had prior chemotherapy for their stage 4 disease,” Dr. Siefker-Radtke said.

The FDA has approved several checkpoint inhibitors for advanced bladder cancer, but only about one in five patients benefit from these agents, according to Dr. Siefker-Radtke.

Promising novel agents are targeting other pathways, including the human epidermal growth factor receptor 2 (HER2) pathway and mammalian target of rapamycin (mTOR) pathway, but trials looking at those pathways in the setting of bladder cancer have not yet demonstrated strong benefit, Dr. Lotan said.

“There have been rare patients who have had success from other targeted therapies. But no other targeted therapy has been uniformly approved for patients with bladder cancer,” he said.

Present, future bladder cancer tests

Molecular testing in bladder cancer is limited at this time, according to Dr. Lotan.

“Most people use urine cytology. Some people use UroVysion, which is a FISH [fluorescence in situ hybridization] assay for patients who have atypical cytology. It is a genetic marker looking for chromosomal abnormalities in cells in the urine. It probably should be used selectively, if at all,” he said. Additional diagnostic urine tests for recurrent bladder cancer are BTA STAT, BTA TRAK, and NMP22.

Another available group of tests is the CxBladder (Pacific Edge), which combines biomarker genes with known bladder cancer risk factors to help rule out cancer in patients with hematuria. (Also see, “Bladder cancer biomarker test accurately adjudicates atypical cytology,” page 9).
was among the researchers to study CxBladder. Dr. Lotan estimates there are 20 to 30 markers in development for bladder cancer detection or surveillance that have yet to be validated. This includes the UroSEEK test, developed by Johns Hopkins researchers, which detects DNA mutations identified with urothelial cancers in urine samples.

Dr. Lotan continues to study the Decipher Bladder test, a genetic test aimed at classifying muscle-invasive bladder cancer's molecular subtype. This test may help determine which patients might benefit from neoadjuvant chemotherapy before radical cystectomy or accurate staging of the disease.

“There is still some validation that needs to be done before the Decipher test should be used routinely,” Dr. Lotan said.

“It’s important to know what the goals of the test are and how it would change management of the patient. For many markers, it’s not yet clear how they would change management.”

YAIR LOTAN, MD

In fact, there are multiple trials using biomarkers looking to predict which patients would and would not likely respond to chemotherapy, according to Dr. Lotan.

“There is significant interest in trials that are trying to identify patients who are highly likely to respond with the hope that they may be enrolled and spare their bladder,” he said. “There is also interest in identifying which patients might have micrometastatic disease after the bladder is removed so they may get adjuvant therapy.”

Understand before you educate

Dr. Lotan said it’s important for urologists and other providers to validate clinical benefits before using any genetic testing.

“It’s important to know what the goals of the test are and how it would change management of the patient. For many markers, it’s not yet clear how they would change management. While they provide additional information over clinical information alone, sometimes that information doesn’t tell you exactly what to do and in many cases it can lead to anxiety and added costs,” he said.

Pursuing more targeted treatment for bladder cancer is one of many areas of study to optimize bladder cancer treatment, according to Dr. Plimack.

“I think we’re looking at every angle we can,” she said. “We’ve looked at immunotherapy and harnessing the immune system. There is cellular therapy on the horizon for urothelial cancer, with engineered T-cell therapy. There is standard targeted therapy like erdafitinib. There’s targeted chemotherapy with enfortumab vedotin, an antibody drug conjugate where the antibody is tagged to the target on the tumor cell but the conjugate is a chemo drug. And we’re still refining how we give regular chemotherapy and whether to give it in combination versus separately.”
Functional outcomes following treatment for clinically localized prostate cancer depend not only on the type of treatment but also the severity of disease and baseline functional characteristics. The prospective, population-based, Comparative Effectiveness Analysis of Surgery and Radiation (CEASAR) study was designed to inform men of the comparative harms of contemporary prostate cancer treatment options. A recent report from this observational study analyzed functional outcomes up to 5 years after treatment of localized prostate cancer stratified by disease risk category (JAMA 2020; 323:149-63).

Men with clinically localized prostate cancer from five population-based Surveillance, Epidemiology, and End Results Program registries and the observational Cancer of the Prostate Strategic Urologic Research Endeavor registry were recruited from 2011 to 2012. Patients completed the 26-item EPIC and 36-Item Short Form surveys (score range, 0-100) at baseline, 6 months, and 1, 3, and 5 years after treatment. Favorable-risk disease was defined as clinical stage cT1 to cT2aN0M0, PSA <20 ng/mL, and Grade Group 1-2) and unfavorable-risk disease defined as clinical stage cT2cN0M0, PSA of 20-50 ng/mL, or Grade Group 3-5. There was no statistically significant difference in prostate cancer-specific survival between favorable- and unfavorable-risk groups at 5 years.

Of the 1,386 men with favorable-risk disease, 675 (49%) underwent nerve-sparing prostatectomy, 363 (26%) underwent active surveillance, 261 (19%) underwent external beam radiation therapy (no androgen deprivation therapy), and 87 (6%) underwent brachytherapy. Clinically meaningful declines in sexual function scores from baseline to 5 years were seen in each group, including −32 for nerve-sparing prostatectomy, −32 for EBRT, −22 for brachytherapy, and −20 for active surveillance. Compared to active surveillance, there was worse sexual function score in the nerve-sparing prostatectomy group (mean difference, −15.2) at 3 years and the brachytherapy group at 1 year (mean difference, −10.1). At 5 years, men who underwent prostatectomy reported a modestly higher rate of erections insufficient for intercourse compared with men on active surveillance (57% vs. 61%, p<0.001).

At 5 years, prostatectomy was associated with worse urinary incontinence score compared with all other options by a median difference of 10-12 points (p<0.001). However, prostatectomy was associated with better urinary irritative function than active surveillance and brachytherapy with a median difference of 5-6 points (p<0.001). At 5 years, nerve-sparing prostatectomy was associated with a slightly higher rate of incontinence than active surveillance (10% vs. 7%, p=0.04). Brachytherapy was associated with worse bowel function score at 1 year compared with active surveillance and nerve-sparing prostatectomy (adjusted mean difference, −5.0, p<0.001).

In the unfavorable-risk group of 619 men, 402 (65%) underwent prostatectomy and 217 (35%) underwent EBRT+ADT. In men who had erections sufficient for intercourse at baseline, 63 of 204 (31%) treated with prostatectomy and 37 of 80 (46%) treated with EBRT and ADT reported sufficient erections at 5 years. At 5 years, EBRT+ADT was associated with a lower likelihood of insufficient erections (75% vs. 80%, p=0.01); however, there was no difference in sexual bother score between the groups.

EBRT+ADT was associated with better incontinence function than prostatectomy (5 year adjusted mean difference, 23.2, p<0.001). At 5 years, EBRT+ADT had a lower rate of moderate or big problems (bother) with urinary function (13% vs. 17%, p<0.005). Men treated with EBRT+ADT reported a clinically meaningful decline in bowel function. When compared to prostatectomy, EBRT+ADT was associated with worse bowel function scores at 1 year (adjusted mean difference, −4.1, p<0.001).

EBRT+ADT was associated with clinically meaningful decline in hormonal function from a median domain score of 90 at baseline to a low of 81 at 6 months. Men treated with EBRT+ADT had a statistically significantly worse hormone function than prostatectomy, which was clinically meaningful only at 6 months (adjusted mean difference, −5.3, p<0.001).

Decline in sexual function noted with all treatment options
Irrespective of treatment, fewer than half of men reported the ability to maintain erections sufficient for intercourse at 5 years. Prostatectomy was associated with worse 5-year sexual function scores than EBRT+ADT in the unfavorable-risk group; however, sexual bother scores were similar. Prostatectomy was associated with worse urinary incontinence while brachytherapy had worse urinary irritative function and bowel function. Similarly, men who received EBRT+ADT reported clinically meaningful worsening of bowel and hormonal functions.

The data are not clear about unilateral or non-nerve-sparing surgery or the duration of ADT. For unfavorable-risk cancer, it is common practice to use ADT with EBRT for 18 to 36 months. Yet, the clinically meaningful decline in hormonal function in this study was only noted at 6 months. This may be due to shorter duration of ADT, resulting in lesser decline in the hormonal and sexual functions noted with EBRT+ADT.

Men in all treatment groups experienced clinically meaningful declines in sexual function and urinary function, including those on active surveillance, but the differences in functional scores diminished over time. This information on comparative functional decline, especially when stratified for risk category, is quite useful when counseling patients about the comparative adverse outcomes from our most common treatment options.
PSMA-targeted therapy well tolerated in men with mCRPC

≥50% PSA decline observed in 38% of patients treated with lutetium-177

John Schieszer
UT Correspondent

A radiolabeled small molecule that binds to prostate-specific membrane antigen (PSMA) is continuing to show promise for treating progressive metastatic castrate-resistant prostate cancer (mCRPC), according to researchers at the University of California, Los Angeles.

UCLA researchers have been investigating lutetium-177 (177Lu)-PSMA-617, which binds with high affinity to PSMA, allowing beta particle targeted molecular radiotherapy for men with mCRPC. An analysis of 64 men treated with this agent showed that it was well tolerated, and PSA declined by 50% or greater in 38% of patients.

The findings from the RESIST-PC phase II trial, which were presented at the 2019 AUA annual meeting in Chicago, showed that best PSA response rate occurred after three cycles of treatment. Currently, Lu-PSMA-617 is being developed as targeted molecular radiotherapy for mCRPC by Endocyte with an international multicenter randomized phase III trial (VISION).

“The response rate of the patients who responded by a PSA decline of more than 50% at any time was 38%, so we were pretty close to the 40% we expected,” said JEREMIE CALAIS, MD, MSc, assistant professor of nuclear medicine at the David Geffen School of Medicine at UCLA.

He collaborated with investigators in Germany and Houston and conducted an open-label prospective, bi-centric, single-arm phase II clinical trial (NCT03042312) in men who had progressive mCRPC (biochemical, radiographic, or clinical) after one or more novel androgen axis drugs. All the men had sufficient bone marrow reserve and normal kidney function and were screened with PSMA PET/CT to confirm target expression. The 64 men received either of 6.0 or 7.4 GBq of 177Lu-PSMA-617 every 8 +/-1 weeks, and the authors performed kidney dosimetry for the first cycle.

For this investigation, the authors defined efficacy as serum PSA decline of 50% or greater from baseline at 12 weeks, which was the study’s primary endpoint. In this cohort, the median PSA level was 75 ng/mL (range, 0.5-2,425) and 20% of the men were chemotherapy naive and 80% were post-chemotherapy (1.9 chemotherapy regimens on average; range, 1-4). Only 45% of the men completed four cycles of 177Lu-PSMA-617. Androgen deprivation therapy (ADT) was given concomitantly to 83% of the patients and optimization of the radiation dose delivery was made, such as finding tools to better identify responders versus non-responders prior to treatment, optimization of the radiation dose delivery to the tumor targets and enhance efficacy by increasing the amount of injected drug or by reducing the time interval between each cycle. The primary endpoint hypothesis of 40% responders after two cycles was a little bit too ambitious. Maybe after three cycles or at any time (best response) would have been more appropriate,” Dr. Calais told Urology Times.

He said the study was powered for a sample size of 200 patients, and the enrollment of this phase II trial was closed by industry (Endocyte) before reaching the target. Some men did quite well on this agent and 10% to 15% had a deep and durable response with a PSA decline of 90% or greater.

Adverse events mild, transient

The authors were pleased to find that adverse events were mild and transient. They included xerostomia (72%), nausea/vomiting (69%), and bowel movement disorders (45%). Grade 3 toxicity included nausea/vomiting (6%), anemia (8%), leukopenia (5%), kidney failure (5%), thrombocytopenia (3%), and neutropenia (3%).

“The side effects were very well tolerated, especially for a third-line therapy,” said Dr. Calais. The authors found no difference between the efficacy and toxicity for the two doses, and no kidney abnormalities were detected.

Dr. Calais said many improvements could be made, such as finding tools to better identify responders versus non-responders prior to treatment, optimization of the radiation dose delivery to the tumor targets, and moving the treatment indication at an earlier stage of the disease instead of third-line therapy.

Risk of chronic opioid use low after RP

2.3% of European men are chronic users 2 months after prostatectomy, study finds

Jeni Williams
UT Correspondent

CHICAGO—Chronic opioid use is rare following radical prostatectomy (RP) in Europe. Slightly more than half of men undergoing RP in Sweden between 2007 and 2017 were found to have filled an opioid prescription, but the proportion who became chronic opioid users was less than 1%. Using data from nationwide Swedish registries, Walter Cazzaniga, MD, and colleagues found that preoperative opioid use was the strongest predictor of chronic postoperative use following RP. They presented their findings at the 2019 AUA annual meeting in Chicago and also published research on this topic in the Journal of Urology (2020; 203:145-50).

“I think we are under-dosing patients. The safety profile was very favorable. We could maybe get better radiation dose delivery to the tumor targets and enhance efficacy by increasing the amount of injected drug or by reducing the time interval between each cycle. The primary endpoint hypothesis of 40% responders after two cycles was a little bit too ambitious. Maybe after three cycles or at any time (best response) would have been more appropriate,” Dr. Cazzaniga told Urology Times.

He concluded Dr. Cazzaniga, visiting researcher, department of surgical sciences, Uppsala University, Uppsala, Sweden.

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OPIOIDS
continued from page 13

Previous data suggest that up to 7% of opioid-naive patients who receive an opioid prescription after surgical procedures become chronic opioid users, he said. Among a random sample of 10% of patient records from a large U.S. commercial health plan, the probability of continued opioid use was 6.0% at 1 year and 2.9% at 3 years after an opioid prescription following a surgical procedure.

To examine the risk of chronic opioid use following RP, the investigators used data from the Prostate Cancer Data Base Sweden linked to the Prescribed Drug Register to assess opioid prescriptions for 25,703 men who underwent RP from 2007 to 2017. The median age at RP was 64 years. Most men had clinical stage T1c disease, and most were categorized as intermediate risk. Sixty percent of the men underwent robot-assisted RP, 36% had open RP, and 4% had laparoscopic surgery.

At least 1 Rx filled by 64%
The authors examined opioid use 1 year prior to RP and 1 year following RP. At least one prescription for an opioid was filled by 16,368 (64%) of the men.

The proportion of men undergoing RP who received a prescription for an opioid increased from 40% in 2007 to 59% in 2017. The pattern of opioid prescription changed from a preponderance of prescriptions for strong opioids (eg, morphine, fentanyl, oxycodone, buprenorphine, hydromorphone) in 2007 to nearly all opioid prescriptions being weak opioids (eg, tramadol, dihydrocodeine, codeine) by 2017.

Baseline consumption of opioids prior to RP was related to other comorbidities, with 1.9% of men having filled an opioid prescription in the preoperative period. There was a strong peak in opioid use in the first 6 weeks after the procedure, to 59%, which decreased after 2 months to a level (2.3%) that was only slightly higher than that at baseline.

“This is true for the overall opioids and also for the strong and weak opioids, with the biggest peak for the strong opioids,” said Dr. Cazzaniga.

On a multivariable model, the following factors predicted new chronic opioid users after RP: intermediate- (OR=3.30, p=.04) or high-risk cancer (OR=5.29, p=.005); regional (OR=5.67, p=.01) or distant metastases (OR=9.37, p=.004); a Charlson Comorbidity Index of 1 (OR=1.94, p=.0004), 2 (OR=2.51, p=.001) or 3+ (OR=3.30, p=.0006); and being unmarried (OR=1.38, p=.05). Undergoing a robot-assisted RP was associated with a lower risk of conversion to chronic opioid use (OR=0.71, p=.02).

“Our results report the first nationwide investigation in Europe about the opioid issue,” Dr. Cazzaniga said. “Even if we cannot conclude anything on pain management strategies to avoid chronic opioid consumption, physicians and patients should be aware of our results in order to tailor the postoperative pain management strategy in order to minimize potential abuse.”

WALTER CAZZANIGA, MD

“The response rate of the patients who responded by a PSA decline of more than 50% at any time was 38%, so we were pretty close to the 40% we expected.”

Letters
We welcome letters to the editor. Please send correspondence to urology_times@mmhgroup.com

Resident burnout: A multifaceted problem

To the editor:
I completely agree with the title of the guest blog post from James Anaissie, MD: “Addressing resident burnout starts with program’s culture” (bit.ly/anaissieblog). I was surprised, however, that the program’s culture didn’t seem to include the nursing staff, or their perspective. I would be really surprised if any health care professional would call someone at 3 a.m. to tell the person they were going to work. Somehow, we must reach some intermediary level of our profession!

Above all, do no harm.

Colby Peters, PhD, LCSW / Severna Park, MD

To the editor:
It was not surprising to read about the real issue of resident training burnout in our urology housestaff. New York State instituted the 80-hour work week rule a number of years ago to set a time limit for all residents, which has helped somewhat to protect them from being over abused!

In my residency training, which I completed in 1978, my good work week was 96 hours in the hospital (yes, we were residents because we resided in our room in the hospital dorm for call and coverage) and my bad week was 134 hours! Yes, it was every other night and every other weekend on call, with some bad weeks going into the hospital on Saturday a.m. to work until Monday at 6 p.m., with many times having only 2-3 hours of sleep in that period! Was it unsafe, unhealthy, and more like a fraternity hazing... definitely! I often fell asleep on Monday’s OR cases while assisting my attendings, but would never think of leaving a case until completed.

We all somehow survived, but I often thought this system was not in the best interests of our patients and for our training. Now, our residents must leave the hospital, OR, clinics, wards, etc. when their time clock is ringing, since hospitals face severe fines and censure for any violations!

Somewhere, we must reach some intermediary approach to these issues of our training programs. Do we need more attention to regular intervals of R and R during the training? Should there be options for less time in the concentration of in-house presence, electives to give some respite at regular intervals, and more human support services available for the burnout syndrome?

Medical knowledge is estimated to double and triple about every 5 years, so our profession makes us all students for life. You must keep up and remain current or your best care for your patients will be compromised.

The quandary remains for those of us involved in training our best and brightest to be aware of the very real issue of burnout, for all of us, at every level of our profession!

“Above all, do no harm.”

Donald A. Bentrovato, MD / Albany Medical College, Albany, NY
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Catherine & Joseph Aresty Department of Urology  urology.KeckMedicine.org

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BEYOND EXCEPTIONAL MEDICINE™
Prostate cancer is the most common non-dermatologic cancer in men, with approximately 164,690 cases identified in 2018 alone, accounting for almost one-fifth of new cancer diagnoses (CA Cancer J Clin 2018; 68:7–30).

The diagnosis of prostate cancer has evolved since Hugh Hampton Young first described the open perineal prostate biopsy in 1926 (Young’s Practice of Urology. Vol 1. Philadelphia: W.B. Saunders; 1926). For the past 3 decades, urologists have primarily relied on ultrasound-guided transrectal needle biopsy (TR-Bx) and a sextant approach for diagnosis. More recently, extended biopsy schemes involving 12 cores have been employed (Eur Urol 2017; 71:618–29).

Unfortunately, there are various drawbacks to the transrectal approach including suboptimal diagnostic accuracy and various procedure-related complications. The transperineal approach (figures 1 and 2) is slowly gaining traction around the country, given its promise to address many of these issues.

So why are many urologists still struggling to abandon the transrectal approach in favor of the transperineal approach? In the famous words of the esteemed British economist, John Maynard Keynes, “The difficulty lies not so much in developing new ideas as in escaping from old ones.”

**Pitfalls of transrectal biopsy**


Despite this systematic approach, TR-Bx has always maintained a high false-negative rate, missing approximately one-third of clinically significant cancers (J Urol 1989; 142:66-7). Additionally, TR-Bx results were understaged in up to 25% of men based on final pathology following radical prostatectomy (Urology 2008; 72:177-82).

Thanks to the emergence of multiparametric magnetic resonance imaging in fusion TR-Bx, however, urologists have made significant strides in addressing the concerns related to prostate cancer diagnosis (Eur Urol 2016; 70:233-45).

Unfortunately, one issue that remains unaddressed is the rising incidence of infectious complications after TR-Bx in the era of antimicrobial resistance. Halpern et al reported that rates of infection within 30 days of TR-Bx increased from 2.6% to 3.5% from 2011 to 2014 in New York (J Urol 2017; 197:1020-5). Furthermore, post-TR-Bx sepsis is significant not only in terms of outcomes, but also in terms of spending, ranging from approximately $8,500 to $19,000 over the past 10 years (Urology 2011; 78:511).

The transperineal approach has seen a resurgence in clinical practice due to its superiority in sampling both the anterior prostate and apical region.

Reduced infection rate may drive increased use of transperineal approach

**FIGURE 1** / Representative image of transperineal approach to ultrasound-guided prostate biopsy. (Illustration courtesy of Perineologic)
Advantages of transperineal approach
Holm described the first transrectal ultrasound-guided transperineal prostate biopsy (TP-Bx) in 1981 (J Urol 1981; 126:385). This approach has seen a resurgence in clinical practice due to its superiority in sampling both the anterior prostate and apical region (Cancer 2005; 103:1826-32; Eur Urol 2006; 50:266-71).

Multiple systematic reviews and meta-analyses have demonstrated equivalent prostate cancer detection rates between TR-Bx and TP-Bx (Asian J Androl 2012; 14:310-5; World J Surg Onc 2019; 14:31). However, the major driver for increased interest in TP-Bx has been the associated reduction in infection rates. Pepe reported a series of 3,000 patients with an infections complication rate under 1%, and a meta-analysis conducted by Grimmett reported a sepsis rate of less than 0.1% (Urology 2013; 81:1142-1146; BJU Int 2014; 114:384-8).

While these outcomes may exhibit an improvement for TP-Bx over TR-Bx, there are concerns about potential drawbacks leading to a slow rate of acceptance. These concerns seem to be rooted in the perceived need for general anesthesia and increased cost. While the TP-Bx approach has historically been described in the setting of general anesthesia, recent papers have demonstrated efficacy with local anesthetic techniques and acceptable patient-reported tolerability outcomes (BJU Int 2017; 120:164-7; Prostate Cancer Prostatic Du 2017; 20:311-7). Additionally, while TP-Bx has traditionally been performed using a brachytherapy grid and stepper, free-hand approaches to TP-Bx have been shown to minimize costs associated with instrumentation in the outpatient setting.

Conclusion
A plethora of research is growing that suggests TP-Bx offers equivalent prostate cancer detection rates, lower infectious complications, and increased technical feasibility. The ubiquitous adoption of office-based transperineal prostate biopsy appears to be imminent.

OLAPARIB GRANTED PRIORITY REVIEW FOR HRR-MUTATED METASTATIC CRPC
A supplemental New Drug Application for olaparib (LYNPARZA) has been granted Priority Review in the U.S. for adult patients with metastatic castration-resistant prostate cancer (mCRPC) and deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene mutations, who have progressed following prior treatment with a new hormonal agent (NHA). A Prescription Drug User Fee Act (PDUFA) date is set for the second quarter of 2020.

The Priority Review by the FDA is based on results from the phase III trial PROfound, which were presented at the 2019 European Society of Medical Oncology annual congress in Barcelona, Spain.

Results of the PROfound trial showed olaparib met its primary endpoint, significantly reducing the risk of radiographic disease progression or death by 66% in patients with BRCA 1/2 or ATM-mutated mCRPC and improved radiographic progression-free survival (rPFS) to a median of 7.4 months versus 3.6 months for patients receiving abiraterone (ZYTIGA) or enzalutamide (XTANDI) (HR 0.34 [95% CI, 0.29-0.41]; p<.0001).

The trial also met the key secondary endpoint of rPFS in the overall population of men with HRR-mutated (HRRm) mCRPC (those with mutations in BRCA 1/2, ATM, CDK12, or 11 other HRm genes), where olaparib reduced the risk of radiographic disease progression or death by 51% and improved rPFS to a median of 5.8 months versus 3.5 months for those receiving abiraterone or enzalutamide (HR 0.49 [95% CI, 0.38-0.63]; p<.0001).

The safety and tolerability profile of olaparib in the PROfound trial was in line with that observed in prior clinical trials. The most common adverse events ≥20% were anemia (22%), fatigue/asthenia (23%), vomiting (22%), dyspnea (22%), urinary tract infection (22%), decreased appetite (13%), diarrhea (1%), back pain (1%), and nausea (1%). Sixteen percent of patients on olaparib discontinued treatment due to adverse events.

IMPROVED OS SEEN WITH CABAZITAXEL VS. SECOND AR-TARGETED AGENT FOR mCRPC
Data from a recent study show that patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel (Taxotere) and who progressed within 12 months on an androgen receptor (AR)-targeted agent (abiraterone [ZYTIGA] or enzalutamide [XTANDI]) experienced significantly longer radiographic progression-free survival (rPFS) with cabazitaxel (Jevtana) plus prednisone compared with abiraterone plus prednisone or enzalutamide.

Overall survival (OS) with cabazitaxel was also significantly longer. These findings from the CARD study were presented at the 2019 European Society of Medical Oncology annual congress in Barcelona, Spain and published in the New England Journal of Medicine (2019; 381:2506-18).

“In this study, treatment with Jevtana significantly improved radiographic progression-free survival and overall survival compared with enzalutamide or abiraterone,” said Ronald de Wit, MD, PhD, from Erasmus MC University Hospital, Rotterdam, the Netherlands, and the lead investigator of the CARD study. “These results are exciting as they have the potential to impact treatment guidelines for metastatic prostate cancer and current clinical practice.”

Cabazitaxel is currently used to treat men with castration-resistant prostate cancer (prostate cancer that is resistant to medical or surgical treatments that lower testosterone) that has progressed after treatment with other medicines, including docetaxel.
Addressing prostate cancer’s racial disparity starts with you

Several decades of data show that Black men are less likely to be screened and treated for prostate cancer than their white counterparts. In this interview, Kelvin A. Moses, MD, PhD, discusses the reasons for these disparities, potential genetic, cultural, and environmental factors, new data showing improved outcomes in Black men receiving certain treatments, and how practicing urologists can address prostate cancer disparities.

Q: Why do you think there’s still a large disparity between African-American and white men when it comes to prostate cancer survival?
A: It’s been persistent for decades, and there are a lot of factors that go into it. During the PSA screening era—from the late 1980s to 2012 or so—the gap did narrow some. That was likely due to some increased screening and better treatments. But overall, there’s been a disparity in screening, and among men who are diagnosed, a disparity in treatment; Black men are less likely to get treated overall. Insurance, socioeconomic status, and cultural factors all play a role, but the lion’s share of the disparity comes from the factors that we as urologists have some control over.

Q: One of my African-American patients told me that reaching out to the wives of patients to encourage screening is important. What are your thoughts about that?
A: I really support that, and I think it’s very important. It’s an effort that I’ve done, as have Dr. Isaac Powell in Detroit, Dr. Willie Underwood in Buffalo, and Dr. Mark Litwin in Los Angeles, among many others. One of the best methods of community engagement is to involve men who are at risk, as well as their partners and loved ones. It’s very effective.

Bringing in the wives and partners helps because sometimes men are a little fearful or resistant, and having the people who love you encouraging you to seek out health information is very important. Sometimes there is a barrier or a mental hurdle about visiting a large academic center or hospital, and that outreach breaks down the barrier so you can start a conversation about screening.

Q: Do you think there is still a bit of skepticism—a “Tuskegee effect”—among African-American men and a perception that “I’m being experimented on”?

What can the average practicing urologist do about the racial disparity in prostate cancer and help close that gap in the community?

J. BRANTLEY THRASHER, MD

Know the literature. We have 40 years of descriptive analysis showing racial disparities.

KELVIN A. MOSES, MD, PhD

Q: Why do you think there’s still a large disparity between African-American men and white men when it comes to prostate cancer survival?
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Q: I have some men tell me, “I don’t mind getting a blood test. I do not want to have a rectal exam.” Do you hear that?
A: I’ve had men say they’d rather die than have me stick my finger in their rectum, and I tell them, “You just might.” It all goes back to communication and breaking down the barriers. I tell men, the way they came into the office is how they’re going to leave. I explain that this exam isn’t for our fun but for their health. In some cases, men haven’t seen the doctor since they tried out for sports in high school, and now that they’re 50 or 55 years old, they’re back in the health system. We have to break down the male ego to get over that mental hurdle.

Q: What else do you think the field of urology or urologic oncology can do to try to close that gap?
A: It’s all about education. We talk about patients’ literacy and familiarity with their health care, but physicians need education, too. We need to know how to talk with patients and have cultural competency. We also need to diversify. Just as we have emphasized the need for more women in urology, we need more Black faculty and residents in urology, as well as Hispanics. Some of the disparity we have seen in Black men is now being seen increasingly in Hispanic men.

What do you see as other contributors? Are there genetic abnormalities?

J. BRANTLEY THRASHER, MD

The 8q24 gene and CYP3a4 mutations are associated with higher risk disease and are more highly expressed in Black men. The genes that we’re more familiar with, such as TMPRSS2-ERG, may be more highly expressed in white men.

Q: What have we learned from the prostate cancer registry data?
A: I think so. There’s nothing wrong with putting a familiar face with an important issue. It’s what women have been doing much smarter for a long time. In addition, having an NFL player is great, but it’s also important to have somebody from the community that people know—the pastor, the mayor, whoever they see on a daily basis—because it’s easy to idealize somebody and then put them off. But sometimes that person sitting next to you is just as impactful.

Q: Do you have any other take-home messages?
A: We need to believe the data. Again, we have over 40 years of descriptive data showing disparities linked to screening and treatment. We also have new data showing improved outcomes in Black men in certain instances. For example, the IMPACT study and PROCEED registry showed greater overall survival improvement in Black versus white patients after treatment with sipuleucel-T. Additionally, there are data showing Black men have better survival outcomes with enzalutamide and abiraterone acetate.

Physicians examined the data showing that opioids were a serious problem and that we were part of it. We have performed population-level research, created postoperative pain pathways, modified our behaviors, and modified patient interaction and how we manage pain. This proves that we as a field are able to identify a problem and come up with solutions in a timely manner. Let’s do the same thing with prostate cancer in Black men.

Q: The AUA has had the opportunity to use a couple of champions of prostate cancer who are African-American men that were professional football players. Do you think those campaigns are effective?
A: Absolutely, and the literature bears that out. Plenty of studies show that non-white patients who have an ethnically concordant physician have better outcomes and greater satisfaction from the interaction. This holds true in diabetes, blood pressure, and cancer. If you’re part of a smaller proportion of the population and you’re not well represented, but the person across from you looks like you, there is an increased comfort level. I see it in my patients’ face. There’s an automatic level of understanding and communication that happens that I think is critical when making the right treatment decisions. Conversely, white patients receive the same high-quality care and satisfaction regardless of the race/ethnicity of the physician.
NOW APPROVED FOR METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER (mCSPC)*

When your patients present with mCSPC or CRPC†...

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Indications
XTANDI (enzalutamide) is indicated for the treatment of patients with:

- castration-resistant prostate cancer (CRPC)
- metastatic castration-sensitive prostate cancer (mCSPC)

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 seizures, 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 developing symptoms including seizure, headache, lethargy, confusion, blindness, and other visual and neurological disturbances, with or without associated hypertension. A diagnosis of PRES requires confirmation by brain imaging, preferably MRI. Discontinue XTANDI in patients who develop PRES.

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

Embryo-Fetal Toxicity The safety and efficacy of XTANDI have not been established in females. XTANDI can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment with XTANDI and for 3 months after the last dose of XTANDI.

Adverse Reactions (ARs)

In the data from the 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, hot flush, constipation, arthralgia, decreased appetite, diarrhea, and hypertension. In the bicalutamide-controlled study, the most common ARs (≥ 10%) reported in XTANDI-treated patients were asthenia/fatigue, back pain, muscular/skeletal pain, hot flush, hypertension, nausea, constipation, diarrhea, upper respiratory tract infection, and weight loss.

In AFFIRM, the placebo-controlled study of metastatic CRPC (mCRPC) patients who previously received docetaxel, Grade 3 and higher ARs were reported among 47% of XTANDI-treated patients. Discontinuations due to adverse events (AEs) were reported for 16% of XTANDI-treated patients. In PREVAIL, the placebo-controlled study of chemotherapy-naive mCRPC patients, Grade 3-4 ARs were reported in 44% of XTANDI patients and 37% of placebo patients. Discontinuations due to AEs were reported for 6% of XTANDI-treated patients. In TERRAIN, the bicalutamide-controlled study of chemotherapy-naive mCRPC patients, Grade 3-4 ARs were reported in 39% of XTANDI patients and 38% of bicalutamide patients. Discontinuations with an AE as the primary reason were reported for 8% of XTANDI patients and 6% of bicalutamide patients.

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

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

Lab Abnormalities: Lab abnormalities that occurred in ≥ 5% of patients, and more frequently (> 2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies are neutrophil count decreased, white blood cell decreased, hyperglycemia, hypomagnesemia, hyponatremia, and hypercalcemia.

Hypertension: In the combined data from four randomized placebo-controlled clinical trials, hypertension was reported in 12% of XTANDI patients and 5% of placebo patients. Hypertension led to study discontinuation in < 1% of patients in each arm.

Drug Interactions

Effect of Other Drugs on XTANDI Avoid strong CYP3A4 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, CYP2C9, and CYP2C19 substrates with a narrow therapeutic index, as XTANDI may decrease the plasma exposure 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
XTANDI® (enzalutamide) capsules 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 368 (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 injury 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, without or associated with 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 (NCT02294461), and STRIVE (NCT01664923)] that were pooled to conduct safety analyses in patients with CRPC (N=3509) or mCSPC (N=572) treated with XTANDI. Patients received XTANDI 160 mg (N=4081 patients) or placebo orally once daily (N=2472 patients) or bicalutamide 50 mg orally once daily (N=387 patients). 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 a 2% higher frequency in the XTANDI arm compared to the placebo arm.

Table 1. Adverse Reactions in AFFIRM

<table>
<thead>
<tr>
<th>XTANDI N = 800</th>
<th>Placebo N = 399</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Asthenic Conditions</td>
<td>51 9.0 44 9.3</td>
</tr>
<tr>
<td>Peripheral Edema</td>
<td>15 1.9 0 0.0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and Connective Tissue Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Back Pain</td>
<td>26 5.3 24 4.0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>21 2.6 17 1.8</td>
</tr>
<tr>
<td>Musculoskeletal Pain</td>
<td>15 1.9 12 0.3</td>
</tr>
<tr>
<td>Muscular Weakness</td>
<td>9.8 1.5 6.6 1.8</td>
</tr>
<tr>
<td>Musculoskeletal Stiffness</td>
<td>2.6 0.3 0.3 0.0</td>
</tr>
<tr>
<td><strong>Gastrointestinal Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>22 1.1 18 0.3</td>
</tr>
<tr>
<td><strong>Vascular Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>20 0.5 10 0.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>6.4 2.1 2.4 0.6</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>12 0.9 5.5 0.0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9.5 0.5 7.5 0.5</td>
</tr>
<tr>
<td>Spinal Cord Compression and Clauda Equina Syndrome</td>
<td>7.4 6.6 4.5 3.8</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6.6 0.0 4.5 0.0</td>
</tr>
<tr>
<td>Mental Impairment Disorders</td>
<td>4.3 0.3 1.6 0.0</td>
</tr>
<tr>
<td>Hypoesthesia</td>
<td>4.0 0.3 1.8 0.0</td>
</tr>
</tbody>
</table>
that occurred at a ≥ 2% higher frequency in the XTANDI arm compared to the placebo arm. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on XTANDI compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 31% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events reported for 6% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on XTANDI compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.

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

PREVAIL enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 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.

Overall, 32 patients (3.4%) receiving XTANDI died from adverse events. 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 45 months) with placebo.

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

TERRAIN enrolled 375 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 372 received at least one dose of study drug. The median duration of treatment was 11.6 months with XTANDI and 5.8 months with bicalutamide. Discontinuations with an adverse 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.

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

PREVAIL enrolled 1717 patients with metastatic CRPC who had not received prior cytotoxic chemotherapy, of whom 1715 received at least one dose of study drug. The median duration of treatment was 17.5 months with XTANDI and 4.6 months with placebo. Grade 3-4 adverse reactions were reported in 44% of XTANDI-treated patients and 37% of placebo-treated patients. Discontinuations due to adverse events were reported for 6% of XTANDI-treated patients. The most common adverse reaction leading to treatment discontinuation was fatigue/asthenia, which occurred in 1% of patients on XTANDI compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PREVAIL that occurred at a ≥ 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 = 399</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 1-4 (%)</td>
</tr>
<tr>
<td>Grade 3-4 (%)</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
</tbody>
</table>

Infections and Infestations
- Upper Respiratory Tract Infection²
- Lower Respiratory Tract And Lung Infection³
- Onset

Psychiatric Disorders
- Insomnia
- Anxiety
- Sedation

Renal and Urinary Disorders
- Hematuria
- Polydipsia

Injury, Poisoning and Procedural Complications
- Fall
- Non-pathologic Fractures

Skin and Subcutaneous Tissue Disorders
- Pruritus
- Dry Skin

Respiratory Disorders
- Epistaxis

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

<table>
<thead>
<tr>
<th></th>
<th>XTANDI N = 871</th>
<th>Placebo N = 844</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
<td>Grade 1-4 (%)</td>
</tr>
<tr>
<td>Grade 3-4 (%)</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
</tbody>
</table>

Investigations
- Weight Decreased

Reproductive System and Breast Disorders
- Gynecomastia

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

PROSPER (NCT02003924): 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 45 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 9.4% 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 1.6% of XTANDI-treated patients compared to none of the placebo-treated patients. Table 4 shows adverse reactions reported in PROSPER that occurred at a ≥ 2% higher frequency in the XTANDI arm than in the placebo arm.
Table 5 shows adverse reactions reported in ARCHES that occurred at a placebo-treated patients.

- Fatigue/asthenia was the most frequent adverse reaction
- Dose reductions due to an adverse reaction occurred in 4.4% of patients who were arthralgia, and fatigue, each in 0.3%.
- The most common discontinuation in XTANDI-treated patients were alanine aminotransferase increased, aspartate aminotransferase elevation, and seizure, each in 0.3%. The most common reasons for death in ≥2 patients included heart disease (n=3), sepsis (n=2) and pulmonary embolism (n=2).
- Overall, 10 patients (1.7%) receiving XTANDI died from adverse events.

Table 4. Adverse Reactions in PROSPER

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>XTANDI (N = 574)</th>
<th>Placebo (N = 574)</th>
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<tr>
<td>Weight Decrease</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td></td>
<td>4.9</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>2.6</td>
<td>0.0</td>
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<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>5.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td></td>
<td>1.6</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>3.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Cognitive and Attention Disorders</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
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<tr>
<td></td>
<td>4.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Flush</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td></td>
<td>13</td>
<td>0.1</td>
</tr>
<tr>
<td></td>
<td>7.7</td>
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<tr>
<td>Hypertension</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
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<tr>
<td></td>
<td>12</td>
<td>4.6</td>
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<td>2.2</td>
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<tr>
<td>Gastrointestinal Disorders</td>
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<tr>
<td>Nausea</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
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<tr>
<td></td>
<td>11</td>
<td>0.3</td>
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<tr>
<td></td>
<td>8.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Constipation</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td></td>
<td>9.1</td>
<td>0.2</td>
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<tr>
<td></td>
<td>6.9</td>
<td>0.4</td>
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<tr>
<td>General Disorders and Administration Site Conditions</td>
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<tr>
<td>Asthenic conditions²</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
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<tr>
<td></td>
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<td></td>
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<td>Investigations</td>
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<td>Weight Decrease</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
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<tr>
<td></td>
<td>5.9</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Injury, Poisoning and Procedural Complications</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Fall</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>1.3</td>
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<tr>
<td></td>
<td>4.1</td>
<td>0.8</td>
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<tr>
<td>Fractures²</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
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<td></td>
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<td>1.7</td>
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<tr>
<td>Psychiatric Disorders</td>
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<tr>
<td>Anxiety</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
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<td></td>
<td>2.8</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>0.4</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Table 6 shows laboratory abnormalities that occurred in ≥5% of patients, and more frequently (>2%) in the XTANDI arm compared to placebo in the pooled, randomized, placebo-controlled studies.

Table 6. Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>XTANDI (N = 3173)</th>
<th>Placebo (N = 2282)</th>
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</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>Grade 1-4 (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>0.7</td>
<td>0.4</td>
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<tr>
<td>White blood cell decreased</td>
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<td>0.4</td>
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<tr>
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<tr>
<td>Chemistry</td>
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<tr>
<td>Hypoglycemia</td>
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<td>Hyperglycemia</td>
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<td>13</td>
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<td>Hypokalemia</td>
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<tr>
<td>Hypercalcaemia</td>
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</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.

Body as a Whole: hypersensitivity (edema of the face, tongue, lip, or pharynx)

Gastrointestinal Disorders: vomiting

Neurological Disorders: posterior reversible encephalopathy syndrome (PRES)

Skin and Subcutaneous Tissue Disorders: rash

DRUG INTERACTIONS

Drugs that Inhibit CYP2CB

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 CYP2CB inhibitors should be avoided if possible. If co-administration of XTANDI with a strong CYP2CB inhibitor cannot be avoided, reduce the dose of XTANDI.

Drugs that Induce CYP3A4

Co-administration of rifampin (strong CYP3A4 inducer and moderate CYP2C8 inducer) decreased the composite AUC of enzalutamide plus N-desmethyl enzalutamide by 37%. Co-administration of strong CYP3A4 inhibitors (e.g., carbamazepine, phenobarbital, phenytoin, rifabutin, rifampin, 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, increase the dose of XTANDI.

Effect of XTANDI on Drug Metabolizing Enzymes

Enzalutamide is a strong CYP3A4 inducer and a moderate CYP2C9 and CYP2C19 inducer in humans. At steady-state, XTANDI reduced 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, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), CYP2C9 (e.g., phenytoin, warfarin) and CYP2C19 (e.g., S-mephenytoin, clopidogrel) should be avoided, as enzalutamide may decrease enzyme activity and should be avoided. If co-administration of a strong CYP3A4 inducer with XTANDI cannot be avoided, increase the dose of XTANDI.

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

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

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

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

Females and Males of Reproductive Potential
Contraception
Males
Based on findings in animal reproduction studies, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of XTANDI.

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

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

Geriatric Use
Of 4081 patients who received XTANDI in seven randomized, controlled clinical trials, 78% were 65 and over, while 35% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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] < 60 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.

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.

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
A two-year carcinogenicity study was conducted in male and female rats at oral enzalutamide doses of 10, 30, and 100 mg/kg/day. Enzalutamide increased the incidence of benign Leydig cell tumors in the testes at all dose levels tested (≥ 0.3 times the human exposure based on AUC) and combined incidence of uterine papilloma and carcinoma in the urinary bladder in male rats at 100 mg/kg/day (1.4 times the human exposure based on AUC). The findings in the testes are considered to be related to the pharmacological activity of enzalutamide. Rats are regarded as more sensitive than humans to developing interstitial cell tumors in the testes. Administration of enzalutamide to male and female rASh2 transgenic mice by oral gavage daily for 26 weeks did not result in increased incidence of neoplasms at doses up to 20 mg/kg/day.

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

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

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Revised: December 2019
249693-XTA-USA

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076-4985-PM
What are your thoughts on recent studies regarding AS and radiation in African-American men?

EDITORS NOTE: For this month’s installment of “Speak Out,” urologists were asked to discuss recent studies indicating African-American men with prostate cancer may be put on active surveillance without suffering complications and that they respond to radiation and some chemotherapy better than Caucasian men. The research discussed includes the scientific meeting presentations “Overall survival by race in chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC) patients treated with abiraterone acetate or enzalutamide” (presented at the 2019 GU Cancers Symposium), “Androgen receptor activity and radiotherapeutic sensitivity in African-American men with prostate cancer: A large scale gene expression analysis and meta-analysis of RTOG trials” (2018 ASTRO annual meeting), “Prostate cancer upgrading and upstaging in a multicenter prostate cancer registry” (2018 AUA annual meeting), and a paper published in the Journal of Clinical Oncology (2019; 37:403-10).

DR. BIVINS

If you start from the premise that African-American men have more aggressive prostate cancer, you can break the reasons down into socioeconomic and biology. These studies basically account for socioeconomic status and for staging. If everybody is on the same playing field, according to one study, radiation is a viable option for African-American men, for at least one particular gene expression. Radiation can give them a better response than Caucasian men.

In the real world, however, the playing field is not even, because black men aren’t getting screened. They show up with metastatic disease. If you can get them screened, this study shows they can do just as well, if not better than whites.

It’s the same with active surveillance. If someone is in an active surveillance protocol, they’ve already been screened and qualified for active surveillance. So they’ll do just as well.

People took it for granted that the black men did worse with prostate cancer with no dissection of why. Some of it was just believing that there had to be something different genetically. Maybe that still is likely, but this study dispels the idea that it’s just biology that causes African-American men to have worse cancer.”

Michael Bivins, MD / Birmingham, AL

DR. FREEDLAND

In general, African-American men have more aggressive disease. So here’s a treatment which is actually no treatment: active surveillance. Data suggests African-American men are likely to progress on active surveillance, but that doesn’t mean it shouldn’t be offered. It just means they should be followed closely—not that it’s not worth trying.

We’re also seeing that when African-American men are matched stage-for-stage, grade-for-grade, they do similarly after surgery and with radiation as white men. When you get to late-stage chemo, there is data they’re actually doing better. That’s great, but it opens up a million questions as to why.

From a clinical perspective, we must consider their Gleason, their PSA, and their genomics and come up with a treatment plan. Race shouldn’t really figure into it.

Socioeconomics may contribute to people waiting too long to come in, but even in equal-access centers, black men are diagnosed at younger ages than white men. It’s not simply waiting too long. Socioeconomics clearly is a factor. Being poor is clearly a stress factor, particularly in the United States, and we know stress can increase cancer risk and aggressiveness. So a lot of factors are in play.

I’m hopeful these studies will lead to more men getting screened earlier. They’re more likely to have aggressive disease, but if it’s caught early the outcomes are identical to what we see in white men. That’s the silver lining about this.”

Stephen Freedland, MD / Los Angeles

DR. PALESE

The studies are a bit controversial, and other big-data studies of large databases across Medicare and the country clearly show that African-American men are still more severely affected by prostate cancer.

There are some questions why that is—possibly the biology of the disease—where prostate cancer actually starts. In African-American men, it often occurs in the apex of the prostate. That’s a tougher area to biopsy. We may miss cancers more often than in other races. So I take new studies that show active surveillance is a more likely scenario for African-Americans with a grain of salt.

Until we have better information on genetic makeup that correlates with the biology of the disease, we still have to be vigilant in our approach to prostate cancer in African-American men.

Many studies still stand with the fact that African-American men are also more likely than not to have more aggressive disease. Certainly some patients have a benign course, but we have to monitor these patients very closely.

As for the treatment studies, we know certain men respond to chemotherapy, others to radiation. So it makes sense that some subtypes of population, whether African-American or other races, are going to respond to specific treatments better than others. But until we have a good genetic profile of which cancers respond better, we don’t have much choice except to continue doing what we’re doing.”

Michael Palese, MD / New York

What are your thoughts on recent studies regarding AS and radiation in African-American men?

ADVERTISERS INDEX

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Novel thulium laser fiber appears to outperform Holmium:YAG laser

Fewer fragments, higher amount of dust observed with investigational device

**Jeni Williams**
UT Correspondent

**CHICAGO**—A new tool for kidney stone ablation demonstrates strong potential to dust and fragment stones more quickly and efficiently than devices currently available in the United States. However, clinical studies must be performed before this technology can be used during lithotripsy nationally.

Ben H. Chew, MD, MSc, associate professor of urologic sciences at the University of British Columbia, Vancouver, presented a study of the Super Pulse Thulium Fiber (SPTF) laser during a moderated poster session at the 2019 AUA annual meeting in Chicago. The study compared the SPTF laser’s ability to dust and fragment Begostones to that of a commercially available 120W Holmium:YAG laser, the current lithotribe of choice.

“The SPTF is much smaller and uses less power than the Ho:YAG laser. We basically wanted to show the best foot forward for each of them to compare their efficacy,” Dr. Chew told *Urology Times.*

The results of the study—performed with Bodo E. Knudsen, MD, of The Ohio State University Wexner Medical Center, Columbus, and Wilson Molina, MD, of the University of Kansas Medical Center, Kansas City—show greater potential to control stone fragmentation than lithotrites that are currently used for patient care.

Advancements to the Holmium:YAG laser have supercharged this technology for clinical use, but downsides remain, including high amperage power requirements, upper limits of pulse frequency, and limitations regarding fiber size. The SPTF laser uses Thulium Fiber—not to be mistaken with ThuliumYAG—that offers low-pulse energy settings and pulse frequencies over 600 Hz.

SPTF was significantly faster and more efficient at ablating the entire BegoStone into fragments less than 1 mm in size.

In addition, SPTF produced significantly fewer fragments that were larger than 1 mm than the 120W HolmiumYAG laser. The impact in clinical practice: fewer basket passes. The 120W laser produced smaller fragments, but also produced more fragments. On average, use of the 120W laser would require 7.2 stones to be removed following ablation, accounting for 55% of the stones’ weight. Treatment with SPTF would require removal of 2.1 stones accounting for 85% of the stones’ weight.

SPTF produced a significantly higher number of very fine particles of dust (0.5 mm) compared with the 120W laser. Fragmentation of stones using SPTF results in finer dust compared with the 120W laser. This is likely due to the ability of the SPTF laser to generate very high frequencies and low energy settings that are not available on the 120W laser, Dr. Chew said.

Additional pre-clinical testing on the SPTF laser also was presented at the AUA annual meeting, Dr. Chew told attendees.

“We believe this approach should be more efficacious with fragmenting as well as dusting,” he said.

The study authors are paid consultants of Olympus Corp. of the Americas.

**URETEROSCOPY-ASSISTED RETROGRADE NEPHROSTOMY SYSTEM NOW AVAILABLE**

RetroPerc, LLC recently announced that its RetroPerc Ureteroscopy-Assisted Retrograde Nephrostomy (UARN) set for percutaneous endourologic procedures (eg, percutaneous nephrolithotomy) has been released for sale in the U.S.

RetroPerc is designed as a modernization of traditional retrograde nephrostomy techniques. It features a specialized puncture wire and coaxial microintroducer set that allow the urologist to establish a nephrostomy tract under direct endoscopic vision with minimal fluoroscopic guidance. The puncture wire ensemble is introduced through the working channel of a pre-positioned flexible ureteroscope, and then the puncture wire is advanced through the relatively avascular renal papilla out to the flank in a controlled, predictable, and confirmable fashion. This technique is a complement to antegrade nephrostomy creation techniques, as the retrograde and antegrade approaches are optimally suited for different patient types, according to the company.

The system is performed under the same anesthetic as the subsequent endourologic procedure, eg PCNL, providing renal access that is well located for the kidney stone removal procedure, spares the patient a separate interventional radiology procedure, provides “through and through” renal access, is easy to learn, has minimal risk of bleeding due to the papillary puncture, and requires a minimum of fluoroscopy exposure. Procedural eligibility, planning, and performance are taught in detailed video modules available at www.retoperc.com.

**“We believe [the SPTF laser] should be more efficacious with fragmenting as well as dusting.”**

BEN H. CHEW, MD, MSc

The authors tested the SPTF and a 120W Holmium:YAG laser in ablating standard, homogenous 5-mm³ BegoStones until remaining particles were smaller than 1 mm. To test fragmentation and dusting, resulting particle sizes were measured after delivering a total of 0.5 kJ and 2 kJ, respectively.

At both fragmentation and dusting settings, the SPTF was significantly faster and more efficient than the 120W laser, Dr. Chew said.

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The study authors are paid consultants of Olympus Corp. of the Americas.
Trial supports combined behavioral, medical approach to treating OAB

Starting with behavioral therapy in stepped approach ‘reasonable,’ researcher says

Cheryl Guttman Krader
UT Contributing Editor

Results of a randomized controlled clinical trial provide a rationale for urologists to integrate behavioral treatments into their practice for managing men with lower urinary tract symptoms (LUTS) of overactive bladder (OAB), according to the study’s authors.

The findings were published in JAMA Internal Medicine (Jan. 13, 2020 [Epub ahead of print]). The study, which had a two-stage, three-arm design, assigned men to 6 weeks of behavioral therapy alone, drug therapy alone, or combined therapy. In the second stage, a combined approach was used in all groups.

“Based on our findings, physicians might consider giving patients more treatment options and beginning with behavioral therapy,” said lead author Kathryn L. Burgio, PhD, professor of medicine, division of gerontology and geriatric medicine, University of Alabama School of Medicine, Birmingham.

“Based on our findings, physicians might consider giving patients more treatment options and beginning with behavioral therapy,” said Dr. Burgio.

Not only does behavioral therapy have a better side effect profile, but based on our study, it yields better 6-week outcomes than drug therapy such that results are achieved more quickly than starting with drug alone.”

STEPHEN R. KRAUS, MD

Behavioral treatments are recommended as a first-line therapy for OAB symptoms. Most physicians do not provide them, but they can be implemented by nurses, nurse practitioners, and physical therapists,” said lead author Kathryn L. Burgio, PhD, professor of medicine, division of gerontology and geriatric medicine, University of Alabama School of Medicine, Birmingham.

Most physicians do not provide behavioral treatments because they are not completely cured with initial therapy, we thought it was important to investigate the potential benefit of initial combined therapy and to study approaches to using them in combination,” said Dr. Burgio.

It enrolled community-dwelling men age 40 years and older. A total of 204 men were randomized. Mean voids per 24 hours at baseline were 11.7 or 11.8 across all treatment groups.

In the study, drug therapy consisted of sustained-release tolterodine (Detrol LA), 4 mg once daily, and tamsulosin (Flomax), 0.4 mg once daily. Behavioral therapy focused on strategies for postponing urination, controlling urgency, and preventing urge incontinence. It combined pelvic floor muscle training and use of daily bladder diaries to track increasing voiding intervals and enhance awareness of bladder habits.

At the end of the second stage, improvements from baseline voiding frequency remained greatest in the group that began with combined therapy, but there were no significant differences between groups. Mean percentage change from baseline ranged from 27.1% in the group that began with drug therapy alone to 32.2% in the group starting with combined therapy.

During the first study stage, adverse effects were reported more often in groups receiving drug therapy. Among men receiving behavioral therapy alone, 86% reported no adverse effects or no bothersome adverse effects. Approximately one-third of men in both the combined therapy and drug therapy groups reported no adverse effects or bothersome adverse effects.

Dr. Kraus has received consulting fees from Allergan, Astellas Pharma, and Medtronic and speaking/teaching fees from Astellas Pharma.
Prostatic artery embolization (PAE) offers a safe and durable effective treatment for urinary retention and gross hematuria in challenging non-index BPH patients, according to the results of a retrospective study published in Urology (Nov. 14, 2019 [Epub ahead of print]).

The article reported outcomes from a series of 75 men referred to the Yale New Haven Hospital, New Haven, CT, for BPH-related urinary retention (UR) and/or gross hematuria (GH) or severe hematuria (SH) between December 2013 and August 2018. At 3 months after PAE, 87% of men with UR were catheter-free, and 83% of men remained catheter-free as long as 36 months post-PAE.

Hemostasis was achieved within 2 days post-PAE in approximately 90% of patients who presented with GH or SH. Among men with GH, 92% remained hematuria-free at a mean follow-up of 483 days, and 87.5% of patients with SH were hematuria-free at a mean follow-up of 500 days.

The most common adverse event was Grade II catheter-associated urinary infection requiring antibiotic treatment, which occurred in eight men (11%). The only other adverse event occurring at a rate ≥5% was Grade I dysuria lasting >1 week (5%).

“Surgical intervention is considered when UR or GH are refractory to medical treatment, but some men are not candidates for the standard procedures because their glands are too large or they have comorbidities that make them poor surgical candidates. For these patients who have few acceptable treatment options, the findings of our study support the appropriateness of PAE,” said lead author Raj Ayyagari, MD, assistant professor of radiology and biomedical imaging, Yale School of Medicine, and radiology director for Male Interventional Health, Yale New Haven Hospital.

Of the 75 men included in the study, 20 had UR alone, 29 had GH/SH only, and 26 had both problems. Mean duration of catheterization for UR patients was 162 days. The majority of the patients were catheter-free, and 83% of men remained catheter-free as long as 36 months post-PAE.

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Table: Effect of PAE on Patients with Gross, Severe Hematuria

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<td>Number of hematuria-related visits (gross hematuria patients)</td>
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<td>Number of blood units transfused (severe hematuria patients)</td>
<td>36</td>
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Source: Raj Ayyagari, MD

“The guideline states that PAE is not recommended for the treatment of LUTS attributed to BPH outside the context of a clinical trial, which may be reasonable for index patients. However, the guideline does not address non-index patients, for whom PAE provides real value because these patients are not candidates for standard-of-care surgical procedures,” said Dr. Ayyagari.

“As a short, minimally invasive outpatient procedure without risk of sexual side effects, PAE might also be considered as an option for men who are averse to more aggressive surgery, particularly those who have concerns about developing sexual dysfunction postoperatively.”

Dr. Ayyagari performed all of the procedures under intravenous moderate sedation using 100-300 µm trisacryl gelatin microspheres. “Most interventional radiologists use 300-500 µm particles, but in my experience, the smaller microspheres provide excellent results when compared to other studies without any increased risk of complications from nontarget embolization,” he said.

Other outcomes data collected showed the UR patients achieved and maintained a low symptom burden and low post-void residual (PVR) following PAE. Among the GH patients, the need for hematuria-related visits was reduced from 22 prior to PAE to none during the available post-PAE follow-up. For patients with SH, the number of blood units transfused fell from 36 prior to PAE to four after PAE, with the latter all given in the first 48 hours after the procedure.

Large population size, lengthy follow-up

Dr. Ayyagari noted that other studies have reported benefits of PAE for treating UR and GH of prostatic origin, but the current study stands out for the size of its patient population, length of follow-up, and its focus on non-index patients. Based on available evidence, he believes that the statement on PAE in the AUA Guideline on Surgical Management of Lower Urinary Tract Symptoms Attributed to BPH should be reconsidered.

As a short, minimally invasive outpatient procedure without risk of sexual side effects, PAE might also be considered as an option for men who are averse to more aggressive surgery, particularly those who have concerns about developing sexual dysfunction postoperatively.

REZUM SYSTEM WINS COVERAGE FROM MAJOR INSURERS

Boston Scientific has announced that its Rezum System for the treatment of BPH has won coverage from Cigna, Anthem BlueCross BlueShield, and Blue Cross and Blue Shield of Tennessee, which collectively serve over 53 million covered lives in the United States.

The coverage decisions significantly increase patient choice and access to Rezum, a minimally invasive water vapor thermal therapy for BPH, the company said. Separately, Boston Scientific said the AUA has issued a letter to payers stating that Rezum is a viable treatment for men with BPH and should be covered.

The AUA considers the Rezum procedure “to be a viable treatment of men with benign prostatic hyperplasia (BPH) and therefore should be covered for reimbursement,” the letter said. “The AUA does not consider this procedure to be investigational or experimental.”

The letter, signed by Jonathan Rubenstein, MD, of the AUA’s Coding and Reimbursement Committee, also points out that the AMA CPT Editorial Panel reviewed and accepted the creation of a Category I CPT code for the Rezum System in 2017 and that the Rezum procedure met all Category I criteria. The letter states that the AUA’s current guideline on BPH, published in 2018 and amended in 2019, includes the following statements about the Rezum procedure:

- Water vapor thermal therapy may be offered to eligible patients with LUTS attributed to BPH provided prostate volume is <80 g; however, patients should be counseled regarding efficacy and retreatment rates.

- Water vapor thermal therapy may be offered to eligible patients who desire preservation of erectile and ejaculatory function.

“The clinical effectiveness has been proven by virtue of going through the CPT and is part of our guidelines,” the AUA letter said.
Low-fat diet associated with lower testosterone level

Researchers recommend personalized dietary advice for individual patients

Cheryl Guttman Krader
UT Contributing Editor

Results of a cross-sectional study of adult American men show that adherence to a low-fat diet is associated with a lower serum testosterone level. The implications of the findings for patient care, however, must take into account the limitations of the study and the effects of a low-fat diet on overall health, according to the investigators.

The research was recently published in the Journal of Urology (2020; 203:398-404). Study author Joshua A. Halpern, MD, MS, told Urology Times, "On the one hand, our study provides compelling evidence that a fat-restricted diet is associated with mildly decreased testosterone levels, regardless of body mass index. On the other hand, caution should be used when interpreting the results and applying them to counseling men with low testosterone considering that the potential benefits of fat-restricted diets, which could include improvement in lipid profiles and optimization of cardiovascular health, could outweigh the decrease in serum testosterone they may experience.

"Our study provides compelling evidence that a fat-restricted diet is associated with mildly decreased testosterone levels, regardless of body mass index."

Joshua A. Halpern, MD, MS

“In addition, it is important to recognize that our study did not track the longitudinal impact of diet on testosterone. Rather, due to the cross-sectional nature of our study, the associations we identified between diet and serum testosterone are merely a snapshot from one point in time,” added Dr. Halpern, assistant professor of urology at Northwestern University Feinberg School of Medicine, Chicago.

“Some prior studies examining the effects of popular diets upon weight loss reported that weight loss can lead to increases in serum testosterone, but there have not been studies examining the direct effect of diet on testosterone levels,” lead author Richard J. Fantus, MD, told Urology Times. “Our investigation is the first to use a large, population-based cohort to understand the association between some of the most popular diets and serum testosterone.

“Our recommendation is that dietary advice should be personalized for each patient and their specific health goals, rather than use a ‘one-size-fits-all’ approach. We hope that our research will enable both physicians and patients to make more educated decisions in pursuing an individualized approach,” added Dr. Fantus, a urology resident at the University of Chicago Medicine.

To examine the relationship between serum testosterone and diet, the authors extracted data collected in three National Health and Nutrition Examination Surveys from adult men (ages 18 to 80 years) who completed the 2-day dietary history and underwent serum testosterone. Their analysis included 3,128 men.

Based on Dietary Intervention Randomized Controlled Trial group criteria, 457 men (14.6%) were identified as following a low-fat diet and 764 men (24.4%) were identified as following a Mediterranean diet. Less than 1% of the cohort were following a low-carbohydrate diet, and no additional analyses were done for that subgroup.

Mean serum testosterone in men on a low-fat diet was significantly lower than in men on a nonrestrictive diet (410.8 vs. 443.47 ng/dL; p<.002). On multivariable analysis controlling for a number of potential confounders, serum testosterone level remained significantly lower in the low-fat diet group compared with the men on nonrestrictive diets (p<.05).

Mean serum testosterone for the men adhering to a Mediterranean diet was 412.90 ng/dL and significantly lower than in the group on a nonrestrictive diet in univariable analysis (p=.005), but the statistical difference between groups was not maintained on multivariable analysis.

The study also compared the diet groups for the proportion of men with serum testosterone <300 ng/dL, representing the AUA cutoff for low testosterone. The analyses found no statistically significant differences comparing either the low-fat diet or the Mediterranean diet groups to the nonrestrictive diet group.

"Our recommendation is that dietary advice should be personalized for each patient and their specific health goals, rather than use a ‘one-size-fits-all’ approach."

Richard J. Fantus, MD

FDA Clears Malleable Penile Prosthesis

The FDA has cleared the Rigi10 New Generation Malleable Penile Prosthesis for implantation into the corpora cavernosa of the penis for men who are diagnosed with erectile dysfunction. The prosthesis is implanted to provide adequate penile rigidity for sexual intercourse.

Rigi10 is easy to implant and easy to use, according to manufacturer Rigicon, Inc. The Flexible Rod Technology enables higher bending angles with no spring-backs. Rigi10 is offered in five different diameters and two sizes for a better fit to the patient’s anatomy.

Source: Joshua A. Halpern, MD, MS, and Richard J. Fantus, MD

Mean serum testosterone for the men adhering to a Mediterranean diet was 412.90 ng/dL and significantly lower than in the group on a nonrestrictive diet in univariable analysis (p=.005), but the statistical difference between groups was not maintained on multivariable analysis.
Drug-coated balloon found efficacious for recurrent strictures

Meaningful increased maximum urinary flow rate, decreased IPSS observed

John Schieszer
UT Correspondent

Use of the Optilume paclitaxel-coated balloon appears to be a safe and effective method for the treatment of recurrent bulbar urethral strictures, producing a low 12-month recurrence rate and no treatment-related serious adverse events, according to researchers in Minnesota, Virginia, and Latin America.

They reported 1-year data on this novel drug-coated balloon (DCB) at the 2019 AUA annual meeting in Chicago that showed the treatment is safe and the device produces urethral luminal gain that achieves significant clinical results with meaningful increased maximum urinary flow rate (Qmax) and decreased International Prostate Symptom Score (IPSS).

The authors conducted a multicenter, non-randomized clinical trial (NCT0304726) with this device, which combines mechanical balloon dilation with a paclitaxel drug coating. The DCB is designed to limit hyperactive cell proliferation and subsequent fibrotic scar formation in an effort to achieve significant clinical results with meaningful increased maximum urinary flow rate (Qmax) and decreased International Prostate Symptom Score (IPSS). The authors note that paclitaxel has been used extensively in cardiovascular medicine for prevention of restenosis following angioplasty and/or stenting.

<table>
<thead>
<tr>
<th>TABLE</th>
<th>EFFECT OF PACLITAXEL-COATED BALLOON TREATMENT FOR STRICTURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean International Prostate Symptom Score</td>
<td>Baseline</td>
</tr>
<tr>
<td>Mean maximum urinary flow rate</td>
<td>25</td>
</tr>
<tr>
<td>Mean maximum urinary flow rate</td>
<td>5 cc/s</td>
</tr>
</tbody>
</table>

Source: Sean P. Elliott, MD, MS

"If the long-term results prove to be as positive as the short-term results, then this could provide an intermediate option for patients with recurrent bulbar urethral strictures."

SEAN P. ELLIOTT, MD, MS

The ROBUST I study included 53 men with a single recurrent bulbar urethral stricture. All the men had undergone one to three previous endoscopic treatments. However, the majority were performing self-dilation at home. Following treatment with the DCB, the 12-month anatomic success rate (defined as urethral lumen ≥14F) was 70%. No treatment-related serious adverse events within 90 days following the procedure were reported.

"I was not surprised by any of the findings. I expected the drug-coated balloon to perform as well as or better than an uncoated balloon," said study investigator Sean P. Elliott, MD, MS, professor and vice chair of urology at the University of Minnesota, Minneapolis.

In this current study, men with bulbar urethral strictures ≤2 cm were enrolled at four study sites. All the men underwent mechanical balloon dilation or direct visualization internal urethropotomy just prior to DCB treatment. The authors assessed patients at 2 to 14 days, 14 days, 3 months, 6 months, and 12 months after treatment. They used anatomic success as the primary efficacy endpoint, and it was defined as urethral lumen ≥14F.

The study revealed that anatomic success was achieved in 32 of the 46 men (70%; 95% CI: 54-82%) at 12 months. Among the 14 patients who failed to meet the primary efficacy endpoint, seven were due to cystoscopic recurrences, five were due to retreatments, and two patients exited the study early due to symptom recurrence.

Success rate ‘encouraging’

"Our 70% success rate is encouraging. If they were treated with an uncoated balloon, I would have expected it to be closer to far less than 70% and closer to 10% at 1 year. The initial results are encouraging. The average number of prior endoscopic treatments in our cohort was 1.7. Historically, such a group should have a low success rate with this, their third dilation. So compared to historical controls, the Optilume performed well," Dr. Elliott told Urology Times.

He said there were no severe urinary adverse effects and the moderate side effects that did occur were not of serious concern. Overall, the most common adverse events were urinary tract infection (15%), fever (12%), acute urinary retention (8%), headache (8%), and dysuria (6%). The majority were classified as mild (58%) or moderate (38%), based on the Common Terminology Criteria for Adverse Events.

In this cohort of 53 men, the mean age was 51 years (range, 22-81 years) and stricture etiology was due to traumatic (31%), iatrogenic (45%), and idiopathic factors (4%). The men were treated between Nov. 29, 2016 and Sept. 9, 2017. Mean IPSS and mean Qmax were also significantly improved at 1 year. IPSS improved from 25 to 5 (p<.05) and Qmax from 5 cc/s to 20 cc/s (p<.05).

The authors now plan to follow this group of patients for 5 years and will report long-term success rates as they become available.

“If the long-term results prove to be as positive as the short-term results, then this could provide an intermediate option for patients with recurrent bulbar urethral strictures. By intermediate, I mean it would be an alternative that would sit in between urethral dilation and urethroplasty,” Dr. Elliott said.

Urotronic provided funding for the study.
What are Category III codes, and how are they best used for billing?

CPT subset tracks utilization of emerging technologies, procedure

Category III codes are designated as temporary codes by the AMA. Even though the codes are considered temporary, they are an integral and important part of the system.

Category III codes do not need to meet the same standards required by the CPT editorial process for Category I CPT codes. According to the AMA: “For Category I codes, the Panel requires that the service/procedure be performed by many health care professionals in clinical practice in multiple locations and that FDA approval, as appropriate, has already been received.”

Obtaining a Category III code does not require FDA approval or clearance (of a drug or medical device used in the procedure if required) nor published peer-reviewed evidence for the procedure/service or if required the drug or supply. The CPT editorial panel does require at least one of the following for the procedure/service and the integral drug/supply if required to approve a new Category III code:

- support from the specialties who would use the procedure
- availability of U.S. peer-reviewed literature
- descriptions of current U.S. trials outlining the efficacy of the procedure.

There are no restrictions on the entity or individual that may submit a request for a CPT code (regardless of category). As part of the process, all submissions for new codes are reviewed by the AMA staff. If the application and applicant meet the requirements set forth by the AMA, the code application is presented to the CPT editorial panel. The editorial panel includes specialty society-appointed members; urologists are appointed by the AUA. Therefore, all codes performed by urologists will likely require the support and recognition by the AUA before they are added to the CPT code set.

Many Category III codes are submitted to the AUA by companies for a technology or procedure for which they would like tracked and monitored for use. When applying for a Category III code, there is an expectation that within 5 years the Category III code will be converted to a Category I code.

Advantages, disadvantages of Category III codes

When deciding whether or not to apply for a CPT code, the group or individual considering application must consider the advantages and disadvantages of obtaining a Category III code. Advantages include:

- publication of codes every 6 months, allowing faster adoption of the code (Category I codes are released only once per year)
- as mentioned previously, lower thresholds of supporting data
- early and accurate tracking of the service, which may help with the future application for a Category I CPT code, because the company will be able to provide an accurate count of utilization

In summary, Category III codes are unique because they are temporary, allowing faster adoption of emerging procedures and technologies while still requiring peer-reviewed evidence to support their use. Urologists can use these codes to track emerging procedures and ensure they stay current with the latest advancements in the field.
TABLE  NEW UROLOGY-RELATED CPT CATEGORY III CODES FOR 2020

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0582T</td>
<td>Transurethral ablation of malignant prostate tissue by high-energy water vapor thermotherapy, including intraoperative imaging and needle guidance</td>
</tr>
<tr>
<td>0548T</td>
<td>Transperineal perurethral balloon continence device; bilateral placement, including cystoscopy and fluoroscopy</td>
</tr>
<tr>
<td>0549T</td>
<td>Transperineal perurethral balloon continence device; unilateral placement, including cystoscopy and fluoroscopy</td>
</tr>
<tr>
<td>0550T</td>
<td>Transperineal perurethral balloon continence device; removal, each balloon</td>
</tr>
<tr>
<td>0551T</td>
<td>Transperineal perurethral balloon continence device; adjustment of balloon(s) fluid volume</td>
</tr>
<tr>
<td>0587T</td>
<td>Percutaneous implantation or replacement of integrated single device neurostimulation system including electrode array and receiver or pulse generator, including analysis, programming and imaging guidance when performed, posterior tibial nerve</td>
</tr>
<tr>
<td>0588T</td>
<td>Revision or removal of integrated single device neurostimulation system including electrode array and receiver or pulse generator, including analysis, programming, and imaging guidance when performed, posterior tibial nerve</td>
</tr>
<tr>
<td>0589T</td>
<td>Electronic analysis with simple programming of implanted integrated neurostimulation system (e.g., electrode array and receiver), including contact group(s), amplitude, pulse width, frequency (Hz), on/off cycling, dose lockout, patient-selectable parameters, responsive neurostimulation, detection algorithms, closed-loop parameters, and passive parameters, when performed by physician or other qualified health care professional, posterior tibial nerve, 4 or more parameters</td>
</tr>
<tr>
<td>0590T</td>
<td>Electronic analysis with simple programming of implanted integrated neurostimulation system (e.g., electrode array and receiver), including contact group(s), amplitude, pulse width, frequency (Hz), on/off cycling, burst, dose lockout, patient-selectable parameters, responsive neurostimulation, detection algorithms, closed-loop parameters, and passive parameters, when performed by physician or other qualified health care professional, posterior tibial nerve</td>
</tr>
</tbody>
</table>

Source: CPT 2020 manual

- the possibility of payment assignment and specific coverage rules during the investigation-
a/early adoption phase of a procedure.
- Disadvantages include:
  - system biases that Category III codes are all unproven or lack FDA approval, resulting in blanket non-coverage decisions for services described by Category III codes
  - difficulty in locating the codes for new services as they are not located in sections typically searched by payers, physicians, and groups.

Although coverage and payment for the performance of a procedure with a Category III code is not common among the majority of payers when initially released, physicians are required to use the most appropriate code to describe the service provided. Thus, reporting of a Category III code for a service accurately described by the code is appropriate. In the long run, the determination for coverage should be based upon clinical evidence and medical necessity, and not the CPT code category.

It is imperative to check with your Medicare contractor and insurer guidelines to determine if a procedure, no matter which category, is a covered benefit. In urology, we have seen times when a Category III code is covered where a Category I code is not covered. Since some Category III code procedures are only provided within a clinical trial, it is important to determine whether the Category III code will be submitted for tracking purposes or billing purposes.

Before proceeding with the performance of a procedure with a Category III code, it is important to determine if the reimbursement covers the cost of the device/procedure. We have seen some cases where this is not true and the practice risks losing money for providing the service. Finally, if a provider believes that any of the procedure or technology has been proven both safe and effective as well as reasonable and necessary, some insurers allow coverage on a case-by-case basis or may request coverage through a reconsideration process.

In other words, the same rules that apply to Category I CPT codes apply to Category III codes. Check with the payer prior to providing the service to determine how to proceed.
Can you afford to avoid MIPS participation?

Score of 0 results in 9% negative fee schedule adjustment

The complexities of the Merit-based Incentive Payment System (MIPS) have prompted some physicians to claim they would rather absorb the penalties in Medicare payments than incur the costs of reporting under the program (bit.ly/ignoringmips). Indeed, one of the most common questions I am asked is, “Is MIPS really worth it?”

Remember that MIPS is not “optional” for most contemporary urology practices that wish to participate in Medicare. If minimum patient volume, service volume, and charges are exceeded, clinicians are automatically subject to MIPS, unless they are a qualified participant in an advanced alternative payment model. (Few urologists are participating in an advanced payment model as of 2019). So the real question is what is the potential upside, downside, and cost of participation?

In order to calculate the cost of not participating in MIPS, one need only project the revenues for professional Medicare services for the year. For example, a mature, stable practice might have $400,000 in such revenue. The cost of ignoring MIPS composite score of 100. (This includes some adjustment for exceptional performance.) Results were similar in year 1 of MIPS.

The accompanying figure from the CY 2020 MPFS Final Rule (bit.ly/finalruleinfo) may make this a little easier to understand. In the current year 2020, a clinician must achieve a MIPS composite score of 45 to avoid a negative payment adjustment in 2022. A score of 30 would result in a –3% payment adjustment in 2022; a score of 20, a –5% adjustment; and a score of 0, a –9% adjustment. However, adjustments for scores over 45 cannot be determined until all of the projected penalties for negative adjustments are determined by actual results. Therein lies the uncertainty: The potential downside is clearer than the potential upside, according to the rules of the game as currently understood.

In performance year 2 of MIPS (2018), the maximum negative adjustment was 5%, but because so many clinicians achieved positive scores, scaling had to be applied such that the maximum positive adjustment was only about 1.67% for a perfect MIPS composite score of 100. (This includes some adjustment for exceptional performance.) Results were similar in year 1 of MIPS.

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MIPS altogether would be $36,000 (9%), a substantial penalty.

What about trying to just do the “easy” reporting to avoid some or all penalty? Quality reporting is without doubt the most time-intensive and complex part of the reporting burden for clinicians. What if you could just avoid that, which accounts for 45/100 points in 2020? The main problem with this approach is that you will have to score almost perfectly in the Promoting Interoperability category (25% weight) and the Improvement Activities category (15% weight), and do reasonably well in the Cost category (15% weight) to meet or exceed 45 points.

The Cost category is based on data that are not currently available to you (and there is no reporting burden/cost), so your only predictor of “success,” perhaps, is past performance. Furthermore, the threshold for 0 adjustment and the weight of the Cost category are increasing each year, leading to more uncertainty in the ability to predict your MIPS score in real time. Taken together, ignoring the entire Quality category may be a risky strategy in 2020 and beyond.

Cost of participating
What is the cost of participating fully in MIPS, and is it offset by the upside? In our same example, a 1% positive fee schedule adjustment—$4,000—may not seem like much annual gross revenue. MIPS participation costs over and above baseline overhead might include: paying a consultant or EHR vendor for turnkey services (data collection and submission)—typically much less than $4,000/provider, registry fees (typically a few hundred per provider), paying an internal resource, and intangible costs like data entry (clinical staff and physicians) and tracking solely to support MIPS.

Again, most of these costs pertain to the Quality category and your experience will vary tremendously based upon your EHR vendor’s ability/willingness to create reports, export data, or communicate with qualified clinical data registries. Economies of scale are important, and large groups are better positioned to reduce the costs of participation/provider. Small practices may wish to investigate “virtual groups,” a relatively new option in MIPS designed to allow disparate practices to achieve economies of scale. With respect to the intangible burden of “data entry,” MIPS is simply an intermediate version of value-based care, the central paradigm of which is to improve quality and reduce cost. If your providers are having to click boxes in the EHR to document quality or your billing staff is applying G codes on claims, there may be an opportunity to reexamine their work flow to eliminate redundant work, or even take a fresh look at a newer EHR. Value-based care is probably here to stay, and the next generation of documentation should passively contribute to quality metrics, with minimal special effort by the user to separately comply with a government program.

Bottom line: There is now and for the foreseeable future a 9% negative fee schedule adjustment for practices that ignore MIPS because “it isn’t worth it.” While the costs of participation may offset or exceed the potential revenue increase in a small practice, these costs of data collection and reporting are the new normal in a value-based reimbursement paradigm and are likely to become the cost of doing business even outside of Medicare.
The Division of Urology at the University of Vermont Larner College of Medicine in alliance with the University of Vermont Medical Center, is seeking Clinical Practice Physicians who are board eligible/board certified Urologists to join the Urology service at our affiliate community medical center, Champlain Valley Physicians Hospital (CVPH) in Plattsburgh, New York. CVPH is a progressive medical center with nine state-of-the-art OR’s and Ambulatory Surgery Center. This position offers the unique opportunity to work in a community setting while having an active affiliation with Vermont’s only Academic Medical Center; the only ACS verified Level I trauma center in the state providing tertiary care to patients from Vermont and Northern NY. Serving the patients from Upstate New York for decades, the local urologic surgery practice recently joined the faculty at the University of Vermont and are now seeking additional colleagues to join the dynamic Urology faculty that span the network hospitals. Specifically, the Division seeks applications from individuals seeking a community Urology employment opportunity with a collegial and collaborative setting with University support. Plattsburgh is located on the shores of Lake Champlain with easy access to the Adirondack Mountains, Olympic-Lake Placid region, Montreal and Burlington, VT.

Applicants must be board certified or board eligible and eligible for medical licensure in the state of New York. This is a full-time, 12 month, salaried position.

Interested individuals should apply online at https://www.uvmjobs.com/postings/31529 (position number 00024781). Inquiries may be directed to Mark Plante, MD, FRCS(C), FACS, Chief of Urology via Kristin Allard at Kristin.Allard@uvmhealth.org

The Division of Urology at the University of Vermont Larner College of Medicine in alliance with the University of Vermont Medical Center, is seeking a Clinical Practice Physician who is a board eligible/board certified Urologist to join the Urology service at our affiliate community medical center, Central Vermont Medical Center (CVMC). This position offers the unique opportunity to work in a community setting while having an active affiliation with Vermont’s only Academic Medical Center; the only ACS verified Level 1 trauma center in the state providing tertiary care to patients from Vermont and Northern NY. Duties will include general urologic patient care (adult and minor pediatric) with the opportunity to teach medical students and potentially urology residents. Specifically, the Division seeks applications from individuals seeking a community Urology practice opportunity with a collegial and collaborative setting with University support. The central Vermont region, 30 minutes from Burlington, Vermont, offers easy access to numerous outdoor activities with several ski areas just a short drive away.

Applicants must be board certified or board eligible and eligible for medical licensure in the state of Vermont. This is a full-time, 12 month, salaried position.

Interested individuals should apply online at http://www.uvmjobs.com/postings/33676 (position number 00023212). Inquiries may be directed to Mark Plante, MD, FRCS(C), FACS, Chief of Urology via Kristin Allard at Kristin.Allard@uvmhealth.org

The University is especially interested in candidates who can contribute to the diversity and excellence of the academic community through their research, teaching, and/or service. Applicants are requested to include in their cover letter information about how they will further this goal.

The University of Vermont is an Equal Opportunity/Affirmative Action Employer. All qualified applicants will receive consideration for employment without regard to race, color, religion, sex, sexual orientation, gender identity, national origin, disability, protected veteran status, or any other category legally protected by federal or state law. The University encourages applications from all individuals who will contribute to the diversity and excellence of the institution.
The Department of Urology at Mayo Clinic in Florida seeks an office-based general Urologist for a full-time staff position to complement a thriving and expanding surgical practice. Successful candidates must be proficient in office-based procedures such as cystoscopy, vasectomy, and prostate biopsy. Requires Board Eligibility or Board Certification (BE/BC) in Urology and eligible for Florida licensure. The Department of Urology at Mayo Clinic Florida is ranked in the top 50 nationally by US News and World Report. The Urology residency program is a strong and expanding program ranked in the top 0 programs in the Southeast United States by Doximity. Mayo Clinic in Florida is an integrated multi-specialty practice with over 400 physicians covering all specialties. You are invited to partner with the nation’s best hospital, U.S. News & World Report 2020, ranked #1 in more specialties than any other care provider. Practicing at Mayo Clinic provides a rewarding career that promotes excellence in patient-centered care. You can thrive in an environment that supports innovation and has a wealth of resources available to you – including an integrated EMR and collaboration with top specialists – to give your patients the quality of care you want to achieve.

Interested?
To apply online: jobs.mayoclinic.org   Keyword search: 115-1008BR
Questions? Email: culbertson.nicole@mayo.edu

Garden State Urology (GSU) is proud to announce a General Urology job opening in Wayne, N.J. The physician will participate in office coverage, shared call, and surgeries. Candidates must be trained in general urology, with fellowship training preferred. The ideal candidate will be board certified/eligible and be able to obtain an active, unrestricted New Jersey medical license. This is a wonderful opportunity to join a large and reputable Urology group in Northern New Jersey.

This is a great location offering multiple points of interest including museums, history, fine dining, theater and more. Physicians may live within 30-60 minutes of New York City, the Pocono Mountains and the Jersey shore. It is easy to access 3-4 international airport hubs as well as local and national railway systems. This part of New Jersey is known for its natural beauty and an extensive network of parks and trails which are well-maintained for hiking, biking and cross-country skiing. The area boasts some of the best public and private schools in the country.

Assistance with hospital privileges will be provided. GSU, a leased practice of Atlantic Health System offers a competitive benefits package and salary. Along with providing office hours, this position serves the patients within the Chilton Medical Center. To learn more, give us a call today and speak with the Director of Human Resources for details.

Please email CV with cover letter to careers@gsunj.com
Equal Opportunity Employer
IRS releases updates for 2020; here’s what you need to know

Notable changes include increased contribution limits for 401(k)s, 403(b)s

Traditional and Roth IRAs. There was no change to the annual contribution limits for traditional and Roth IRAs. That amount remains $6,000 if under age 50 and $7,000 if over age 50.

Savings Incentive Match Plan for Employees (SIMPLE) and Simplified Employee Pension IRAs. The contribution limit for SIMPLE IRAs increased to $13,500 from $13,000. The SIMPLE catch-up contribution limit for those over age 50 remains at $3,000. The SEP maximum compensation limit increased to $285,000 from $280,000.

Health savings accounts (HSAs). If you are in a high-deductible health plan, you may have access to an HSA. If you are the only person covered by your health plan, the HSA contribution limit was increased to $3,550 from $3,500. If family members are also on the plan, the contribution limit was increased to $7,100 from $7,000.

Flexible spending accounts (FSAs). The health care FSA contribution limit was increased to $2,750 from $2,700.

Lifetime gift and estate tax exemption. This exemption amount was increased to $11.58 million per individual, up from $11.40 million. For married couples, the exemption amount is $23.16 million.

Annual gift exclusion. This amount remains unchanged at $15,000.

Child tax credit. This credit has been increased to $2,000 and is refundable up to $1,400. However, the adjusted gross income phaseout to claim this credit remained the same at $200,000 for married couples filing jointly.

Student loan interest deduction. The deductible amount remained at $2,500. However, this deduction is phased out for married couples filing jointly having between $70,000 and $140,000 of modified adjusted gross income. Single tax filers with annual income of $85,000 or more are completely phased out.

There are many other small changes that go into effect this year. We recommend you speak with your CPA or financial professional to get a comprehensive list.

Q: What is the newly passed Secure Act and how might it impact me?
A: If you are not yet retired, the Secure Act will have little impact on your retirement planning strategies. However, if you are in or approaching retirement, it may impact you in the following ways:

• The age you must start taking required minimum distributions (RMDs) has been increased to 72. Previously, you had to start taking distributions from traditional IRAs and employer-sponsored retirement plans starting at age 70½. Roth IRAs are exempt from RMDs.

• There may be more opportunities to complete Roth conversions. A Roth conversion is when you convert pre-tax assets in a traditional IRA to Roth assets and pay the income tax in the year the conversion takes place. This is typically advised when you have a low-income year in retirement and will be in a lower tax bracket. Once the assets have been converted to a Roth, they are no longer subject to RMD rules and can continue to grow tax free until you are ready to take the money from the account.

• The rules changed for inherited or “stretch” IRAs. Previously, if you inherited a retirement account from a non-spouse (parent, grandparent, etc.), you could stretch out the distributions based on your life expectancy. This could have significant tax benefits. Under the Secure Act, you are no longer able to stretch the required distributions. The entire account must be distributed within 10 years of the year the IRA owner died.

FINANCIAL TIPS

- The standard deduction increased to $12,400 from $12,200 for single filers. For married couples, it increased from $24,400 to $24,800.

- There was no change to the annual contribution limits for traditional and Roth IRAs. That amount remains $6,000 if under age 50 and $7,000 if over age 50.

- Under the newly passed Secure Act, if you are in or approaching retirement, the age you must start taking required minimum distributions has been increased to 72.
Non-compete clauses: What physicians need to know

Following these strategies could help you avoid costly legal fees

Physicians are often faced with non-compete business agreements when signing employment contracts. These may also be required of physicians when obtaining hospital privileges. A non-compete agreement, also often referred to as a non-compete clause, is when a physician agrees not to work for a competing practice or hospital within a certain period of time after leaving a job. Breaking the non-compete agreement may incur a hefty fine that is typically spelled out in the physician’s contract.

Often, addressing the fine details of a non-compete clause after the fact adds costly legal fees. There are a few strategies that doctors can adopt before and after signing a contract to avoid problems with non-compete issues.

Negotiating

Young doctors may be worried that a contract could be withdrawn after requesting concessions such as removal of a non-compete clause. Jon Appino, principal and founder of Contract Diagnostics, a firm that helps physicians with contract reviews, says that dealing with these types of hesitations is a skill.

“There are careful ways to approach the conversation. Just like good bedside manner, you can learn how to negotiate,” he said.

Appino explains that a physician can be creative with the requests made of an employer.

“They may not be able to change the non-compete, but that doesn’t mean there aren’t many compromises you can make around it,” he said.

Of course, sometimes a physician absolutely cannot avoid being penalized for breaking a non-compete agreement. Some of these agreements can impose a fine ranging from $10,000 to $250,000 for doctors. And geographic limitations may range from within 5 miles to 100 miles of the practice.

For doctors who work in large hospital systems with many satellite offices, the non-compete can even encompass all of the satellite locations. These agreements can cover a duration ranging between 1 years and 3 years after leaving a practice.

Locum tenens work, often in different states, can provide temporary employment in various geographic regions during this time period.

Telemedicine can be another option as well. Tisha Rowe, MD, founder of Rowe Network, a multi-specialty telemedicine network, has worked with doctors who use telemedicine as a way to bridge the gap before they can start another job in the same town without violating a non-compete agreement.

There are some positive aspects of non-compete agreements. A practice can be faced with losing patients after a disgruntled physician leaves to set up a practice in the same town, and a non-compete agreement can reduce the chances that this could happen.

“Many states do not allow non-competes and some states have legislation in the works.”

JON APPINO
PRINCIPAL AND FOUNDER, CONTRACT DIAGNOSTICS

Some physicians, particularly those who have worked hard to build their group structure, often see benefits to these arrangements.

“A physician who is happy with their role could see that a non-compete agreement would protect the group and their colleagues from leaving and causing harm to the group,” Appino said.

Newly trained physicians may want some time to decide if they want to stay in a city or town long term.

Often, taking an employed position for a few years before starting a practice is the most practical way to do that. And even for those who know they want to start a private practice, most doctors need to work and save up money before they can afford the cost of opening their own practices.

With a non-compete agreement, employers have less incentive to be fair to a physician because leaving the practice may require the physician to relocate. And patients may become confused and straightforward after their physician leaves without offering to continue to be their doctor.

Telemedicine

Telemedicine is emerging as a new way of delivering patient care. However, as this patient care model is emerging, doctors may switch from one telemedicine company to another.

Dr. Rowe explains that telemedicine companies generally do not place non-compete agreements in their contracts, and that doctors can work for more than one telemedicine firm at a time or sequentially without incurring any non-compete violations.

Dr. Rowe explains, however, that she has encountered several doctors who were prevented from taking on telemedicine as a side job due to a non-compete clause imposed by their employers.

Hospitals and medical practices can’t survive without physicians. A physician could certainly take his or her good reputation and loyal patients and leave a practice. A non-compete agreement often presents an obstacle to doing that.

When a physician is considering an employed position or group practice with a non-compete agreement, it is a good idea to discuss the expectations. A doctor needs to openly acknowledge with potential employers or partners that the working relationship needs to be evaluated first before anyone can agree to taking a major financial loss for breaking ties. And working out a non-compete agreement that is fair for everyone is one of the ways to ensure that all parties have a reasonable timetable to evaluate the professional partnership and see if it is a good fit.

Non-compete agreements are frequently challenged in legal cases.

“Many states do not allow non-competes and some states have legislation in the works,” Appino said.

Yet he still encourages doctors to check all local laws, explaining that even when a doctor hears that a non-compete is unenforceable, the contract may have predetermined damages that are tough to fight against.
Urologist recruitment challenges stem from multiple factors

Physician shortage, geographic variations among elements to keep in mind

I have a fantasy that everyone likes me. It’s not a true statement, I realize, but it does make me sleep better at night. As a result, I thought that recruiting a new partner to join my group would be easy. Unfortunately, that is not true either.

I live and practice in Colorado Springs, CO, which ranked third in the nation in the 2019 U.S. News and World Report’s ranking of best places to live. (Our neighbors to the north, Denver, ranked second, and Austin, TX was number one.) I am part of a large single-specialty group and do just above the average number of RVUs with just above the average compensation.

It seems like a good job in a great city. But recruiting was still hard work.

The challenge of recruiting new physicians isn’t specific to urology. The first problem we have is that the supply just isn’t there. By 2030, the Association of American Medical Colleges estimates there will be an overall physician shortage of at least 120,000 doctors.

But the situation is worse than that. Not only are we all competing for an ever-shrinking pool of doctors, the timeline to recruit a physician keeps expanding. Many physicians wrongly assume that if they start looking 12 to 18 months before they want a new doctor to start, they’re planning well ahead. Unfortunately, and my own experience supports this, most residents expect to have a signed contract well before their chief year begins.

When you do the math, that means if a group is looking to hire a newly minted, fresh-out-of-residency urologist, they need to plan 24 to 30 months ahead. At that time frame, do you even know yet if you need a new doctor for your practice? At what age do we now have to start asking the senior partners about their retirement plans and then make sure they stick with those plans? The burdens of planning that far ahead can be significant.

Geographic variations in play

So, let’s assume a group makes the decision 3 years out that they definitely need a new doctor. Can they actually find someone? Even with that timeline, it’s still not guaranteed. We all know that urologists are in short supply, but when you look at local-regional variations in doctors, the problem becomes even worse. An interesting article looking specifically at the VA system but with lessons for everyone shows that urologists tend to concentrate in larger cities, leaving a large number of patients completely unserved (Fed Pract 2015; 32:18-22).

Most urology groups remain relatively small and a new partner is someone who had better be able to get along with most of your group.

Being one of those physicians who lives in a metropolitan area, I understand the trend. I enjoy the conveniences of a city both personally and professionally. Personally, my wife won’t move to a rural area, so that’s that. Professionally, there are advantages to working in a city where I have access to well-trained physicians in every subspecialty. While I also run an outreach clinic in a wonderful small town full of great people staffed by intelligent and caring professionals, I doubt that town will ever find a urologist willing to work there full time, leaving the town underserved.

Being on call every night with no colleagues for miles is not something I am interested in signing up for. Unfortunately, this creates significant problems for rural centers when it comes to recruitment, as Adam Smith’s “invisible hand” sometimes doesn’t work.

What is Adam Smith’s invisible hand? Compensation. In a perfect market-driven model, as the demand for urologists increases and their volume decrease, compensation would simply increase. It’s Economics 101. Unfortunately, federal rules on fair market-driven compensation prevent this from happening. But those same rules also warp graduating residents’ views on what “normal” compensation is!

We all receive flyers promising incredible compensation packages and while even the greenest of residents realize that when a job offer is too good to be true, it is too good to be true, the numbers being offered cause problems. Why? Because while large hospital systems continue to offer impressive starting salaries on short-term contracts (before the inevitable pay decrease when the contract is renegotiated 2-3 years later), those of us in the real world are having problems matching it.

Lastly, and most challenging, is finding the right person. Most urology groups remain relatively small and a new partner is someone who had better be able to get along with most of your group. If you think dating is hard, finding a partner who is a good “fit” is even harder. Now I realize that most groups have a period when a new hire can be let go for little reason if the group feel it is not working out, but given the challenges of recruiting a new doctor, that is not an easy decision. But it is clearly one that is made both by groups and by new hires.

My group was lucky. We had known for a few years we needed someone and had started to look. We found a candidate who was leaving the military and moving into private practice and had practiced in our geographic area for many years. We knew and liked him and were able to fend off the local hospital systems because he was smart enough to realize how terrible those systems was. Further, he knew the local community well and understood what a reasonable offer entailed.

We ended up with a great partner when we needed one at a price that was fair to everyone. I’m not sure if we’ll be able to pull off that trick the next time around, but that is a story for another day.
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Lack of emergent VCUG leads to costly settlement

Urologist unsuccessfully defends claim of negligence

Several weeks before his birth, it appeared that “J.D.” suffered from antenatal hydronephrosis. His mother was induced to deliver the child at 36 weeks. J.D. had an Apgar score of 9/9 at the time of his birth. Thereafter, a pediatrician saw the child, examined him, and requested a neonatology consult for the next day. That pediatrician went away for the weekend and turned J.D.’s care over to another pediatrician. A neonologist examined him the following day, ordered an ultrasound with a notation that the result of the ultrasound should determine the course of action, and noted that a pediatric urologist should be consulted. The day after birth, an ultrasound confirmed that J.D. suffered from bilateral moderate to severe hydronephrosis.

Following this diagnosis, the pediatrician discharged the child 2 days after birth with instructions to see a pediatric urologist, without ordering a voiding cystourethrogram (VCUG) to determine the cause of the hydronephrosis. The day after discharge, J.D. was examined by a urologist who performed an ultrasound and released the child home with instructions to call and schedule the VCUG for the following week. After the visit with the urologist, J.D. developed jaundice that required in-home bilirubin lights.

VCUG reveals Grade IV reflux

J.D.’s mother called and scheduled the VCUG as instructed, and the procedure was set just 7 days after birth. On the day of the surgery, the mother brought J.D. to the hospital for the procedure. The VCUG revealed Grade IV reflux. J.D. was immediately hospitalized, suffering from urinary tract infection, sepsis, and Enterobacterieae coli meningitis. As a result, J.D. suffered mild mental retardation. J.D.’s mother brought suit against all the involved pediatricians, the neonotologist, and the urologist, alleging that they were negligent in failing to properly treat her son who was diagnosed with antenatal hydronephrosis prior to birth. The plaintiff alleged that the physicians fell below the standard of care by failing to order a VCUG before discharge (pediatricians and neonologist) or on an emergent basis (urologist), and failing to order any antibiotics to keep J.D.’s urine sterile pending a diagnosis of his condition (all defendants). All defendants denied liability.

Following an adverse liability verdict, this defendant urologist did not also want the jury deciding damages.

The defendant pediatricians contended that J.D.’s condition was consistent with mild jaundice due to prematurity and that they acted within the standard of care by referring the child to a pediatric urologist and neonologist. The neonatologist contended that he was called to consult solely for the purpose of ordering the ultrasound and that was the extent of his involvement with the infant.

The defendant urologist claimed that there was no deviation from the standard of care. He maintained that he observed J.D.’s urine during examination and had no reason to order the VCUG test on an emergent basis since the child was voiding. The defendant urologist also argued that at the time of the care, there was no standard of care that required the dispensation of prophylactic antibiotics under these circumstances and consequently there was not negligence on his part.

Matter proceeded to trial against urologist only

Prior to trial, the neonatologist settled with the plaintiff for $100,000. The hospital that was sued on a respondent superior theory settled prior to trial for the sum of $50,000. The remaining defendants, the two pediatricians, and the urologist participated unsuccessfully in mediation. They made a joint offer of $1,500,000 at mediation. The plaintiff accepted the $500,000 offer from the two pediatricians and rejected the $500,000 offer from the urologist. The matter proceeded to trial against the urologist only. The plaintiff petitioned the court for separate jury trials on the issues of liability and damages. This request was granted by the court. The trial on liability lasted 10 days. After 3 hours’ deliberation, the jury returned a verdict in the plaintiff’s favor, finding that the defendant urologist fell below the standard of care and proximately caused J.D.’s injury. The issue of damages was next to be tried. Prior to the damages trial, the defendant urologist agreed to settle for $3,200,000.

LEGAL PERSPECTIVE: The facts involving a young mentally retarded child may have resulted in a staggering damage award. Following an adverse liability verdict, this defendant urologist did not also want the jury deciding damages. As you may know from reading these columns, a plaintiff in a medical negligence action must prove both liability and damages. In this case, the trial was bifurcated, meaning the issue of liability was separated from the issue of damages. The jury’s return verdict on liability altered the landscape for the defendant urologist, who may have been more confident in his position prior to trial.

MIPS MEASURES CAN ALSO REDUCE MALPRACTICE RISK

Coverys, a provider of medical professional liability insurance, identified quality measures within MIPS that align with its recommendations to primary care physicians to reduce their liability, according to Todd Shryock and Logan Lutton from Urology Times sister brand Medical Economics. Learn more about these measures at bit.ly/mipsmalpractice.
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