Managing ADT-related adverse events

BENIGN PROSTATIC HYPERPLASIA
5-year data sustain long-term effectiveness of Aquablation vs TURP

KIDNEY CANCER
“Encouraging” disease-free survival data are seen with avelumab/axitinib

BLADDER CANCER
Combo shows promise in bladder and kidney cancers

KIDNEY STONES
Nelson on pediatric stone prevention and treatment

SEXUAL DYSFUNCTION
Is neuromodulation beneficial for patients with female sexual dysfunction?
Dear AACU Members:

More than 50 years ago, the AACU became the first national organization solely dedicated to advocacy on behalf of clinical urologists’ interests. At the time, Medicare was a new program and the federal government’s role in healthcare quickly grew by leaps and bounds. Today, the AACU continues to steadfastly advance health policies that protect our patients, practices, and profession through initiatives such as UROPAC, the AACU State Advocacy Network, and our recent partnership with Urology Times.

This strategic alliance gives us the opportunity to share news of our work, and the work of AACU members, on a national stage, including showcasing members in Urology Times publications and on the website at www.urologytimes.com/sap-partner/aacu.

In addition to opportunities to publish, the partnership brings AACU members access to case-based roundtable sessions and discounted educational programs. We are pleased to be able to provide these valuable resources and hope that you and your colleagues find them informative. If you would like additional copies of this publication sent to your office, please email info@aacuweb.org.

We are excited about the partnership and look forward to highlighting AACU and its members through our collaboration with Urology Times.

Best regards,

Damara L. Kaplan, PhD, MD
President
American Association of Clinical Urologists
www.aacuweb.org

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masturbatory behaviors. The study suggests that these behaviors may contribute to an increased risk of prostate cancer. Further research is needed to fully understand the relationship between masturbation and prostate cancer risk.
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Managing ADT-related adverse events

10

KIDNEY CANCER
Clinical Updates
24 “Encouraging” disease-free survival data are seen with avelumab/axitinib in RCC

BLADDER CANCER
Clinical Updates
25 Combo shows promise in bladder and kidney cancers

KIDNEY STONES
Question & Answer
26 Nelson on pediatric stone prevention and treatment

SEXUAL DYSFUNCTION
Question & Answer
28 Is neuromodulation beneficial for patients with female sexual dysfunction?

CANCERS & DISEASES

PROSTATE CANCER
Journal Article of the Month
15 Findings support safety, feasibility of partial-gland treatment

BENIGN PROSTATIC HYPERPLASIA
Clinical Updates
18 5-year data sustain long-term effectiveness of Aquablation vs TURP
CONTENTS

COLUMNS

Malpractice Consult
30 Presentation, diagnosis, and management of a rare case of urachal adenocarcinoma

Case-Based Presentation
34 Chanie discusses treatment of patient with high-risk MIBC

UroView
37 New devices are poised to help in overactive bladder treatment

Conference Highlights
40 ASCO Genitourinary Cancers Symposium
42 ASCO GU Lookback

Diversity in Urology
46 What it means to build an inclusive urology practice

Speak Out
48 Do you think patients on active surveillance would be willing to participate in a high-intensity interval exercise training program?

Medical Economics®
49 Teens and older adults are not getting medications to treat opioid abuse

Coding Q&A
54 Can one choose a cancer diagnosis code without tissue?

Practice Matters
56 Leuprolide tops urology spending for Medicare Part B drugs

Money Matters
58 Rising interest rates could affect your investments

Malpractice Consult
62 Affidavits of merit and why they matter

The return of in-person conferences

The recent wave of in-person urology-related conferences, including (but not limited to) the LUGPA Annual Meeting, the Society of Urologic Oncology, and the Genitourinary Cancers Symposium, appears set to continue on into spring with the American Urological Association Annual Meeting in New Orleans, Louisiana. All of us at Urology Times® eagerly anticipate the return of this event and its robust scientific program, which we will cover across print and digital fronts.

In the meantime, you’ll find plenty of coverage of the Genitourinary Cancers Symposium in this month’s issue, including highlights from interviews with Urology Times® Co-Editor in Chief Michael S. Cookson, MD, MMHC, and Editorial Council member Janet Kukreja, MD. They address several of the noteworthy abstracts from this meeting.

Also featured in this issue is our continuing 50th Anniversary Innovation Celebration. This month, in addition to an editorial from Co-Editor in Chief Gopal H. Badlani, MD, look for an interview with Veda N. Giri, MD, who discusses the role genetic testing has played in a new era of prostate cancer therapeutics.

Among our usual coverage of prostate cancer, bladder cancer, benign prostatic hyperplasia, and more, be sure to also look for an interview with David F. Jarrard, MD, in which he discusses managing complications of androgen deprivation therapy for patients with prostate cancer.

In Coding Q&A, Jonathan Rubenstein, MD, and Mark Painter apply their expertise to questions involving whether one can choose a cancer diagnosis code without tissue and whether code 0649T can be used as an add-on code for multiparametric MRI of the prostate. For Practice Matters, Robert A. Dowling, MD, analyzes drug spending in the Medicare Part B program. “Urology practices continue to derive substantial revenue from administering ‘buy-and-big’ drugs, including from the Medicare Part B program (14% of revenue). Of 21 Part B drugs commonly used by urologists, total spending in 2020 increased for 5 drugs and decreased for 16 drugs over the previous year,” Dowling writes.

Finally, in Speak Out, Karen Nash asks 3 urologists for their thoughts on whether they feel patients on active surveillance would be willing to participate in a high-intensity interval exercise training program. “Certainly, my experience with patients who are on surveillance, who meet the criteria for active surveillance, [is that they] tend to be younger and healthier patients, so I don’t see why not. I certainly think it’s a reasonable thing to tell them,” said one urologist.

In this month’s Diversity in Urology column, Polina X. Reyblat, MD, summarizes a recent presentation she made at the Society of Women in Urology Annual Clinical Mentoring Conference on building an inclusive medical practice for patients. “You can be the best physician and clinician out there, but if the patient who walks in at your check-in gets misgendered and disrespected before they even see you, that encounter and that relationship with the patient are already broken. So I would highly recommend [that we] educate ourselves and our staff in terminology and make our urologic offices a comfortable place for our LGBTQA patients,” Reyblat says.

We close this issue with Malpractice Consult, in which Amanda K. Wager, Esq, explains what affidavits of merit are and why physicians should know about them. Thanks for reading.

MIKE HENNESSY JR
Mike Hennessy Jr is president and CEO of Urology Times® parent company, MJH Life Sciences®.
**FDA approves 177Lu-PSMA-617 for PSMA-positive metastatic castration-resistant prostate cancer**

The FDA has approved the targeted radioligand therapy 177Lu-PSMA-617 (LuPSMA; Pluvicto) for the treatment of patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) in the post-androgen receptor pathway inhibition, post-taxane-based chemotherapy setting. The approval of LuPSMA, now also known as lutetium Lu 177 vipivotide tetraxetan, is based on findings from the phase 3 VISION trial (NCT03511664). In the study, adding LuPSMA to standard of care (SOC) led to a nearly 40% reduction in the risk of death vs SOC alone in patients with progressive PSMA-positive mCRPC.2

The findings, which were presented during the 2021 American Society of Clinical Oncology Annual Meeting, showed that at a median follow-up of 20.9 months, the addition of LuPSMA improved the median overall survival (OS) by 4 months over SOC alone (HR, 0.62). Adding the targeted radioligand therapy also led to a 5.3-month improvement in median radiographic progression-free survival (rPFS), translating to a 60% reduction in the risk of progression or death (HR, 0.40). Along with the approval of LuPSMA, the FDA also approved a kit for the preparation of gallium Ga 68 zoetide injection (Locamet). Following radiolabeling, this imaging agent can identify PSMA-positive lesions through a PET scan.

The open-label phase 3 VISION trial included 831 patients (1,179 initially screened) with progressive PSMA-positive mCRPC, who received at least 1 novel androgen axis drug (eg, enzalutamide [Xtandi] or abiraterone acetate [Zytiga]) and were previously treated with 1 to 2 taxane regimens. PET imaging with 68Ga-PSMA-11 was used to determine PSMA positivity. Patient demographics and baseline characteristics were well balanced at baseline. Patients were randomized in a 2:1 ratio to LuPSMA (7.4 GBq every 6 weeks x 6 cycles; n = 551) plus SOC or SOC alone (n = 280). Individual investigators determined the SOC; however, radium 223 (Xofigo) and cytotoxic chemotherapy were not allowed. The coprimary end points of the trial were OS and rPFS. The median OS was 15.3 months in the LuPSMA arm vs 11.3 months in the SOC alone arm, translating to a 38% reduction in the risk of death (HR, 0.62; 95% CI, 0.52-0.74; P < .001). The rPFS was 8.7 vs 3.4 months, respectively (HR, 0.40; 95% CI, 0.29-0.57; P < .001).

**REFERENCES**


**New sacral neuromodulation system for bladder/bowel dysfunction**

The FDA has approved Axonics F15, a recharge-free sacral neuromodulation (SNM) implantable neurostimulator (INS) for the treatment of patients with bladder and bowel dysfunction, according to Axonics, Inc, developer of the device.

The company announced the approval in a news release, in which they listed the following device characteristics:

• type of INS: primary cell battery

• longevity: At standard stimulation parameters the device is expected to function for 15-plus years; at lower energy settings, this extends to 20-plus years.

• volume: 10 cm³

• stimulation: constant current automatically adjusts stimulation output

• MRI compatibility: full body with 1.5 T and 3.0 T whole-body scanners

• Remote control for patient: recharge-free, intuitive fob

“Our rechargeable system introduced innovations to the SNM category in late 2019 that clinicians and patients had been requesting for years—longevity in the body, full-body MRI compatibility, a miniaturized implant, fuss-free therapy, and a patient remote control that is easy for patients to use. The new Axonics F15 recharge-free SNM system is similarly groundbreaking—a small and thin INS with an expected life in the body of well over a decade that does not require any element of the system to be recharged—and sets a new standard for what is possible in this category. We expect to begin shipping the Axonics F15 system in April,” said Raymond W. Cohen, chief executive officer of Axonics, in the release.

**REFERENCE**


**Enfortumab vedotin approaches approval in Europe for urothelial cancer**

The European Commission (EC) should approve enfortumab vedotin (Padcev) for adult patients with locally advanced or metastatic urothelial cancer who have previously received platinum-containing chemotherapy and a PD-1/L1 inhibitor, according to the European Medicines Agency Committee for Medicinal Products for Human Use (CHMP).

CHMP had initially recommended the approval, 2 in December 2021, based on data from the phase 3 EV-301 trial (NCT03474107). Results indicated that enfortumab vedotin reduced the risk of death by 30% versus chemotherapy in patients with heavily pretreated locally advanced or metastatic urothelial carcinoma.3,4

The EC subsequently commenced its approval evaluation, during which time the CHMP was made aware of additional safety information regarding the use of enfortumab vedotin in this setting. At the EC’s request, CHMP reviewed the new information and readopted its recommendation for approval.

The EC will now make a final decision and, if approved, the antibody-drug conjugate would be commercially available for the indication in European Union countries, as well as Iceland, Norway, and Liechtenstein.

**REFERENCES**

Benign urology: How can we do better?

In my previous editorial, I recounted the advances we had made in the past 50 years in benign disease. It also provided a good opportunity to reflect on conditions or situations for which we must, still, strive to do better. Although it might be easier to enumerate the cancer conditions, in the benign world, struggles continue to overcome patients challenged with these conditions.

**BLADDER.** The underactive or acontractile bladder remains an enigma with no pharmacological or surgical solutions. Mechanical drainage remains the standard treatment. Neuromodulation or bladder stimulation have been attempted, but it is not a current therapy. There is no pharmacological intervention. The advance we have made is in naming the condition differently. The other aspect of bladder dysfunction affecting a smaller portion of the population is interstitial cystitis. We now understand that it is not a single entity; a segment may not be bladder driven; but the clinical ability to make that decision and apply standard treatment is still elusive, despite strong research support from the National Institute of Diabetes and Digestive and Kidney Diseases.

**STONES.** The evolution of endourology and devices has made the modern management of stones an art form; however, we have not made a significant advance in their prevention or recurrence. Despite guidelines on medical management, such as those from the American Urological Association, and improved knowledge of metabolic pathways, there has been no decline in incidence, visits to the emergency department, or the acute pain of renal colic.

**PROSTATE.** The ever-increasing options to manage the benign prostate have been a technical marvel; however, in the rearview mirror I see all the ones we abandoned after a few years of enthusiastically embracing them as the next big thing. The concern is that we did not learn from the mistakes and continue to accept new treatment options without waiting for durable success. Heating the prostate with low-energy or high-energy microwave, focusing the interstitial laser or radiofrequency current on it, injecting it with agents or dilating it with balloon or stents, and waving certain lasers at it are all in “rest in peace” mode. Yet we are enthusiastically heating, placing devices, or using new lasers, each method promising to let us have our cake and eat it too.

**RECONSTRUCTIVE UROLOGY.** Despite the advances in tissue engineering and cell therapy, reconstructive urology still relies on the host for providing the graft for replacement or augmentation. The morbidity of harvesting bowel, skin, fascia, muscle, or mucosal flaps remains a challenge to conquer. Off-the-shelf material has made female and male incontinence surgery a new paradigm, but genitourinary reconstructive surgeons, despite advances in surgical techniques, cannot take advantage of minimally invasive surgical techniques due to a lack of constructs.

**URINARY TRACT INFECTION (UTI).** Recurrent UTIs in women continue to fill the schedules at urology clinics. A variety of techniques and rituals has failed to conquer this challenge. The advance in genetic testing for urinary pathogens has led to a decrease in the time to identify the organism responsible. A recent report of a vaccine may be groundbreaking if the study results can be replicated in the general population.

I am fortunate to see and review many new research applications to conquer these challenges. The hope is that we see improving quality of life as important as correcting an anatomical defect or curing cancer.

From the Co–Editor in Chief

GOPAL H. BADLANI, MD
Badlani, a professor and vice chair of urology at Wake Forest School of Medicine in Winston-Salem, North Carolina, is a co–editor in chief for Urology Times®.
Androgen deprivation therapy (ADT) is a mainstay treatment for prostate cancer, but it comes with adverse effects including bone density loss, hot flashes, cardiac risks, and others. In this interview, David F. Jarrard, MD, discusses new data regarding adverse events and how they are best managed. Jarrard is a professor and vice chair of urology and the John P. Livesey Chair in Urologic Oncology at the University of Wisconsin School Of Medicine and Public Health, and an associate director at the University of Wisconsin Carbone Cancer Center in Madison.

Q. What factors influence your choice of ADT?

JARRARD: There are a number of considerations. It’s important to remember that there are several “flavors” of ADT. These include gonadotropin-releasing hormone (GnRH) agonists and antagonists. There are also androgen receptor blocking agents, but as monotherapy, they’re less commonly used.

There is also the mode of administration to consider. Some of these are injections. There is now an oral agent, relugolix [Orgovyx], which is a GnRH antagonist. Another option is orchietomy. Another aspect to consider is whether this is continuous ADT or is it going to be intermittent?

Q. How does the duration of ADT influence your choice of therapy?

JARRARD: The oral agents are fast acting and can be used acutely. In addition, if one is thinking about a length of time for ADT, these can be cycled on and off relatively easily. When you’re looking at efficacy between these GnRH antagonists and agonists, they’re both effective. The recent HERO trial [NCT03085095] looked at relugolix vs leuprolide acetate. In this study, they looked at 1-year outcomes with regard to efficacy; namely, castration rate or testosterone less than 50 ng/mL. There was noninferiority—and even superiority—when comparing relugolix vs leuprolide acetate. It should be noted that castrate levels occur very rapidly with these GnRH antagonists, and castrate levels of testosterone occur at 4 days in about half of patients. With leuprolide acetate, there’s a spike in testosterone that occurs and so those patients are not castrate at that early point. In terms of cycling and length of time, the immediate need for ADT suppression is generally better handled with these GnRH antagonists.

Q. What are the most common adverse events of ADT, and how do you manage them?

JARRARD: Hot flashes are something that occurs commonly in patients. We have several newer options with regard to drug therapy, including venlafaxine and gabapentin, that can be utilized for these patients. Osteoporosis is another adverse event. Patients often feel fatigued, although routine exercise can help mitigate that to a certain extent. There are also issues such as metabolic syndrome, decreased libido, and erectile dysfunction. Cardiovascular disease is one that’s received increasing attention more recently as well.

When you think about some of these adverse events, with regard to some of the metabolic consequences, there’s weight gain, dyslipidemia, and loss of lean muscle mass. Some of the strategies for treating these patients include getting a dietitian involved. Again, exercise is important. And it’s important in these older patients to assess their fall risk with regard to making sure that treatment doesn’t make them even more frail. And finally, diabetes management is important with regard to metabolic adverse events.

There are a number of skeletal-related adverse events that also occur, including a decrease in bone density. It’s important to assess bone density status prior to receiving ADT. That
would include a DEXA [dual-energy x-ray absorptiometry] scan, which should be repeated every year or 2. Blood tests for calcium, creatinine, and vitamin D are also important in assessing men before they enter or begin ADT and even during their course.

Another aspect we’ve become more aware of in the modern era is the need for cardiovascular assessment. In patients receiving ADT, there was a warning added to leuprolide acetate, in part because of concerns over worsened cardiovascular outcomes. Indeed, the American Urological Association [AUA] in 2010 recommended evaluation of cardiovascular risk factors prior to patients being started on ADT, looking at hypertension, lipids, blood glucose, and other related features. There have been a number of meta-analyses of the cardiovascular effects of ADT. One issue is many of the randomized controlled trials looking at ADT approaches aren’t really powered to look at cardiovascular adverse events. One way of getting around that is to use meta-analyses. When one looks at these studies, they have demonstrated associations between ADT and an increased risk of vascular outcomes. Indeed, the American College of Cardiology has suggested that ADT may be associated with things like memory and visual-motor function. There certainly are some potential links between ADT and increased risk of cardiovascular events, as well as death. That is something to keep in mind with regard to those patients starting ADT.

Q. What impact does ADT have on cognition, and how do you manage it?

JARRARD: It’s been something we’ve suspected for a long period of time, and emerging research has suggested that ADT may be associated with cognitive impairment. This can in turn be linked to a loss of independence, increased falls, fracture risk, and other aspects. When looking at specific aspects of cognitive dysfunction, this includes things like memory and visual-motor function. The big question, obviously, is how do you mitigate this. That’s an area that’s ripe for research. There certainly are some potential links between exercise and improved cognitive function, but further studies are needed to confirm that and other approaches.

Q. What impact does ADT have on libido, and how do you manage it?

JARRARD: That’s one of the more problematic areas with regard to ADT. With the vast majority of these drugs, you’re decreasing testosterone, and that clearly has an effect on libido. With androgen receptor blocking agents, these first-generation ones like bicalutamide [Casodex], you don’t see the decrease in testosterone as a single agent. However, due to the reduced efficacy and adverse events, these agents are not recommended by guidelines panels as monotherapy. Exercise may mitigate this, but it is an area that needs more research. Intermittent ADT may be an option for selected patients, giving individuals periods of time without testosterone suppression.

Q. For which type of patient is intermittent ADT recommended, and when should ADT be started?

JARRARD: It’s important to recognize that there has been a shift in the way we approach ADT. In the past, for patients that have essentially exhausted all their treatment options and failed primary treatment with a rising [prostate-specific antigen (PSA)] level, the current recommendation by the AUA and other guidelines is observation. It’s often a challenge because the patients are nervous, the families are nervous, and even the physicians can be nervous. In situations like this, clinical trials are one option. If the patient must do something, intermittent hormone therapy may be utilized in that population. It’s important to note that there are no convincing data to really suggest a benefit with regard to survival in this population.

In a randomized trial in this early PSA failure, the TOAD trial [NCT00110162], 293 patients were randomized to early vs delayed androgen deprivation in this population. There was a slight overall survival benefit to early ADT, but the study did not accrue well. It was underpowered, and most experts don’t feel that these are enough data to suggest using early ADT in these patients, especially when considering the increased risk of adverse events.

So the question then becomes for patients with advanced disease: Is intermittent androgen deprivation an option for patients with significant adverse events? In a meta-analysis performed several years ago looking at intermittent vs continuous ADT, there was not an overall or cancer-specific survival. In addition, the advantage of intermittent ADT in patients is that significant adverse events related to ADT are often decreased, including hot flashes and better quality of life. There is improvement in physical and sexual functioning in these patients, so it’s an option to consider in selected situations.

Q. After prolonged ADT treatment, when does the testosterone level usually return to normal?

JARRARD: We’re often asked that question by our patients, especially after radiation therapy. It’s important to realize that not all patients will recover testosterone function. There are a number of factors that may predict this. Age is a factor and longer duration of ADT also can decrease the number of patients that recover. But for the average patient, testosterone recovery is generally about a third at 12 weeks, and about 90% at 24 weeks.

Q. What future advances in ADT are you looking forward to?

JARRARD: There was a really interesting trial, the PATCH trial [NCT00176644], that recently looked at the transdermal administration of estradiol. In the past, diethylstilbestrol was given orally. There was increased cardiovascular morbidity associated with this. One aspect about using a transdermal administration of estradiol is that you can avoid those adverse events; apparently it has something to do with metabolism through the liver. In the PATCH trial, the castration rates were actually the same at 3 months as [those for] leuprolide acetate, and [estradiol] actually mitigated some of the adverse events that we normally see with ADT. There was a reduction in hot flashes, osteoporosis, some of the metabolic profiles. Additionally, there was a decrease in the cardiovascular toxicity that is normally seen with oral estrogen. It’s interesting [that] what goes around comes back around, and this is potentially a situation in which we may be using estradiol in the future, in the form of transdermal, for patients that need ADT.

REFERENCES
**INDICATION**

NUBEQA® (darolutamide) is an androgen receptor inhibitor indicated for the treatment of patients with non-metastatic castration-resistant prostate cancer.

**IMPORTANT SAFETY INFORMATION**

**Embryo-Fetal Toxicity:** Safety and efficacy of NUBEQA have not been established in females. NUBEQA can cause fetal harm and loss of pregnancy. Advise males with female partners of reproductive potential to use effective contraception during treatment with NUBEQA and for 1 week after the last dose.

**Adverse Reactions**

Serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥1% of patients who received NUBEQA were urinary retention, pneumonia, and hematuria. Overall, 3.9% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Adverse reactions occurring more frequently in the NUBEQA arm (≥2% over placebo) were fatigue (16% vs 11%), pain in extremity (6% vs 3%) and rash (3% vs 1%).

Clinically significant adverse reactions occurring in ≥2% of patients treated with NUBEQA included ischemic heart disease (4.0% vs 3.4% on placebo) and heart failure (2.1% vs 0.9% on placebo).

**Drug Interactions**

**Effect of Other Drugs on NUBEQA** – Combined P-gp and strong or moderate CYP3A4 inducers decrease NUBEQA exposure, which may decrease NUBEQA activity. Avoid concomitant use.

Combined P-gp and strong CYP3A4 inhibitors increase NUBEQA exposure, which may increase the risk of NUBEQA adverse reactions. Monitor more frequently and modify NUBEQA dose as needed.

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40.4 months vs 18.4 months for ADT alone

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31% reduction in the risk of death vs ADT alone

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40.3 months vs 25.4 months for ADT alone
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POSTPONED CYTOTOXIC CHEMOTHERAPY—MORE TIME WITHOUT CHEMO1,3

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Drug Interactions (cont’d)

Effects of NUBEQA on Other Drugs – NUBEQA inhibits breast cancer resistance protein (BCRP) transporter. Concomitant use increases exposure (AUC) and maximal concentration of BCRP substrates, which may increase the risk of BCRP substrate-related toxicities. Avoid concomitant use where possible.

If used together, monitor more frequently for adverse reactions, and consider dose reduction of the BCRP substrate.

NUBEQA inhibits OATP1B1 and OATP1B3 transporters. Concomitant use may increase plasma concentrations of OATP1B1 or OATP1B3 substrates. Monitor more frequently for adverse reactions and consider dose reduction of these substrates.

Review the prescribing information of drugs that are BCRP, OATP1B1, and OATP1B3 substrates when used concomitantly with NUBEQA.

Metastasis-free survival (MFS) was the primary endpoint, and overall survival (OS) was a key secondary endpoint.1

*Time to pain progression was defined as at least a 2-point worsening from baseline of pain score on BPI-SF (a validated health-related quality-of-life instrument) or initiation of opioids and reported in 28% of all patients on study.

Study design

The efficacy and safety of NUBEQA were assessed in a randomized, double-blind, placebo-controlled phase III study (ARAMIS) in nmCRPC patients on ADT with a PSA doubling time ≤10 months. 1,509 patients were randomized 2:1 to 600 mg NUBEQA twice daily (n=955) or placebo (n=554). MFS was defined as time from randomization to time of first evidence of BICR-confirmed distant metastasis or death from any cause ≤33 weeks after the last evaluable scan, whichever occurred first. Treatment continued until radiographic disease progression, as assessed by CT, MRI, bone scan by BICR; unacceptable toxicity, or withdrawal.1,3

ADT=androgen deprivation therapy; HR=hazard ratio; CI=confidence interval; BPI-SF=Brief Pain Inventory Short Form; PSA=prostate-specific antigen; BICR=blinded independent central review; CT=computed tomography; MRI=magnetic resonance imaging.

Please see the following page for the brief summary of Prescribing Information.
NUBEQA® (darolutamide) tablets, for oral use

Initial U.S. Approval: 2019

**BRIEF SUMMARY OF PRESCRIBING INFORMATION**

**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

1 **INDICATIONS AND USAGE**

NUBEQA is indicated for the treatment of patients with non-metastatic castration resistant prostate cancer (nmCRPC).

2 **CONTRAINDICATIONS**

None.

3 **WARNINGS AND PRECAUTIONS**

5.1 Embryo-Fetal Toxicity

The safety and efficacy of NUBEQA have not been established in females. Based on its mechanism of action, NUBEQA can cause fetal harm and loss of pregnancy when administered to a pregnant female [see Clinical Pharmacology (12.1)].

5.2 Lactation

The safety and efficacy of NUBEQA have not been established in females. There is no data on the presence of darolutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

5.3 Females and Males of Reproductive Potential

Contraception

Males

Based on the mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 1 week after the last dose of NUBEQA [see Use in Specific Populations (4.9)].

5.4 Pediatric Use

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

5.5 Geriatric Use

Of the 954 patients who received NUBEQA in ARAMS, 88% were patients 65 years and over, and 49% were 75 years and over. No overall differences in safety or efficacy were observed between these patients and younger patients.

6 **ADVERSE REACTIONS**

5.1 Embryo-Fetal Toxicity

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.

ARAMS, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had non-metastatic castration-resistant prostate cancer (nmCRPC). In this study, patients received either NUBEQA at a dose of 600 mg, or a placebo, twice a day. All patients in the ARAMS study suffered a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchidectomy. The median duration of exposure was 14.8 months (range: 0 to 44.3 months) in patients who received NUBEQA.

Overall, serious adverse reactions occurred in 25% of patients receiving NUBEQA and in 20% of patients receiving placebo. Serious adverse reactions in ≥ 1% of patients who received NUBEQA included urinary retention, pneumonia, and breast enlargement. Overall, 3.5% of patients receiving NUBEQA and 3.2% of patients receiving placebo died from adverse reactions, which included death (0.4%), cardiac failure (0.3%), cardiac arrest (0.2%), general physical health deterioration (0.2%), and pulmonary embolism (0.2%) for NUBEQA.

Permanent discontinuation due to adverse reactions occurred in 9% of patients receiving NUBEQA or placebo. The most frequent adverse reactions requiring permanent discontinuation in patients who received NUBEQA included cardiac failure (0.4%), and death (0.4%).

Dose interruptions due to adverse reactions occurred in 13% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage interruption in patients who received NUBEQA included hyperglycemia (0.6%), diabetes (0.5%), and pneumonia (0.5%).

Dose reductions due to adverse reactions occurred in 6% of patients treated with NUBEQA. The most frequent adverse reactions requiring dosage reduction in patients treated with NUBEQA included fatigue (0.7%), hypertension (0.3%), and nausea (0.3%).

Table 1 shows adverse reactions in ARAMS reported in the NUBEQA arm with a ≥2 absolute increase in frequency compared to placebo. Table 2 shows laboratory test abnormalities related to NUBEQA treatment and reported more frequently in NUBEQA-treated patients compared to placebo-treated patients in the ARAMS study.

### Table 1: Adverse Reactions in ARAMS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Grades ≥ 3</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

1 Includes fatigue and asthenia.

2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

### Table 2: Laboratory Test Abnormalities in ARAMS

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>NUBEQA (n=954)</th>
<th>Placebo (n=554)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil count decreased</td>
<td>20</td>
<td>14</td>
</tr>
<tr>
<td>AUC increased</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Bilirubin increased</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

1 Denominator used to calculate the rate varied based on the number of patients with a baseline value and at least one post-treatment value.

2 Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

7 **DRUG INTERACTIONS**

7.1 Effect of Other Drugs on NUBEQA

Combined P-gp and Strong or Moderate CYP3A4 Inhibitor

Concomitant use of NUBEQA with a combined P-gp and strong or moderate CYP3A4 inducer decreases darolutamide exposure which may decrease NUBEQA activity [see Clinical Pharmacology (12.3)]. Avoid concomitant use of NUBEQA with combined P-gp and strong or moderate CYP3A4 inducers.

Combined P-gp and Strong CYP3A4 Inhibitors

Concomitant use of NUBEQA with a combined P-gp and strong CYP3A4 inhibitor increases darolutamide exposure [see Clinical Pharmacology (12.3)] which may increase the risk of BCRP substrate-related adverse reactions. Monitor patients more frequently for NUBEQA adverse reactions and modify NUBEQA dosage as needed [see Dosage and Administration (2.2)].

7.2 Effects of NUBEQA on Other Drugs

Breast Cancer Resistance Protein (BCRP) and Organic Anion Transporting Polypeptides (OATP) 1B1 and 1B3 Substrates

NUBEQA is an inhibitor of BCRP transporter. Concomitant use of NUBEQA increases the AUC and Cmax of BCRP substrates [see Clinical Pharmacology (12.3)]. Avoid concomitant use with drugs that are BCRP substrates where possible. If used together, monitor patients more frequently for adverse reactions, and consider dose reduction of the BCRP substrate drug.

NUBEQA is an inhibitor of DATP1B1 and OATP1B3 transporters. Concomitant use of NUBEQA may increase the plasma concentrations of DATP1B1 or OATP1B3 substrates. Monitor patients more frequently for adverse reactions of these drugs and consider dose reduction while patients are taking NUBEQA [see Clinical Pharmacology (12.3)].

Review the prescribing information of the BCRP, DATP1B1 and OATP1B3 substrates when used concomitantly with NUBEQA.

### References


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Findings support safety, feasibility of partial-gland treatment

The advent of enhanced imaging and detection of localized prostate cancer through targeted biopsy has improved the feasibility and safety of targeted or focal therapy for men with prostate cancer. Once thought to be an option only suitable for men with low-risk prostate cancer, focal therapy is being used as a viable option for those with clinically significant prostate cancer.

A recent article by Reddy et al reports updated results on patients with localized prostate cancer in the high-intensity focused ultrasound (HIFU) Evaluation and Assessment of Treatment (HEAT) registry from the United Kingdom over the past 15 years, where focal HIFU has been used as a standard alternative to whole-gland treatment.1

A total of 1379 patients from 13 UK centers were reported in the HEAT registry between November 2005 and July 2020. Men with prostate cancer whose Gleason score was 6 to 9 and with a clinical stage up to T3bN0M0 were offered focal therapy using the Sonablate. Patients were classified as having D’Amico low-, intermediate-, or high-risk disease. Only patients with MRI-visible lesions, and without any high-volume (6 mm) Gleason score 6 or any-volume Gleason score 7 disease in the untreated gland, were considered suitable candidates for focal ablation.

The primary outcome was failure-free survival (FFS), defined as no evidence of cancer requiring whole-gland salvage treatment or third focal therapy treatment, any systemic treatment, development of metastases, or prostate cancer-specific death. Secondary outcomes included adverse events and complications classified by the Clavien-Dindo system, as well as other oncologic outcomes.

Follow-up included prostate-specific antigen (PSA) test and multiparametric MRI at variable intervals, as well as per protocol and for-recur repeat prostate biopsy. If clinically significant cancer (defined as Gleason score ≥ 3 + 4) was identified as occurring in field (residual disease) or out of field (de novo or progressive disease), patients were offered either repeat focal treatment or radical radiotherapy, or radical prostatectomy.

The median follow-up was 32 months for the entire cohort, and 82 months for the 325 (23%) patients with at least 5 years’ follow-up. The median age of patients was 66 years and median PSA level was 6.9 (4.9-9.4) ng/mL. Seventy-nine percent of patients (1093 of 1379) had grade group 2 or higher (19%, grade group 1; 78%, grade group 2).

The FFS at 7 years was 69%, and 7-year FFS for intermediate- and high-risk cancers was 68% and 65% (P=.3), respectively. Significant differences in FFS were noted at 7 years between grade group 2 and 3 (P=.05). Of the 609 patients who underwent repeat prostate biopsy, recurrent/residual cancer was reported in 403 (66%). Of these, 314 patients demonstrated residual/recurrent Gleason score 7 prostate cancer during their follow-up period.

Retreatment-free survival at 7 years was 43%; in other words, more than half of patients required some additional treatment. There was a statistically significant difference in retreatment-free survival between D’Amico risk groups (P<.0001). Overall, 132 patients underwent salvage whole-gland treatment or systemic treatment, including 53 salvage radical prostatectomy and 39 salvage radiotherapy. Salvage treatment-free survival at 7 years was 75%, with 3 patients developing metastases and 1 of whom subsequently died from prostate cancer.

Postoperative complications were noted in 83 of 1379 (6.0%) patients after focal therapy. The rate of complications in those with a Clavien-Dindo score greater than 2 was 0.5% (7 of 1379), and most complications were self-limiting, without hospital admission or intervention.

There are inherent differences in the definition of success following partial-gland or focal ablation and whole-gland treatment (surgery or radiation). For example, retreatment with another ablative procedure for tumor persistence or recurrence is not viewed as treatment failure, whereas any subsequent therapy after whole-gland treatment is considered failure of initial treatment. A microscopic positive margin or pg of detectable PSA is classified as residual disease after radical prostatectomy, whereas repeat biopsy showing obvious residual disease following focal ablation is viewed as an opportunity for further ablation without being classified as salvage treatment.

This, along with short follow-up, precludes oncologic efficacy comparison between focal ablative therapy and whole-gland treatment. If adequate cancer control can be achieved by focal or partial-gland treatment, then the favorable adverse event profile could make this a preferred option for a number of men with localized intermediate-risk (and possibly selected high-risk) prostate cancer. Until the ongoing randomized controlled trials with adequate follow-up can provide data on comparative effectiveness, physicians will have to rely on single-cohort studies demonstrating the feasibility and safety of focal treatment to guide patient counseling and clinical decision-making.

REFERENCE
Can you provide an overview of the development of genetic testing to direct prostate cancer therapeutics?

GIRI. Genetic testing for prostate cancer is indeed an innovation in this field. What’s interesting about the way genetic germline testing for prostate cancer came to the forefront is that it really took off during the “precision medicine” era. Prior to that point, insights into certain genetic mutations and prostate cancer risk had been described; for example, higher rates of prostate cancer were reported in men who came from families with $BRCA_1$ mutations, breast cancer, and [who were] of Ashkenazi Jewish ancestry. There was evidence that prostate cancer was linked with Lynch syndrome, so linked with the DNA mismatch repair genes. Major insights into genetics of prostate cancer came with reports of high rates of DNA repair mutations in men that had metastatic prostate cancer. Those reports started surfacing in 2016. This really spearheaded this era of precision medicine for prostate cancer, and this is really what’s led to the direction of therapeutics. As I mentioned, there were high rates of DNA repair mutations described in men with metastatic castration-resistant prostate cancer [CRPC], and this was confirmed in multiple reports. What is important to recognize is that men with metastatic prostate cancer can have up to a 12% to 15% rate of having a germline mutation, and from the therapeutic standpoint, what started to occur was the understanding that these mutations could be targeted for clinical outcomes for men with metastatic CRPC. Multiple trials have been going on over the years, particularly in the precision medicine era.

2020 was a landmark year as far as therapeutic advancement for men with metastatic castration-resistant disease. The FDA approved 2 PARP inhibitors for men with metastatic CRPC, those being olaparib [Lynparza] and rucaparib [Rubraca]. These were approved based on 2 important studies. The first study was the PROfound trial [NCT02987543] for olaparib. This was a randomized trial looking at olaparib vs abiraterone [Zytiga] or enzalutamide [Xtandi] in 2 arms of patients. The first arm was for men that had $BRCA_1$, $BRCA_2$, or $ATM$ mutations. The second arm looked at a host of mutations in other DNA repair genes. What they found was that there was superior clinical activity for those patients that were treated with olaparib. So the FDA granted approval for olaparib for men with...
deleterious or suspected deleterious germline or somatic mutations in homologous recombination repair genes, and this would be for men who had metastatic CRPC after progression on abiraterone or enzalutamide. Patients need to have tried these prior therapies and progressed on those therapies.  

The TRITON2 study [NCT02952534] led to the approval of rucaparib, and this was based upon improved clinical responses for men in the setting of metastatic CRPC. In that setting, particularly for men with BRCA mutations, rucaparib was shown to have superior responses. So here again, the FDA granted accelerated approval for rucaparib. This was specific to BRCA mutations, and again, they needed to have prior treatment with an androgen receptor-directed therapy and a taxane-based chemotherapy. These approvals open options for therapeutics for men, in terms of after progression, to consider PARP inhibitors if they are positive for DNA repair mutations, and also can open the door for additional clinical trials.  

**Q. What makes genetic testing an innovation in urology?**  
**GIRI.** We can think of innovation in a couple of different ways when it comes to genetic testing in urology, specifically for prostate cancer. One is that for a very long time, there was suspicion that prostate cancer can be inherited, but there was a limited amount of information as to the genetic basis for that. Now with the advancements in understanding and the scientific contributions of experts across the field, we know that genes such as BRCA2 and HOXB13 have a strong predisposition to prostate cancer. BRCA2 is associated with aggressive prostate cancer as well. BRCA1 also has some modest association to prostate cancer. There are multiple other genes, such as the DNA mismatch repair genes associated with Lynch syndrome, that also have modest association to prostate cancer. And of course, as I mentioned, lots of genes, particularly in the DNA repair pathways, can be important in therapeutic decision-making for men with prostate cancer. Now, these insights into some of the genes that are linked with prostate cancer risk actually carry strong hereditary risk not just for prostate cancer but for multiple cancers that can impact men, as well as males and females in their families. So I think one of the biggest innovations was insight into the hereditary nature of prostate cancer and what this means for men and their families.  

For urology specifically, this is a real practice innovation because now urologists are on the forefront of being able to be a doorway into a family for identifying a hereditary cancer syndrome, such as hereditary breast and ovarian cancer, or Lynch syndrome. This way, these patients can be identified, their cancer risks can be estimated based upon the genetic mutations identified, and tailored cancer screening and risk reduction measures can be given to these patients. That’s a huge innovation, and that is impacting urology when it comes to genetic testing for prostate cancer.  

A major innovation [affecting] urology and oncology is the therapeutic advances based on genetic information. There are many clinical trials that are going on to help improve outcomes, responses, [and] patient selection for targeted therapies. So I think you're going to see innovation going forward [and]...scientific insights being reported going forward, linked with the genetic understanding of what it means to be at risk for prostate cancer, and how that can impact men and their families.  

**Q. How has genetic testing improved the treatment of patients with prostate cancer?**  
**GIRI.** As I mentioned, genetic testing certainly opens the door for targeted therapies for men with metastatic castration-resistant disease, such as, for example, PARP inhibitors for patients that carry DNA repair mutations, particularly BRCA mutations, and then also eligibility for ongoing clinical trials. This is an important thing to keep in mind so that we can not only explore ways to improve treatment, but also increase our understanding to help populations across the board from the trials. We also see trials that are going on not only just in the metastatic setting but across the spectrum of care. This is really important when we think about where we’re headed. We see trials going on in the high-risk localized space for men with prostate cancer. Regarding genetics, can genetics help inform targeted therapies in that setting, or strategies for management? An important space where I think we’re going to see a lot of advancement is for men with early-stage localized disease, in terms of strategies for active surveillance based upon genetic information. A really important point is the hereditary implications of genetic testing when it comes to men and their families. We know that this can impact screening strategies for men, so beginning prostate cancer [screening] at a younger age, perhaps tailoring the screening strategy for these men who carry high-risk genetic mutations, is also really important in terms of reducing the burden of prostate cancer in our populations.
Aquablation therapy demonstrated strong efficacy and safety vs transurethral resection of the prostate (TURP) for the treatment of men with lower urinary tract symptoms (LUTS) related to benign prostatic hyperplasia (BPH). Five-year results from the pivotal WATER (NCT02505919) trial were published in the Canadian Journal of Urology.

International Prostate Symptom Score (IPSS) data at 5 years showed that among patients receiving Aquablation, the IPSS improved by 15.1 points compared with 13.2 points among patients receiving TURP (P = .2764). Of note, across all follow-up visits for patients with larger prostates (> 50 mL), the reduction in IPSS was 3.5 points higher with Aquablation vs TURP (P = .0123). Peak urinary flow rate compared with baseline improved by 125% vs 89% in the Aquablation and TURP groups, respectively. The rate of retreatment (needing surgical intervention or BPH medication) for patients receiving Aquablation was about 1% per year. Compared with TURP, this represented a 51% reduction.

“Given the broader range of prostate size and anatomy Aquablation can treat, this technology has the potential to change the paradigm of how BPH is treated,” Alexis E. Te, MD, a WATER study investigator and professor of urology at Weill Medical College at Cornell University, said in a news release.

The prospective, randomized, double-blind, multicenter WATER trial (NCT02505919) compared the safety and efficacy of Aquablation and TURP as surgical treatments for BPH-related LUTS in men aged 45 to 80 years who had a prostate size of 30 to 80 mL. Patient characteristics at baseline were well balanced between the study arms. Patients were randomly assigned in a 2:1 ratio to Aquablation or TURP. The 5-year analysis included 116 patients who received Aquablation and 65 patients who received TURP.

It was previously determined that the study met its primary end point with Aquablation leading to a 16.9 mean IPSS decrease from baseline compared with a mean decrease of 15.1 points with TURP (P < .0001 for noninferiority; P = .1346 for superiority).

Regarding safety, the event rate at 3 months was 26% with Aquablation vs 42% with TURP (P = .0149). The rate of procedure-related ejaculatory dysfunction was 7% vs 25%, respectively (P = .0004).

“Based on our 5-year WATER data and real-world experience, we believe Aquablation therapy is poised to become the treatment of choice for BPH as it addresses the compromise between safety and efficacy. This study reinforces the durability of Aquablation therapy, and we are thrilled that men everywhere suffering from BPH now have a surgical treatment option with proven clinical outcomes, independent of the size and shape of the prostate, and a reduced risk of sexual [adverse] effects,” Reza Zadno, president and CEO of PROCEPT BioRobotics Corporation, developer of Aquablation treatment, said in the news release.

REFERENCES
"Encouraging" disease-free survival data are seen with avelumab/axitinib

Combination induced a partial response in 30% of patients, data indicate

JASON M. BRODERICK
Associate Editorial Director, Urology Times®

The combination of PD-L1 inhibitor avelumab (Bavencio) and tyrosine kinase inhibitor (TKI) axitinib (Inlyta) showed promise as a neoadjuvant therapy for patients with high-risk, nonmetastatic clear cell renal cell carcinoma (RCC), according to findings from the NEOAVAX trial (NCT03341845), presented during the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium.1

In the open-label, single-arm phase 2 trial, neoadjuvant avelumab/axitinib induced a partial response in 12 (30%) of 40 patients. Median primary tumor downsizing was 20% (range, +3.8% to 43.5%). Among patients with a partial response, 10 of 12 were disease-free at the study data cutoff. At a median follow-up of 23.5 months, the median overall survival (OS) and median disease-free survival (DFS) had not yet been reached. No patients had progression of their primary tumor.

“This is the first neoadjuvant trial reporting results from a combination of an immune checkpoint inhibitor [ICI] and VEGFR-TKI for locally advanced high-risk RCC,” said lead study author Axel Bex, MD, PhD, of the Netherlands Cancer Institute. “The DFS data are encouraging, supporting further evaluation, although currently there are no randomized neoadjuvant vs adjuvant ICI trials or neoadjuvant vs adjuvant ICI/VEGFR-TKI combination [trials in this setting].”

Explaining the background of the NEOAVAX trial, Bex said, “Antibodies targeting PD-1/PD-L1 combined with VEGF inhibitors are a first-line standard of care for metastatic RCC. Neoadjuvant use of these combinations may lead to downstaging and reduce the risk of recurrence.”

Overall, there were 40 patients enrolled in the trial between May 2018 and October 2021. The median patient age was 63 years (range, 47-74), 30% of patients were women, and 70% of patients were men. The World Health Organization performance status was 0 for 30 patients and 1 for 10 patients. Baseline cTNM were as follows: T1b to T2b (n = 4), T3a (n = 24), T3b (n = 4), and T4 (n = 8). “Ninety percent of patients had at least [stage] T3 disease and higher,” Bex said. Biopsy grades were grades 1 to 2 (n = 27), grades 3 to 4 (n = 11), and grade x (n = 2).

“The DFS data are encouraging, supporting further evaluation, although currently there are no randomized neoadjuvant vs adjuvant ICI trials or neoadjuvant vs adjuvant ICI/VEGFR-TKI combination [trials in this setting].”

AXEL BEX, MD, PHD

Across the population, 42.5% (n = 17) of patients were clinically node positive. “Baseline lymph node diameter was a mean of 2.6 cm, and the mean diameter of the primary tumor was 10.3 cm. So by no means was this a low-risk or intermediate-risk population,” Bex said.

Study dosing was axitinib at 5 mg twice daily and avelumab at 10 mg/kg every 2 weeks. The primary end point was partial response at week 12. Secondary end points included DFS, OS, and safety. Biomarker analysis on sequential tissue specimens from post-treatment compared [with] patients without recurrence. “With regards to biomarkers, patients with recurrence had lower CD8+ densities after treatment compared [with] patients without recurrence. Spatial transcriptomics of post-treatment primary tumor tissue revealed focal intratumoral differences in immune signatures, and we are currently investigating this further to see whether this may be one of the reasons why these patients have recurrence.”

The combination of avelumab and axitinib is currently approved by the FDA for the front-line treatment of patients with advanced RCC. The approval was based on results from the pivotal phase 3 JAVELIN Renal 101 trial (NCT02684006), which showed that the combination was associated with a 31% reduction in the risk of disease progression or death compared with sunitinib (Sutent) in patients with treatment-naive advanced RCC.2

REFERENCES
Findings from the phase 1/2 NICARAGUA study, shared during the 2022 American Society of Clinical Oncology Genitourinary Cancers Symposium, showed clinical activity with an acceptable safety profile for the combination of the PARP inhibitor niraparib (Zejula) and the multikinase inhibitor cabozantinib (Cabometyx, Cometriq) in patients with metastatic urothelial carcinoma (mUC) or renal cell carcinoma.¹

Lead author Daniel E. Castellano, MD, of University Hospital October 12 in Madrid, Spain, reported 0 dose-limiting toxicities (DLTs) for dose level (DL) 1 (n = 5), stomatitis at DL 1.1 (n = 6), and decreased platelet count and anemia, diarrhea, and hepatotoxicity at DL 2 (n = 8). Two patients achieved partial response, both of whom had mUC, and 17 patients had stable disease. The total clinical benefit rate (CBR) was 82.6%. When stratified by dose level, the CBR for DL 1 was 71.4%; for DL 1.1, 100.0%; and for DL 2, 77.8%.

Patients with UC whose tumors overexpress c-Met may benefit from this unique combination; thus, investigators sought to evaluate the maximum tolerated dose (MTD) of the combination in patients with advanced kidney/UC, as well as preliminary efficacy in advanced UC.

Overall, the NICARAGUA trial (NCT03425201) followed a traditional 3+3 dose escalation design that measured safety, tolerability, DLT, and MTD. The primary objective of phase 1 was to determine the MTD of niraparib and cabozantinib in patients with advanced UC or renal cell carcinoma. Secondary objectives were to determine the safety profile for the combination at administered dose levels. In phase 2, investigators measured the efficacy of the combination in patients with advanced UC. Phase 2 objectives were to determine the safety profile of the combination at selected dose levels, and efficacy based on objective response rate, disease control rate, duration of response, and overall survival.

The most common toxicities observed were hypertension (31.8%), constipation (31.8%), and asthenia (31.8%), followed by palmar-plantar erythrodysesthesia (27.3%) and platelet count decrease (22.7%). One patient each reported anemia, diarrhea, hepatotoxicity, platelet count decrease, and palmar-plantar erythrodysesthesia, of grade 3 toxicity. No grade 4 or 5 toxicities were reported.

REFERENCE
Kidney Stones | QUESTION & ANSWER

Nelson on pediatric stone prevention and treatment

Kidney stones are a significant medical problem that continues to grow in severity. Yet beyond technological advances in surgical instruments, little development has occurred in the basic science surrounding stones or concerning their prevention. In this interview, Caleb Nelson, MD, MPH, discusses the current state of the evaluation and treatment of stones in pediatric patients.

Q. What is the scope of the problem of kidney stones in children in the United States, and how is it projected to change over the next several years?

NELSON. It’s a significant problem, and what’s worrisome is that it has become a much more significant problem over the past 10 to 20 years. If you look at the incidence data that have been reported, they consistently show that everybody has seen an increase in pediatric stone disease. It has been looked at in a number of different settings and [via] different methodologies, and it [the data have] all been pretty consistent [in] that the number of stones we’re seeing is going up. There’s always a debate about how much of it is a real increase in disease vs just more diagnoses because of, say, improved or more frequent imaging tests [and] more utilization of ultrasounds or CTs that see stones that maybe would have remained undiagnosed in the past. But I think the general feeling is that even accounting for that, the number of cases has gone up.

Stone disease in the adult world is...incredibly common. Approximately 10% of all adults will get stones in their lifetime. Obviously, it’s miserable to have them; they can be very morbid in terms of causing other consequences [such as] kidney failure, infection, and things like that, especially if they become recurrent stone problems. But if you’re a healthy person who doesn’t form their first stone until [age] 50, chances are, if that’s a one-time thing, you’re not going to have a lot of issues. If you’re not going to have another stone for another 50 years, we’re probably not going to worry about it. But if someone forms their first stone when they’re 8, or 12, or 14, we see that as a very concerning sign that it’s highly likely to become a recurrent problem, and they’ve got many years of life left to live during which those stones are going to be an issue. So the stones you have now are obviously a concern, but the lead time and the future implications of continuing to form those stones are really significant. That’s why we push so hard to do metabolic testing on all the children and try to figure out why stones are forming because unlike the 50-year-old, if you’re 8 and [have] your first stones, there’s a very significant chance that there’s an underlying situation going on in terms of cause and you’re going to keep forming them as time goes by.

Q. What does the current treatment landscape for pediatric stones look like? What sort of treatments are indicated for use with pediatric patients?

NELSON. It’s pretty analogous to how adults are treated. There are 3 primary modalities that we use to treat stones. There is shock wave lithotripsy, which has been around for 40 years now. It started in adults but quickly followed in [children] and for quite a few years was considered the gold standard for the treatment of stones in [children]. The second modality is the ureteroscopy procedure, using a scope going retrograde in from the bladder up toward the kidney. That has dramatically increased in utilization over the past 20 years, primarily because of progress with the equipment, just like it has in adults as well. But for [children] in particular, the smaller they are, the smaller the equipment has to be, so the availability of some of these really small scopes has made treatment feasible that would not have been 20 or 30 years ago other than through open surgery. The third option is percutaneous nephrolithotomy, which is done through a small hole in the skin, again using scopes and other devices to break up the stones. That, just like in adults, is reserved primarily for patients with very large stones or a stone burden that’s so substantial that you’ll never be able to clear it by the other modalities. In children, at least in the United States, that represents a very small percentage of all the cases that are done, maybe 1% or 2%.

Q. What are some risk factors for stones in pediatric patients?

NELSON. We’re still trying to figure it out. Some of it is analogous to what you see in adults. Poor hydration is clearly a major factor. Things like high-salt diets and sedentary lifestyles happen in [children] too, and all those other things that seem to predispose [one] to stones. We know that in any humans with stones, there is some risk [that] if you carry out a metabolic assessment, you will find things that are abnormal in a percentage of people with stones. But in some people with stones, you don’t find any abnormalities. It doesn’t mean nothing is wrong, it just means we don’t understand the biology enough to figure out why that person is forming stones. But of the identified and known abnormalities that you see, they are significantly more common among [children] who have stones compared with adults who have stones. So if you do this...
work-up, you're much more likely to find something in a child than in an adult. That involves factors [such as] high urine calcium levels, low urine citrate levels, and all sorts of other urine and blood chemistry abnormalities. Those different findings can have different causes. Some of them are environmental, some are genetic, some are medication driven. Part of the work-up is sorting out for any individual [child] what the factors are that are going into this.

In the pediatric population, there's a big chunk of our patient population with severe medical comorbidities, a lot of them related to neuromuscular dysfunctions and mobility problems. So [there are] conditions [such as] cerebral palsy, spastic quadriplegia, and severe developmental delay, [and children] who spend almost all of their time on a stretcher or in a wheelchair and don't move around very much. They have very artificial diets; they are fed by tubes or have very limited food intake and possibly limited fluid intake as well. The stone prevalence in that population is pretty significant. And again, it's probably due to multiple factors that are unique to that population: the lack of mobility, the very artificial diet, and the fact that many of them are on medications for seizures or other conditions that change their urine chemistry in ways that are not helpful from the urology standpoint. That's a big subpopulation of the pediatric stone world that is unique to what we see. Certainly, we see lots of otherwise perfectly healthy [children] who come in with stones, but that is a big chunk of them.

Q: How do you evaluate stones in pediatric patients?
NELSON. The biggest single difference is that in pediatric stone disease, ultrasound is where we always start. And ultrasound is the only thing we do in the vast majority of our patients, unlike with adult stones, [for which] sometimes it seems like everyone who walks through the door gets a CT. We do see [children] who were referred to us for their stones but who [received a diagnosis] when they were seen at a community hospital somewhere and were immediately given a CAT scan, even though they're 12 or 14 or 16 years old, because that's just how things work in the adult world. They just CAT scan everybody. ...In a stone program at a children's hospital, [on the other hand], we almost never start with a CAT scan. Ultrasound is the mainstay of what we image with. To some extent, that's because it's easier, especially in prepubertal kids, because they're small, they're usually thin, and you can image very well with an ultrasound. It's harder...if you have a 17-year-old who weighs 240 lb, but we still almost always start with it. Diagnostically, that's the single biggest difference between us and the adult stone area. We certainly still do CAT scans, because there are many situations [in which] they're helpful or necessary, especially for surgical planning or for cases [in which] there might be a stone but the ultrasound is not finding it. But certainly, that's the exception.

The other main difference diagnostically is that we basically recommend metabolic testing for every patient we see after a first stone. That is definitely not the case in the adult world.

Q: What sort of preventive measures do you encourage in patients?
NELSON. Hydration is the foundation of everything. It's not particularly sexy, but that is the key thing that people have to do. That's what we hammer across every time. Almost every kid we test is underhydrated, so we focus a lot on ways to increase their fluid intake. Nowadays, there are lots of tools, [such as] apps on your phone that will alert you when you're supposed to drink [and] smart bottles that have little chips in their lid that record every time you drink. There are a number of ways we can get people to try to drink more. That's true in the adult world too, but it's more challenging in children because they don't necessarily do what we say and they don't do what their parents say.

There are some exciting new medications available for certain indications. One of the metabolic conditions is primary hyperoxaluria, which is a rare genetic abnormality that leads to stone formation. ...A recently approved medication called lumasiran [Oxlumo]...treats that and seems to be very effective in terms of reducing and correcting the metabolic abnormality in the urine, so...those [children] hopefully will be much less likely to form stones over time. That's an important group because although the condition is rare, those [children] tend to form stones relentlessly; they have multiple stones a year and need multiple surgeries. There are not a huge number of adults with those conditions because they tend not to survive that long; they [experience] renal failure, [for example,] and other consequences of that condition. Hopefully, that will be a bit of a game changer for the small subset of [children] that we see with that. That's exciting, but it doesn't reflect the needs of the vast majority of stone patients.

Huge amounts of research and development have gone into the technology of the surgical interventions—the scopes, the lasers, all the toys we get to use within the OR [operating room]—which are transformative and night-and-day [different] to what stone surgery was like 40 or 50 years ago. That has been revolutionary. But on the prevention side, it's amazing how little there is compared with 20 or 30 years ago. There's just not much that's different.

Cystinuria is one of the other genetic stone conditions we see that, again, is rare, but patients that have it form stones over and over again. The primary medication used for that, tiopronin [Thiola], came out 30 to 35 years ago, and there has been nothing new since then. That's true in a general sense for almost all of this. It's an area that has not been studied enough. The resources and the basic science have not been where they need to be. Look at all the new drugs in urologic oncology; look at all the new drugs for overactive bladder. There's very, very little in stone prevention. That's something that needs to change in the future. It's hard because stones are a little bit of an orphan area, in that the only people who really deal with it are urologists and a handful of nephrologists who have an interest in stones.

[As] urologists, being surgeons, we spend all our time thinking about the surgeries we do and the equipment we need for that. That's why I think the revolution in stone surgery that has happened over the past 40 years has been driven by urologists who wanted better devices and better tools. All this amazing progress has happened. But in terms of the number of urologists who study stone formation in the lab—how the kidney actually produces stones—you can probably count them on 1 hand. Similarly, nephrologists, who would be the natural people to study that [as] they're medicine doctors, not surgeons, are all focused on glomerular nephritis and diabetes-related kidney failure and all the other conditions that nephrologists deal with. Stones is not a priority for the vast majority of them. That's why it has been so slow in terms of producing new prevention tools. It's unfortunate, but that's where we are. Fortunately, the surgical devices have progressed enormously so we don't have to cut people open for every stone like they used to [do] in the 1970s.
Although percutaneous tibial nerve stimulation (PTNS) is commonly used to treat overactive bladder, investigators continue to assess whether this neuromodulation technique could be beneficial for patients with other urologic conditions.

For instance, findings from a study evaluating the safety and efficacy of PTNS in patients with female sexual dysfunction were presented at the 2022 Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) Winter Meeting.¹ In this interview, coauthor Varun R. Talanki, MD, discusses the study’s objectives and findings and what they mean for future management of female sexual dysfunction.

Q. Please summarize the main points of your presentation.

TALANKI. My SUFU presentation was on the treatment of female sexual dysfunction with PTNS. This was a project that we developed after a grant we [received] from SUFU when I was a resident at Stony Brook in New York. Female sexual dysfunction is characterized by lack of sexual arousal and sometimes even pain with sexual activity. Female sexual dysfunction has many factors that can contribute to it, so this makes it very difficult to treat. There are multiple medications as well as nonmedical therapies that can help. We were studying to see if PTNS would be a good treatment for [the condition and] did a randomized controlled trial [in which] we compared PTNS to a validated sham. We found that treatment with PTNS was a safe and very effective way of improving sexual function. We treated women weekly over 12 weeks and found that a fair proportion...converted from having sexual dysfunction to no longer having sexual dysfunction. That was an incredible finding that mimics some other research that...exists. Our study was the first randomized controlled trial to show these results.

Q. What other innovations regarding female sexual dysfunction are on the horizon?

TALANKI. Constant research [is] being done looking at the different pathways. There are different hormonal pathways that are being studied actively. We have a few now that are FDA approved; however, as we get a better understanding of these pathways, we can start developing new drugs to target them.

“We found that treatment with PTNS was a safe and very effective way of improving sexual function.”

– VARUN R. TALANKI, MD

Q. What else should our audience know about this topic?

TALANKI. One of the main difficulties with dealing with female sexual dysfunction is that it’s underreported. I think that as providers, we can do a better job of screening for it and asking our patients if they have any of the risk factors or any of the signs or symptoms that can contribute to female sexual dysfunction. We need to really take a stand and screen for it, as it really can affect our patients. And then, at the same time, we have to create a culture where patients feel that they can bring it up. Make sure you give patients time and create a setting where they are willing to talk about it.

REFERENCE


Is neuromodulation beneficial for patients with female sexual dysfunction?

A urologist at Tri Valley Urology in Murrieta, California.

SEXUAL DYSFUNCTION

QUESTION & ANSWER

VARUN R. TALANKI, MD

Talanki is a urologist at Tri Valley Urology in Murrieta, California.
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Presentation, diagnosis, and management of a rare case of urachal adenocarcinoma

CHRISTOPHER PIECZONKA, MD; PETER FIORAMONTI, BS
Pieczonka is director of clinical research and Fioramonti is a clinical research assistant with Associated Medical Professionals in Syracuse, New York.

+ CLINICAL PRESENTATION
A 56-year-old Caucasian woman presents to her urologist with gross hematuria and a nontender infraumbilical mass approximately 3 cm in size. There is no drainage from the umbilicus. In-office cystoscopy suggests a mass effect to the dome of the bladder and friable mucosa. Representative CT imaging as shown in FIGURE.

During the first trimester of prenatal development, urine drains from the fetal bladder through the allantois that exits the umbilicus. This channel closes at the umbilical end during the second trimester to form a remnant hollow tube between the bladder and the umbilicus, known as the urachus.1 Typically, the urachus closes and elongates to form a fibrous cordlike structure running along the retropubic space, connecting the apex of the bladder to the umbilicus. Disruption of the closure of the urachus can result in a series of uncommon congenital urachal anomalies known as urachal remnants, such as a patent urachus, umbilical polyp, bladder diverticulum, or urachal cyst. These anomalies are usually asymptomatic, but they can present early in life with symptoms such as drainage from the umbilicus, redness around the umbilicus, or abdominal pain.2 Although asymptomatic congenital urachal anomalies are usually discovered incidentally from CT or MRI studies performed for other reasons, they can also be evaluated based on their type via ultrasonography, cystography, sonography, or cystoscopy.3

In cases where congenital urachal anomalies persist through adulthood, the urachal remnant may cause complications, such as infections or neoplasms. Infections are the most common complication of urachal remnants and may present with nonspecific symptoms such as abdominal tenderness, fever, pyuria, erythema, and sometimes a palpable mass.2 In this patient, a rare case of urachal adenocarcinoma was the diagnosis. Although urachal remnants are lined by urothelium, 80% of urachal cancers are adenocarcinomas. The remaining 20% of urachal cancers are urothelial, squamous, and sarcomatoid neoplasms.4-5 Urachal cancers are highly aggressive malignancies with a 5-year cancer-specific survival rate of less than 60%, and account for less than 1% of bladder cancers.6-12 The poor prognosis for patients with urachal carcinoma is partly a result of the low incidence of malignant urachal neoplasms, which has hindered the implementation of large-scale clinical studies that could provide evidence to create guidelines for the diagnosis and treatment of these rare malignancies. Currently, no standardized guidelines exist for the management of malignant urachal neoplasms.6-12

DIAGNOSTIC EVALUATION
The initial manifestation and presentation of urachal carcinoma shares several similarities with urothelial carcinoma. For example, hematuria, suprapubic pain, and voiding difficulties such as urinary frequency, urinary urgency, dysuria, and urge incontinence are observed in 82%, 24%, and 12% of patients, respectively.7 The risk for urachal carcinoma is also higher in males and in patients older than 55 years.6,8 Signs and symptoms unique to patients with urachal carcinoma include the presence of a palpable infraumbilical mass or mucosuria, both observed in 9% of patients.9

Although the criteria for the diagnosis of urachal carcinoma are still somewhat controversial, most investigators agree with those set forth by Sheldon and Mostofi.10,11 These include:

1. location in the dome or anterior wall of the bladder;
2. sharp demarcation between the tumor and the normal surface epithelium;
3. lack of prominent cystitis glandularis in adjacent mucosa;
4. bulk of the tumor in the bladder wall rather than luminal;
5. presence of urachal remnants within the tumor; and
6. exclusion of primary adenocarcinoma located elsewhere that has spread secondarily to the bladder.10,11

Certain institutions believe these criteria are too restrictive and instead use the following diagnostic criteria proposed by Johnson:

1. location in the dome or elsewhere in the midline of the bladder;
2. sharp demarcation between the tumor and the surface epithelium; and
3. absence of primary adenocarcinoma of another organ.13,14

Diagnostic techniques performed during the diagnosis of urachal carcinoma include cystoscopy, CT urography (CTU), ultrasonography, MRI, and endoscopic biopsy. In this case, in which a nonpregnant 56-year-old woman without acute kidney injury or findings suggestive of glomerular bleeding presents with gross hematuria, the patient should receive a CTU and cystoscopy. The combination of CTU and cystoscopy provides a complete evaluation of the urinary system and can be used to identify the location of the tumor and rule out other malignancies.13,14 Additional imaging findings indicative of urachal carcinoma include the presence of a solid urachal adenocarcinoma, continued on page 32.
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URACHAL ADENOCARCINOMA, CONTINUED FROM PAGE 30

mass or a mass with macroscopic calcification, which occurs in 50% and 35% of urachal carcinomas, respectively. Finally, a transurethral biopsy is required to collect a tumor sample for use in subsequent histological studies.

MANAGEMENT

Given the rare nature of the disease, there are no standardized guidelines for the treatment of malignant urachal neoplasms, and knowledge about this disease is primarily derived from case reports and single-institution case series. The primary treatment for urachal carcinoma is total urachectomy in conjunction with partial cystectomy, which entails the excision of the bladder dome and urachal remnant along with the peritoneal, fascial, and umbilical segments to ensure adequate surgical margins. Although partial cystectomy is not considered standard of care for urothelial bladder cancer, urachal cancer-specific survival rates are similar in those treated with radical cystectomy and partial cystectomy is not considered standard of care for urachal carcinoma.

Urachal carcinoma occurs locally, usually following partial cystectomy, and tend to occur within the first 6 to 24 months after surgery. Nevertheless, repeat surgical resection following local recurrence has demonstrated a 15-year cure rate of 67%.

Radiotherapy and chemotherapy are rarely used in a neoadjuvant or adjuvant setting, and their efficacy remains unclear due to the lack of published data. Additional treatment options are used to treat unresectable or metastatic urachal carcinomas. As is the case with urothelial carcinomas of the bladder, radiotherapy is scarcely implemented in the treatment of urachal carcinoma and is likely an underutilized tool as we move toward bladder-preserving management.

Additional case studies and large-scale case series are needed to assess the efficacy of radiotherapy regimens for urachal carcinomas. Furthermore, without access to standardized chemotherapeutic protocols for the management of urachal carcinoma, treating physicians are responsible for defining the best therapeutic strategies for their patients. This task is complicated by the lack of published findings from studies on the efficacy of different treatments. Currently, the cisplatin-based combination therapies are believed to be the optimal treatment of urachal carcinoma. Interestingly, urachal carcinomas have been shown to have similar histological and molecular profiles to those of colorectal adenocarcinoma. Thus, the same chemotherapy regimens are often used for the treatment of urachal carcinoma and colorectal cancer.

Urachal carcinoma is a rare and aggressive malignancy. The low incidence of the disease results in limited large-scale clinical trials that could provide standardized guidelines for its diagnosis and management. Despite this obstacle, physicians can derive insight from the available case studies and large-scale case series that provide data on this rare disease. Although the criteria for urachal carcinoma diagnosis are controversial, diagnoses typically involve cystoscopy and a CT urogram to characterize the localization of the tumor, other necessary imaging studies to rule out the possibility of other primary adenocarcinomas, and transurethral biopsy for pathologic examination.

The primary mainstay treatment for urachal carcinoma is the surgical removal of the bladder dome and the urachal remnant along with the peritoneal, fascial, and umbilical segments. More case studies and large-scale case series are necessary to determine the efficacy of radiotherapy and chemotherapies in neoadjuvant, adjuvant, and metastatic settings.

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Chamie discusses treatment of patient with high-risk MIBC

Q. Could you describe your impressions of the case?

CHAMIE. Patients with bladder cancer most often present with non–muscle-invasive disease. In fact, 70% of patients with bladder cancer present with non–muscle-invasive disease. Only about 25% to 30% of patients have had disease that often makes them a candidate for either systemic chemotherapy, systemic immunotherapy, radiation therapy, or a cystectomy. Follow-up of patients with muscle-invasive bladder cancer is often disease-stage-dependent. Patients with more advanced disease at the time of cystectomy require more frequent monitoring. Those who have complete response require less monitoring. Nevertheless, patients will still require imaging of the thorax, the abdomen/pelvis, laboratory work-up, and urine cytology as patients still have either urethra or ureter that’s still intact and may harbor urothelial carcinoma in the future, as well as vitamin B12 levels that are checked annually.

Q. What are the currently available treatments for muscle-invasive bladder cancer?

CHAMIE. The standard of care for patients with muscle-invasive bladder cancer is neoadjuvant chemotherapy followed by either radiation or a radical cystectomy. The decision to pursue one vs the other is dependent upon the patient, their quality-of-life preferences, the tumor biology, and underlying symptomatology of the patient. For instance, to be a good candidate for radiation therapy, patients should have solitary tumors, no evidence of carcinoma in situ, no evidence of extravesical disease or hydronephrosis, and usually no variant histology.

Patients who are good candidates for radical cystectomy are the counter: patients who have multifocal disease, variant histology, carcinoma in situ, evidence of hydronephrosis, or extravesical extension. With regards to patients who receive radiation therapy, most of those patients go on and complete their radiation therapy. There is about a 29% chance that patients who have undergone radiation therapy would ultimately go on to get a cystectomy. Now, that’s based on a historical series by William Shipley[,]’s research group.¹ We think that that incidence of needing a cystectomy has gone down, as some of those patients who went on to get a radical cystectomy after radiation likely had non–muscle-invasive recurrences. Those patients may be adequately treated with intravesical therapy.

Q. How do you go about assessing the risk profile of a patient?

CHAMIE. We assess risk as far as a need or access to chemotherapies based on their performance status, on their renal function, and on hearing loss if any. Determination of getting a cystectomy and variant histologies is based on performance status, their ability to catheterize themselves if they need to, whether the urethra is involved, and tumor biology. As far as radiation therapy, a patient may not be a good candidate if they’ve had, aside from tumor biology, prior radiation to the pelvis.
**Q. What kinds of adjuvant treatments are available, and how do you choose between them for patients?**

**CHAMIE.** Patients who undergo radical cystectomy may require adjuvant therapy, which is a therapy that is based on tumor biology discovered at the time of radical cystectomy. For instance, if a patient has a positive margin, which is unusual, in the urethra or in the bladder neck or around the bladder, they may benefit from radiation therapy. If patients have had neoadjuvant chemotherapy, and at the time of cystectomy they were found to have muscle-invasive disease or node-positive disease, they may be good candidates for adjuvant immunotherapy. If patients didn’t have neoadjuvant chemotherapy and were found to have T3 disease or higher, basically extravascular disease or node-positive disease at the time of cystectomy, they may be good candidates for adjuvant therapy with either chemotherapy or adjuvant immunotherapy. The decision to pursue adjuvant chemotherapy vs adjuvant immunotherapy is dependent upon the patient, their underlying symptomatology of the patient.

In the adjuvant setting, we do have an FDA-approved drug: nivolumab [Opdivo]. Nivolumab is an anti-PD-1 inhibitor that has been shown in the CheckMate 274 study [NCT02632409] to demonstrate a recurrence-free survival benefit. Patients who’ve mostly either undergone neoadjuvant chemotherapy or not, I believe that 40% of them had neoadjuvant chemotherapy and 60% didn’t, underwent a radical cystectomy. Then, depending upon the stage of disease—namely if they were T3, T4, or [had] node-positive disease in the setting of non-neoadjuvant chemotherapy or T2 disease or higher or node-positive disease in the setting or prior neoadjuvant chemotherapy—those patients were included in the study. They were randomized 1:1 to receive either 1 year’s worth of nivolumab or placebo. The patients were found to have a statistically significant recurrence-free survival benefit if they were randomized to the nivolumab arm. The median recurrence-free survival in the nivolumab arm was about 20 to 21 months vs 11 months for patients who had placebo. They then looked at factors such as PD-L1 status, and again, patients who had nivolumab and were PD-L1-positive still did significantly better. They looked at non-urothelial tract recurrence-free survival and again found that patients who had nivolumab statistically did significantly better. The data demonstrate that the drug was well tolerated with the most common side effects being fatigue, rash, and pruritis.

In the subanalysis, nivolumab was found to be more beneficial in patients who were PD-L1 positive. It’s also found to be more beneficial when we’re talking about non-urothelial-tract recurrence-free survival. It was found to be less beneficial in patients with upper-tract urothelial carcinoma. Part of the reason with the upper-tract urothelial carcinoma may be related to the fact that they’re measuring recurrence-free survival. About 21% of their cohort were patients who were included in the study for upper-tract urothelial carcinoma and underwent nephroureterectomy. It’s entirely possible that patients underwent nephroureterectomy and had non–muscle-invasive disease recurrences in the bladder; that was deemed to be a recurrence. It’s entirely possible that there may be some noise in patients who have received placebo vs nivolumab and had recurrences in the bladder that were not clinically significant, but were defined as a recurrence.

**Q. Coming back to the case study, would you treat this patient in the adjuvant setting if her disease were under control after having undergone neoadjuvant therapy and cystectomy? And if you were to use adjuvant therapy, what treatment would you use?**

**CHAMIE.** The decision to pursue adjuvant therapy would be based on what we find in pathology. If the patient was found to have a positive margin in the pelvis, she’s someone to whom I probably would offer radiation therapy. If the patient were found to have muscle-invasive disease or higher or node-positive disease, I would probably offer adjuvant nivolumab therapy. I wouldn’t offer her a chemotherapy because she’s already received 4 cycles, and it’s unlikely that she had a clinically meaningful response if she requires adjuvant setting. If she had a complete response, then I wouldn’t offer her anything. However, if she didn’t have a complete response, meaning she had T2 disease or higher or node-positive disease, I probably would move on to nivolumab.

In my experience, patients who would be good candidates for adjuvant therapy are those who didn’t have neoadjuvant chemotherapy and had a complete response, meaning she had T2 disease or higher, basically extravesical disease or node-positive disease at the time of cystectomy. Then, depending upon the stage of disease—namely if they were T3, T4, or [had] node-positive disease in the setting of non-neoadjuvant chemotherapy or T2 disease or higher or node-positive disease in the setting or prior neoadjuvant chemotherapy—those patients were included in the study. They were randomized 1:1 to receive either 1 year’s worth of nivolumab or placebo. The patients were found to have a statistically significant recurrence-free survival benefit if they were randomized to the nivolumab arm. The median recurrence-free survival in the nivolumab arm was about 20 to 21 months vs 11 months for patients who had placebo. They then looked at factors such as PD-L1 status, and again, patients who had nivolumab and were PD-L1-positive still did significantly better. They looked at non-urothelial tract recurrence-free survival and again found that patients who had nivolumab statistically did significantly better. The data demonstrate that the drug was well tolerated with the most common side effects being fatigue, rash, and pruritis.

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“**The standard of care for patients with muscle-invasive bladder cancer is neoadjuvant chemotherapy followed by either radiation or a radical cystectomy. The decision to pursue one vs the other is dependent upon the patient, their quality-of-life preferences, the tumor biology, and underlying symptomatology of the patient.”**

-KARIM CHAMIE, MD
candidates for adjuvant nivolumab would be the ones who have muscle-invasive disease in the setting of prior neoadjuvant chemotherapy or nodal disease, or patients who were unable to tolerate chemotherapy. Those are the patients for whom I see the most benefit. I often find that these patients report very few adverse events; they tend to have fewer complaints compared with adjuvant chemotherapy. The reason that is important is we know that adjuvant chemotherapy is much less tolerated than neoadjuvant chemotherapy. We’ve looked at this, and we know that more than 90% of patients who’ve ever enrolled in a clinical trial for neoadjuvant chemotherapy can complete all 3 or 4 cycles, whereas only about two-thirds of patients who were enrolled in clinical trials were ever able to complete their adjuvant component. In this study, the vast majority, over 80% of patients, were able to tolerate a year’s worth of nivolumab, let alone 4 to 6 cycles, which is 4 to 6 months.

At UCLA [University of California, Los Angeles], all patients who undergo radical cystectomy have their tissue examined for PD-L1 status; for every patient who gets a radical cystectomy, we know whether they’re high PD-L1. Now, that doesn’t necessarily affect our decision-making because in the CheckMate 274 study, everybody had a significant benefit whether patients were PD-L1-positive or not. Patients who were PD-L1 positive had an even greater benefit than those who were PD-L1 negative, but everybody had a benefit from nivolumab.

**Q. What do you see on the horizon over the next several years in the bladder cancer space?**

**CHAMIE.** The field is growing significantly; there are really promising exciting new drugs on the horizon. Drugs that were being used historically drugs. But are also involved in patients who’ve undergone, say, a radical cystectomy and have a positive margin, but are also involved in patients who are not good surgical candidates for a cystectomy and may benefit from bladder preservation. The utilization of some of these novel agents may be synergistic with radiation therapy. It’s going to be an exciting field, and having a multidisciplinary team is key as we utilize and offer these newer drugs to these patients.

**Q. What would you say is the biggest unmet need in bladder cancer?**

**CHAMIE.** In my opinion, the biggest unmet need in bladder cancer has to do with identifying patients who really need adjuvant therapies and some of these more aggressive treatments. For instance, is it possible that some patients who have T2 disease after neoadjuvant chemotherapy may not need adjuvant nivolumab? Is it possible that a patient who gets neoadjuvant chemotherapy may not need a radical cystectomy? Those are things that we’re going to end up trying to answer over the next 5 to 10 years. We’re going to have to utilize things like circulating tumor DNA and other biomarkers to determine who needs more aggressive treatments like a cystectomy after neoadjuvant chemotherapy or adjuvant therapies after radical cystectomy. Those are the unmet needs, and those are the questions that we need answered.

**“The key takeaway is that these drugs are becoming increasingly [better] tolerated. Their adverse event profiles are not as significant as we’ve had with historical drugs.”**

KARIM CHAMIE, MD

I do expect that patients who are treated at academic centers will often see a multidisciplinary team. We have medical oncologists who are going to become increasingly more familiar not only with chemotherapy but also the adverse event profile and the toxicity profiles of antibody-drug conjugates, immunotherapies, and targeted therapies. There’s going to be increasing collaboration not just with medical oncology but with medicine. That is because some of these drugs may have some toxicities and we need to identify those who are at increased risk. I think the radiation oncologists always are involved in patients who’ve undergone, say, a radical cystectomy and have a positive margin, but are also involved in patients who are not good surgical candidates for a cystectomy and may benefit from bladder preservation. The utilization of some of these novel agents may be synergistic with radiation therapy. It’s going to be an exciting field, and having a multidisciplinary team is key as we utilize and offer these newer drugs to these patients.

**REFERENCES**


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New devices are poised to help in overactive bladder treatment

According to the American Urological Association Urology Care Foundation, “as many as 30% of men and 40% of women in the United States live with OAB [overactive bladder] symptoms.” It is a condition with a significant effect on the quality of life, as “Scott A. MacDiarmid, MD, FRCPSC, and Alexandra Rogers, MD, discussed in a recent UroView™ program.

“There’s no question that people lose their self-esteem and are embarrassed. It’s associated with anxiety and depression,” said MacDiarmid, a urologist with Alliance Urology Specialists in Greensboro, North Carolina.

Because of embarrassment and other factors, Rogers noted, there is often a delay in patients receiving a diagnosis for their condition, which complicates their care.

“The maze to diagnosis is full of roadblocks, and when they finally reach us, their incontinence needs to be clearly defined, both verbally and with care pathways, given that many women have both, and we need to tackle the most bothersome symptom. Diagnosis is a mess,” said Rogers, a urologist in Boulder, Colorado.

Treatment of OAB ranges from behavioral therapy to medications to device-based treatments and onabotulinumtoxinA (Botox). Device-based treatments include peripheral tibial nerve stimulation (PTNS) and sacral neuromodulation, which along with onabotulinumtoxinA are considered third-line treatments in OAB. MacDiarmid said he doesn’t “have a favorite” when it comes to these treatment options.

“They all work differently. They’re all imperfectly good. Any one of them can work for an individual,” he commented.

Rogers said she generally progresses quickly to third-line treatments.

“If it’s going to be covered, I move on immediately. For PTNS in California, you have to fail 2 medications. That being said, many patients who see me have already tried an anticholinergic medication. For patients who are new or returning, having failed, I’m putting them on the newest β agonist for 2 weeks. I’m trying to get them to the third line on the next step,” she said.

Rogers and MacDiarmid discussed TNS and emerging devices in the space.

“It’s pretty exciting. There are a lot of devices in development. These will be a nice addition to the OAB toolbox,” Rogers said.

“Many patients who see me have already tried an anticholinergic medication. For patients who are new or returning, having failed, I’m putting them on the newest β agonist for 2 weeks. I’m trying to get them to the third line on the next step.”

—ALEXANDRA ROGERS, MD

One such device, the RENOVA iStim, is a battery-free electrical power receiver implant with 2 bipolar electrodes. Rogers discussed results of a feasibility trial of the device.

“They had a 71% responder rate for all OAB syndrome symptoms of urgency, urge incontinence, and frequency. And they had a roughly 52% responder rate for urge urinary incontinence at 6 months. Forty-seven percent of the [participants] experienced adverse events,” Rogers said.

Implantation took 35 minutes and was performed under local or general anesthesia per the discretion of the implanter, according to Rogers.

BlueWind Medical, the developer of RENOVA iStim, recently finished enrollment for the OASIS study (NCT03596671), which is evaluating the device in patients in the United States, Belgium, the Netherlands, and the United Kingdom. The primary end point, according to Rogers, is urge urinary incontinence after 6 months of treatment. Results are expected in summer 2022.

MacDiarmid and Rogers also discussed the eCoin device, a tibial neurostimulator that is the shape and size of a nickel. It is implanted in the lower leg under local anesthetic in an office or outpatient procedure by a urologist or urogynecologist and the procedure takes about 20 minutes. Pivotal data for eCoin, which was approved by the FDA in March 2022, were published last year in the Journal of Urology.1 MacDiarmid provided a recap of the study (NCT03556891) during the discussion, which is evaluating eCoin in patients with refractory OAB. A total of 121 patients were included in the intent-to-treat population, 98% of whom were women. The mean number of daily urgency urinary incontinence episodes was 4.3, and the mean history of OAB was 11 years.

The primary end point was the percentage of patients at 48 weeks who had a reduction in urge incontinence of at least 50%, as measured by a 3-day voiding diary at 48 weeks following activation of eCoin.

The results from the primary efficacy analysis of an open-label, single-arm trial showed that eCoin met the study’s primary end point by achieving at least a 50% improvement in urgency urinary incontinence in 68% of patients after 48 weeks of treatment.

“As far as tolerability and safety...[eCoin] was very well tolerated. There were a lot of mild and moderate adverse effects, like some swelling in the ankle, some discomfort, and maybe a little redness, and those settled down. As far as infections, there were 4 explantations.... The infection rate was around 2.3%, which is what was expected,” MacDiarmid said.
During the conversation, Rogers asked MacDiarmid how eCoin addresses the shortcomings of other third-line therapies in OAB. “These are all imperfectly good treatments, and if you look at the perceived or real weakness of each of the other 3, eCoin would address the retreatment rate and the need to come to the office by the patient with PTNS. There are some long-term third-party payer issues with PTNS. There’s a perception by physicians, perhaps an economic one, that you need nurses and infrastructure. If you think through those, it likely will address most, if not all, of those…. Botulinum toxin is another great treatment, but there’s a retreatment rate that some patients don’t like…. With sacral nerve stimulation, whether it’s perceived by the patient, it’s more invasive. I like the fact that it has a test, but it is surgery and the patient perceives that, and they may or may not wish to have an operation,” MacDiarmid said.

Regarding the reimplantation of eCoin, MacDiarmid explained, “There are a few tricks, but overall, the replacement is easy and equally safe. It’s a little more challenging, but it’s easy to do and safe.”

MacDiarmid and Rogers ended the program talking about the future of OAB treatment.

“Seventy-five percent [of OAB cases] aren’t managed. We….need to adapt to the heightened level of customer service that is expected, where it’s not just about the efficacy for patients. They want low risk, high return, and they want it to be easy on them, so we need more therapies like that,” Rogers said.

MacDiarmid echoed Rogers’ call for more treatments, saying, “There are a lot of tibial nerve stimulators in development, and that’s wonderful, because whether they come out with rechargeable batteries or leads that work well, we need more tools.”

REFERENCE

“There are a lot of tibial nerve stimulators in development, and that’s wonderful, because whether they come out with rechargeable batteries or leads that work well, we need more tools.”

– SCOTT A. MACDIARMID, MD, FRCPC
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ADDING DAROLUTAMIDE TO STANDARD CARE IMPROVES SURVIVAL IN METASTATIC CASTRATION-SENSITIVE PROSTATE CANCER

Findings from the placebo-controlled phase 3 ARASENS trial showed that adding darolutamide (Nubeqa) to standard androgen deprivation therapy (ADT) and docetaxel boosted overall survival (OS) vs ADT/docetaxel alone in patients with metastatic castration-sensitive prostate cancer.1

Results reported at the 2022 Genitourinary Cancers Symposium and published in the New England Journal of Medicine2 showed that at a median follow-up of 43.7 months for darolutamide plus ADT/docetaxel and 42.4 months with placebo plus ADT/docetaxel, the active therapy resulted in a 32.5% reduction in the risk of death (HR, 0.68; 95% CI, 0.57-0.80; P < .001).

In ARASENS (NCT02799602), patients with cytologically confirmed metastatic adenocarcinoma of the prostate were eligible to enroll. All participants needed to be candidates for ADT and docetaxel, have an ECOG performance status of 0 or 1, and have adequate organ function.

Patients were randomized 1:1 to either 600 mg of daily darolutamide (n = 651) or matched placebo (n = 655) plus ADT/docetaxel. Factors for stratification included extent of disease (M1b/c) and alkaline phosphatase (ALP) levels. The primary end point was OS, with secondary outcome measures of time to CRPC, time to pain progression, time for first symptomatic skeletal event (SSE), time to initiation of subsequent systemic antineoplastic therapy, and safety.

Median OS in the darolutamide arm was not estimable (NE; 95% CI, NE-NE) vs 48.9 months (95% CI, 44.4-NE) with placebo. Rates of OS at 48 months were 62.7% and 50.4%, respectively. The effect of active therapy was consistent across patient subgroups, including by ALP level below (HR, 0.64; 95% CI, 0.46-0.88) or above (HR, 0.69; 95% CI, 0.56-0.85) the upper limit of normal, and by either de novo (HR, 0.71; 95% CI, 0.59-0.85) or recurrent (HR, 0.61; 95% CI, 0.35-1.05) metastatic disease status.

Moreover, darolutamide was associated with superior secondary outcomes despite the patients in this arm receiving fewer subsequent life-prolonging systemic antineoplastic therapies (56.8%) vs the placebo arm (75.6%). Common subsequent therapies included abiraterone acetate (35.6% vs 46.9%), enzalutamide (Xtandi; 15.2% vs 27.5%), cabazitaxel (Jevtana; 18.1% vs 18.0%), and docetaxel (14.6% vs 18.0%). Notably, 66% of patients in the placebo arm went on to receive life-prolonging therapy with an AR pathway inhibitor. Time to first subsequent antineoplastic therapy was NE (95% CI, NE-NE) in the active therapy arm vs 25.3 months (95% CI, 23.1-28.8) in the placebo group (HR, 0.39; 95% CI, 0.33-0.46; P < .001).

TIVOZANIB SUSTAINS PFS BENEFIT OVER SORAFENIB IN METASTATIC RCC

Treatment with tivozanib (Fotivda) was associated with a fivefold increased likelihood of experiencing long-term progression-free survival (PFS) compared to treatment with sorafenib (Nexavar) among patients with pretreated relapsed/refractory renal cell carcinoma (RCC), according to the latest findings from the TIVO-3.3

TIVO-3 (NCT02627963) included 350 patients with relapsed/refractory RCC who received 2 or more prior lines of systemic therapy. Half were randomized to receive tivozanib, while the other half received sorafenib. Superior PFS findings for the tivozanib arm led to the tyrosine kinase inhibitor’s (TKI) approval last March, while longer-term follow-up with a data cutoff of May 24, 2021, continued to show that, on average, tivozanib was superior.
“In this analysis, we assessed the proportion of TIIVO-3 patients with relapsed/refractory mRCC who achieved a [long-term] PFS at regular intervals up to 4 years after initiation of [tivozanib] or [sorafenib],” the investigators wrote on their poster presentation, noting that they tracked survival data from the TIIVO-3 trial at 6-, 12-, 18-, 24-, 30-, 36, 42, and 48-month marks.

However, since there was a low number of patients at the 42- and 48-month marks at the time of the data cutoff, the investigators could not conduct any inferential statistical analyses.

At the 3-year mark, landmark long-term PFS rates, as assessed by the investigators, were 12.3% (95% CI, 8.8%-15.8%) and 2.4% (95% CI, 1.1%-6.1%) in the tivozanib and sorafenib arms, respectively. Tivozanib continued to best sorafenib at the 4-year mark, too, with PFS rates at 7.6% (95% CI, 4.0%-13.2%) and 0%, respectively.

The patient population was well-balanced between the tivozanib and sorafenib arms, with 34, 109, and 32 patients in the favorable, intermediate, and poor risk groups, respectively, in the tivozanib arm. Meanwhile, on the sorafenib arm, there were 36 patients with favorable risk, 105 with intermediate risk, and 34 with poor risk disease. The majority of patients in each group (128 for tivozanib and 131 for sorafenib) had no prior immunotherapy, and 79 patients in the tivozanib group had treatment with 2 TKI therapies, compared with 80 patients in the sorafenib group. All patients included in the analysis had an ECOG score of 0 or 1. Of note, subgroups with 15% long-term PFS at 3 years include IMDC favorable risk, female gender, ECOG performance score of 0, and an average age of 65 years old.

**ADJUVANT PEMBROLIZUMAB CONTINUES TO DEMONSTRATE DFS BENEFIT IN RCC**

An updated analysis of the phase 3 KEYNOTE-564 trial (NCT03142334) found that adjuvant treatment with pembrolizumab (Keytruda) continued to demonstrate improved disease-free survival (DFS) vs placebo in patients with renal cell carcinoma (RCC) who are at high risk of recurrence.

The findings were reported by Toni K. Choueiri, MD, director of the Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Brigham and Women’s Hospital, and Jerome and Nancy Kohlberg Chair and Professor of Medicine at Harvard Medical School in Boston, Massachusetts.

Previously reported data from KEYNOTE-564 found that treatment with adjuvant pembrolizumab yielded a statistically significant and clinically meaningful DFS benefit vs placebo in the intent-to-treat population (HR, 0.68; 95% CI, 0.53-0.87; \(P = .001\)). The 2022 GU Symposium presentation consisted of an updated efficacy and safety analysis with 30.1 months of follow-up.

**KEYNOTE-564 evaluated patients with RCC defined as intermediate-high risk (pT2, grade 4 or sarcomatoid, N0, M0; pT3, any grade, N0, M0), high-risk (pT4, any grade, N0, M0; any pT, any grade, N+, M0) and M1 no evidence of disease (NED) following surgery. Patients were randomized 1:1 to receive either pembrolizumab, 200 mg every 3 weeks (n = 496) or placebo every 3 weeks (n = 498).**

Median patient age was 60 years in both the treatment and placebo groups. A total of 347 patients in the pembrolizumab group were male (70.0%) vs 359 patients (72.1%) in the placebo group. Regarding risk category, 427 patients were intermediate-high risk (86.1%), 40 patients (8.1%) were high risk, and 29 patients (5.8%) were M1 NED in the treatment group vs 433 (86.9%), 36 (7.2%), and 29 (5.8%) in the placebo group, respectively. In the treatment group, there were 427 patients (10.5%) in whom sarcomatoid features were present vs 414 patients (83.5%) in whom sarcomatoid features were absent, compared with 59 (11.8%) and 415 (83.3%) in the placebo group.

For the primary end point of DFS, benefit was maintained in patients receiving pembrolizumab (HR, 0.63; 95% CI, 0.50-0.80; nominal \(P < .0001\)) and as was follows across the 3 subgroups:

- Intermediate-high risk: HR, 0.68 (95% CI, 0.52-0.89)
- High risk: HR, 0.60 (95% CI, 0.33-1.10)
- M1 NED: HR, 0.28 (95% CI, 0.12-0.66)

“The estimated DFS rate at 24 months was 78.3% with pembrolizumab vs 67.3% with placebo...The estimated [overall survival] rate at 24 months was 96.2% with pembrolizumab vs 93.8% with placebo,” wrote the authors.

**LENVATINIB/PEMBROLIZUMAB SHOWS EFFICACY AND SAFETY IN EAST ASIAN PATIENTS WITH ADVANCED RCC**

An analysis of lenvatinib (Lenvima) plus pembrolizumab in an East Asian subgroup of patients with advanced RCC from a phase 3 trial found efficacy and safety consistent with that seen in the overall study population.5

The findings from the phase 3 CLEAR trial (NCT02811861) were presented at the 2022 Genitourinary Cancers Symposium.

The makeup of the East Asian subset consisted of patients from Japan and the Republic of Korea. Their characteristics were generally consistent with the baseline characteristics of the overall patient population from the CLEAR trial. Investigators found that PFS, similar to the global population, was longer in the combination arm compared with sunitinib alone at a median of 22.1 months compared to 11.1 months, respectively.

The HR was comparable in both groups with an HR of 0.38 (95% CI, 13.8-NE) in the East Asian subset compared to the global population HR of 0.39. This consistency extended to the comparison of overall survival (OS) with a HR of 0.71 (95% CI, 0.30-1.71) in the East Asian subset of patients and an HR of 0.66 in the global population.

The phase 3 CLEAR trial had previously reported significant improvements in PFS (HR, 0.39; 95% CI, 0.32-0.49; \(P < .001\)), OS (HR, 0.66; 95% CI, 0.49-0.88; \(P = 0.005\)) and objective response rate (ORR) (odds ratio, 4.35; 95% CI, 3.16-5.97) in the global population for patients with advanced RCC in the combination arm. Patients included in the trial had no prior systemic therapy and were randomized 1:1 to receive either 20 mg of lenvatinib orally 4 times a day plus 200 mg of pembrolizumab intravenously every 3 weeks, or 50 mg of sunitinib 4 weeks on and 2 weeks off.

ORR was improved in the lenvatinib and pembrolizumab arm in the East Asian subset at 65.3% compared with 49.2% in the monotherapy arm (OR, 2.14, 95% CI, 1.07-4.28). Furthermore, duration of response was longer in this subset at 20.3 months compared with 12.9 months. Broken down by complete response (CR) and partial response (PR), the combination therapy remained stronger in this patient subset with a 17.3% CR and 48% PR vs 7.7% CR and 41.5% PR rates in the sunitinib arm.
PARP inhibitor first-line data are among ASCO GU highlights

**PROSTATE CANCER**

Michael S. Cookson, MD, MMHC | Professor and the Donald D. Albens Endowed Chair in Urology at the University of Oklahoma Health Sciences Center in Oklahoma City, a co-editor in chief for Urology Times®

Abstract 11: PROpel: Phase III trial of olaparib (ola) and abiraterone (abi) versus placebo and abi as first-line (1L) therapy for patients (pts) with metastatic castration-resistant prostate cancer: “This abstract from the PROpel study [NCT03732820] looked at moving up the PARP inhibitor olaparib [Lynparza] to an earlier disease state—first-line therapy for metastatic castration-resistant prostate cancer. Currently, PARP inhibitors are approved for patients who have failed multiple therapies, including a novel antiandrogen therapy and/or docetaxel chemotherapy. This was an attempt to look at olaparib more as a first-line therapy in metastatic disease combined with abiraterone [Zytiga] as compared with abiraterone alone. What they found, first of all, was that there was improvement in progression-free survival, so that was good. Perhaps most surprising was that it was agnostic to whether they harbored repair gene defects. That’s exciting because that would open up this type of treatment for many more patients, not just for the 20% to 25% of patients that harbor those DNA repair defects. In addition to that, it would open up the opportunity to give patients that medication at a much earlier part of their disease process. So that’s exciting. We look forward to longer follow-up [data] to see if this translates into an overall survival benefit.”

Abstract 12: Phase 3 MAGNITUDE study: First results of niraparib (NIRA) with abiraterone acetate and prednimouse (AAP) as first-line therapy in patient (pts) with metastatic castration-resistant prostate cancer (mCRPC) with and without homologous recombination repair (HRR) gene alterations: “Abstract 12, or the MAGNITUDE study [NCT03748641], also looked at moving a PARP inhibitor, niraparib, earlier as first-line therapy in patients with metastatic castration-resistant prostate cancer, and it looked at that in combination with abiraterone as compared with abiraterone alone. The study differs a little bit from PROpel in that, although they did find significant improvement and radiographic progression-free survival in patients who were using that PARP inhibitor at a much earlier part of the disease date, it was really restricted to those patients who harbored those DNA repair defects. That represents a little bit of a difference from abstract 11 in that this [might] indicate a more restrictive use for this therapy, given that about 20% to 25% of patients will harbor these types of defects. But again, it is good news that we can move the therapy up earlier and that we’re going to see at least a reduction in their progression of disease. Again, we look forward to longer follow-up [data] to see if this translates into an overall survival benefit.”

**BLADDER CANCER**

Janet Kukreja, MD | Assistant professor of urology at the University of Colorado in Aurora

Abstract 434: TROPHY-U-01 Cohort 3: Sacituzumab govitacan (SG) in combination with pembrolizumab (Pembro) in patients (pts) with metastatic urothelial cancer (mUC) who progressed after platinum (PLT)-based regimens: “This abstract looked at sacituzumab govitacan-hziy [Trodelvy] in combination with pembrolizumab [Keytruda]. This is a novel combination that [data] hasn’t been published on before. But sacituzumab was recently approved as a monotherapy, so it’s very reasonable to look at it with pembrolizumab. The study found that it was manageable; there were encouraging overall response rates. Regarding the safety profiles, there were no new signals. I think the main message that we got from this abstract was that the [adverse] effects did go on top of each other. Although patients did not experience new [ones], they did experience [adverse] effects and some patients had to discontinue treatment due to their [adverse] effect profile. There were some limitations, but for a phase 2 trial, these are really promising data of how we might be able to combine these in the future.”

Abstract 435: Study EV-103 Cohort H: Antitumor activity of neoadjuvant treatment with enfortumab vedotin monotherapy in patients (pts) with muscle-invasive bladder cancer who are cisplatin-ineligible: “This abstract looked at enfortumab vedotin [Padcev] activity in patients who were cisplatin ineligible in muscle-invasive bladder cancer. All the patients were treated with enfortumab and then underwent radical cystectomy. This is a phase 1b/2 trial looking at 22 patients who received 3 cycles of enfortumab prior to surgery. The interesting thing from a surgery standpoint was there were 5 adverse events associated with enfortumab, which is not necessarily a new safety signal. But as phase 3 trials are being planned, how these patients are managed perioperatively to avoid some of those complications needs to be thoughtfully considered. About half of patients had no tumors in their bladder at cystectomy, so [that is] very comparable to cisplatin. This may be a true option for patients who are cisplatin ineligible. But I would say further safety data are needed prior to saying this is something that we should be doing as standard of care.”

To view Cookson and Kukreja’s full comments, scan the QR code or visit bit.ly/3NFG3eO
Next-generation sequencing: A reliable tool for the diagnosis and treatment of complicated and recurrent urinary tract infections

by Meghan Shotwell, MSHS, PA-C

**Urinary Tract Infections (UTIs)** are a common outpatient infection, especially in women aged over 65 years. At least 1 in 2 women will have a UTI in her lifetime. In all, 20% to 40% of these women will have 1 recurrence, and, of those, up to 30% will go on to have multiple recurrences.1,2 The gold-standard diagnostic tool for UTI is urine culture, a technology that relies upon the ability of the causative organism(s) to grow in artificial conditions. The problem with culture is that many organisms that cause symptomatic urinary tract infections will not grow on standard culture medium, or will grow “mixed urogenital flora,” making identification of a causative pathogen difficult or impossible.

Empiric treatment with 5 days of nitrofurantoin or 3 days of sulfamethoxazole-trimethoprim is effective in managing the majority of uncomplicated acute UTIs, yet many patients coming to the urology practice for specialist evaluation are beyond this simple fix. A common line is, “I had a UTI, my primary care provider gave me [empiric antibiotic therapy]. My symptoms never went away, and now, after multiple antibiotics, my cultures are negative, but I still have symptoms.”

What is the next step? Using standard culture only, patients often are left with a diagnosis of chronic interstitial cystitis or chronic bladder pain, and they remain in a cycle of UTI-type flares. At this stage, patients often receive many rounds of empiric antibiotic therapy or other medications and procedures unnecessarily. This should not be the next step; better diagnostic testing must be used to find the pathogen(s).

The good news is that there are better ways to diagnose a UTI and formulate a plan for directed antibiotic therapy!

Advanced microbial analysis exists in 2 primary categories, polymerase chain reaction (PCR) testing and next-generation sequencing (NGS). PCR involves DNA amplification and matching of that DNA to a small set of known organisms. There are many PCR companies in the urology space that offer a test menu of about 18 to 40 organisms and regional antibiotic resistance data. With up to a 91% sensitivity, PCR testing provides a much better chance at getting a positive result than culture does, if the patient harbors 1 of the 40, or fewer, organisms in that test panel.3 However, PCR alone is not enough.

NGS offers the most comprehensive evaluation of the urinary microbiome. In comparison to the 40 organisms detectable by PCR, NGS analyzes all microbial DNA within a sample (eg, urine, semen, or vaginal or rectal specimen) and compares it to a database of species. One company, MicroGenDX, has a database of over 50,000 bacterial and fungal organisms. MicroGenDX’s approach combines quantitative PCR (qPCR) testing with NGS and allows clinicians to receive rapid PCR results in 24 to 48 hours and the full sample microbiome in 3 to 5 days from receipt of the sample with 99% accuracy and a proven noninferiority to culture.4-6 The company has identified approximately 5,800 species in urine from over 157,000 samples processed. Even more astonishing, a recent study of their database found that *Escherichia coli* was the predominant species in 29.6% of samples, calling for further analysis of the belief that *E. coli* is the most common cause of UTI.
CASE REPORT COMPARING PCR TO MICROGENDX QPCR + NGS

An 80-year-old male with known overactive bladder presented to the urology clinic for intermittent dysuria with frequency and urgency of urination, but he had no gross hematuria, fever, or flank pain. His urinalysis showed trace protein levels, but was negative for leukocyte esterase, red blood cells (RBCs), and nitrite. A urine PCR-only test was ordered, which detected no pathogenic organisms; however, a methicillin resistance gene was detected. At his 3-week follow-up, he reported no change in his symptoms. Subsequent urinalysis was negative for leukocyte esterase, RBCs, and nitrite. A qPCR + NGS urine test from MicroGenDX was sent, and results showed a medium (10^5-10^7) bacterial load with *E. coli* (53%), *Klebsiella aerogenes* (26%), and *Enterococcus faecalis* (17%). Neither companies’ PCR test detected the *E. coli*, likely due to mutations in the organism. Genetic resistance was detected to β-lactam and methicillin. Based on these results, the patient was given amoxicillin-clavulanate. He reported improvement in frequency, urgency, and dysuria at his next visit.

Molecular UTI diagnostics are an alternative to culture that provide more sensitive, specific, and timely results. NGS through MicroGenDX eliminates the common equivocal result of “mixed urogenital flora” or “greater than 2 organisms predominate” encountered with standard urine culture. While superior to culture, PCR testing alone lacks the ability to detect many atypical pathogens and mutated organisms. NGS allows clinicians to assess the complete microbiome for pathogens and treat the patient accordingly, using genetic resistance gene information and regional resistance patterns to increase antibiotic stewardship and improve patient outcomes.

REFERENCES


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**FIGURE.**

In a recent survey of more than 70,000 urine samples, MicroGenDX reported 3200 unique bacterial species and found *Escherichia coli* to be the dominant species in only 29.6% of cases.
It’s not always *E. coli*

**NGS DETECTED:**
- 48% *L. amnionii*
- 4% *E. coli*
- 25% *A. vaginae*
- 14% *L. iners*

**NGS TELLS US IT’S NOT ALWAYS *E. coli***

*E. coli* may be the dominant cause of acute UTIs, but recurrent UTI causes are highly variable. A case illustrating this is a UTI patient treated for *E. coli* based on culture but did not improve. The physician tried NGS, which identified *Leptotrichia amnionii* as the dominant species in the patient’s urine — a 48% bacterial load compared to just 4% *E. coli*. The patient was successfully treated based on this finding. *L. amnionii* is difficult to culture and preserve, and is an ideal candidate for DNA diagnostics from MicroGenDX.

MicroGenDX provides answers where culture and PCR alone have failed. Please contact us at for more information or to order your first testing supplies.

**MicroGenDX is the only microbial molecular lab that has:**
- Processed over 197,000 urological samples
- Identified 5,904 urological microbial species
- Identified *Leptotrichia amnionii* 2,661 times in UTI cases
- Published a randomized outcome study proving NGS superior to culture¹
- Published data showing 96.1% concordance with culture²
- 13 years of CAP proficiency testing with results showing 99.2% accuracy identifying to the species level³

³. College of American Pathology proficiency results, 2009–2021

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What it means to build an inclusive urology practice

At the 2022 Society of Women in Urology Annual Clinical Mentoring Conference, Polina X. Reyblat, MD, delivered a presentation called “Building an Inclusive Medical Practice for Patients.” In this talk, she discussed the ways in which urologists can make their practices more comfortable and open environment for patients of all different backgrounds to receive care. She expands upon these themes in the following interview.

Q. Please summarize the main points of your talk.

REYBLAT. I started my [presentation] by talking about [how], before we can fix the problem, we need to really look at the source: What are we trying to accomplish and where [is] our current baseline. I started...by examining where we stand in terms of care for patients from different racial backgrounds [and] different socioeconomic [and] immigrant [statuses] and health care literacy, as well as looking at elderly [communities], LGBT communities, and other marginalized groups. [I] then looked at what immediate and long-term policy changes we can establish to improve care and make our practices more inclusive.

Q. Which specific changes related to inclusion would you like to see in medical practices within the next few years?

REYBLAT. There are certain things we can do immediately in everyday practice, but a lot of work that needs to be done [is] at the system level and an organizational level. [I] talked about hiring culturally diverse staff, ongoing staff training in terms of cultural and racial sensitivity, [and] investing in forms and materials in different languages. [Those should be] reviewed by a native speaker [who can] look for things that can be lost in translation. [At my institution,] we spend some time talking about medically competent interpreters. Features like language line solutions and professional medical interpretation are a gold standard. Additionally, your internal staff can be trained properly to interpret some common care pathways for diagnosis and treatment. I would like to encourage urologists not to rely on the children and grandchildren of our patients because we don’t know the true medical and language competency of these translators. We also talked about the extended hours of operation for a weekend—early evenings and late-night clinics. In no way [do] I encourage people to work longer hours than we do already; we know about physician burnout. But adjusting the schedule and having flexible schedules will allow patients to see us... when they don’t have to take time off work or have their kids [take] off work to provide care. In our experience, Saturday [is] a success. Patients [are] satisfied and it also increases our ability to give care to the patients that really need it.

Q. How can urologists be advocates for an inclusive medical practice?

REYBLAT. I think urologists [have] always been on the forefront of innovation and changes [in] care. Urologists can do a lot of things; [for example], adjusting [your] practice internally, looking...[to] see [how] your offerings and your treatment pathways affect patients, based on your racial and socioeconomic breakdown of your own practice. Urologists can reach out to [communities] outside of [their] practice; [for example], use patient ambassadors [and] include a concept like “promotores de salud,” or community health care workers. [LGBTQ] centers are [also] strong centers where medical trust is built. We also can be promoters of trust, and that’s [something else] we talked about at the conference.... Medical distrust has [experienced] an increased prevalence throughout our community, and some of it lies in [the] historical experiences of patients but some of it is more contemporary. Building trust in the day-to-day interactions [and] acknowledging and respecting patients’ decisions on [a] daily basis can make a huge difference in our delivery of health care.

In addition, I would like to bring up some more specific, concrete steps that we can [take] to build an LGBTQA-inclusive space. We can start small, and every practice can start internally, whether you’re a small private practice or a large institution. I would start with terminology and cultural competency. There are a lot of online resources for that, and having it brought into the open space and for discussion opens doors. You can be the best physician and clinician out there, but if the patient who walks in at your check-in gets misgendered and disrespected before they even see you, that encounter and that relationship with the patient are already broken. So I would highly recommend [that we] educate ourselves and our staff in terminology and make our urologic offices a comfortable place for our LGBTQA patients.

REFERENCE
1. Reyblat PX. Building an inclusive medical practice for patients. Presented at: 2022 Society of Women in Urology Annual Clinical Mentoring Conference; February 4-6, 2022; New Orleans, LA.
LOOKING FOR CLINICAL DATA ON XTANDI EFFICACY AND SAFETY?

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**Speak Out**

**INTERVIEWS WITH RANDOMLY SELECTED UROLOGISTS ON HOT-BUTTON ISSUES**

**Compiled by Karen Nash**

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**Q**

Do you think patients on active surveillance would be willing to participate in a high-intensity interval exercise training program?

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“Certainly, I think it depends on the age of the patient. If you have patients on active surveillance, you can already extrapolate that a lot of them will be younger and perhaps will be in good enough shape to do a high-intensity workout. Those workouts are not for the faint of heart. They’re not for people who are not active to begin with.

Will that be possible among that group of patients? I suppose it could be.

Certainly, my experience with patients who are on surveillance, who meet the criteria for active surveillance, is that they tend to be younger and healthier patients, so I don’t see why not. I certainly think it’s a reasonable thing to tell them.

As far as the concept of high-intensity interval training, I would have to know more about the science behind it and how they make the science work with that.

But...some men would definitely be willing to do it. Certainly, I think a lot of the men who go on active surveillance are patients who are healthy enough to do those types of workouts. I think they would be able to, and I think if they’re willing to watch the cancer in active surveillance that they would be willing to make the effort to control it even better with high-intensity workouts. I don’t see why they wouldn’t.”

**Guillermo Patino, DO, FACS**

Las Vegas, Nevada

“Over the years, we’ve all done general urology, although I haven’t done a lot of prostate cancer for a couple years.

Certainly, I think most men with prostate cancer are very into researching prevention of recurrence and progression. So most men, if they’re physically able, would probably be interested into looking into any kind of research like that and moving forward.

It could depend on the patient’s age, comorbidities, and ability. [From] past [experience], I know a lot of men...would be willing to investigate any kind of adjuvant therapy they could find that would reduce the risks, because if they are on active surveillance, they want to keep it that way. They don’t want any progression of the disease. So if there’s something that actually gives them a little bit more ownership of their disease process, and that they can do to help prevent the cancer from progressing and having to move on to active treatment, a lot of the men would be willing to pursue it.

As far as the concept goes, prostate cancer aside, anytime you’re increasing your physical activity and increasing that cardiac stress, that’s good for every patient, [whether they have] prostate cancer, benign prostatic hyperplasia, [or] prolapse. Anything increasing your physical health overall is beneficial.”

**Stephanie Pothoven, DO**

Clive, Iowa

“Certainly, I think most men with prostate cancer are very into researching prevention of recurrence and progression. So most men, if they’re physically able, would probably be interested into looking into any kind of research like that and moving forward.

It could depend on the patient’s age, comorbidities, and ability. [From] past [experience], I know a lot of men...would be willing to investigate any kind of adjuvant therapy they could find that would reduce the risks, because if they are on active surveillance, they want to keep it that way. They don’t want any progression of the disease. So if there’s something that actually gives them a little bit more ownership of their disease process, and that they can do to help prevent the cancer from progressing and having to move on to active treatment, a lot of the men would be willing to pursue it.

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**Guillermo Patino, DO, FACS**

Las Vegas, Nevada

“The confounding factor, of course, is that people who work out are healthier and have better cardiovascular health anyway. It would be very important to separate out individuals with good cardiovascular health, normal body mass index, normal cholesterol, normal blood pressure, and no diabetes.

If men are already active, the question is how much more this activity would help them vs somebody who was marginally obese, actually lost 20 to 30 lb, and who lowered their cholesterol.

Also, it depends on the genetics of the prostate cancer. Individuals are going to get tested. And to be honest, if those tests show less than a 1% risk of metastatic disease in 10 years, why would they go and exercise?

Because we have genetic tests, which is the genetic behavior of the cancers, this might not even have a marginal impact on the progression of the prostate cancer.

If the patient is obese, but the genes are telling him he’s low risk, what incentive has he to lose weight?

If the patient is intermediate risk and decides on watchful waiting, then loses 45 lb due to high-intensity interval training and is suddenly determined to be low risk, that would be profound. You’d be reversing the course of the cancer by doing exercise. If gene testing already categorizes men as low risk, I don’t see the enormous incentive for them to exercise unless they are already motivated, to be honest.

It’s fine for heart health. There’s a colloquial thing we used to say: ‘Anything that’s good for the heart is good for the prostate.’

Obviously, it’s not a guarantee that solves all prostate issues but I think exercise would have marginal impact in light of the genomics that are widely available.

For sedentary individuals, if genomics show they’re low risk, it will be hard to convince them they have to work out so their prostate cancer risk will be even lower.”

**Matthew Karlovsky, MD**

Phoenix, Arizona

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What distinguishes IsoPSA from other prostate cancer tests?

In this video, Eric A. Klein, MD, explains how IsoPSA differs from other prostate cancer tests. Klein is emeritus professor and chair of the Glickman Urological & Kidney Institute at Cleveland Clinic and Cleveland Clinic Lerner College of Medicine in Cleveland, Ohio.

Using your phone’s camera, hover over the QR code and scan.
Teens and older adults are not getting medications to treat opioid abuse

Insurance is a factor in access to drug treatments, study findings indicate

RICHARD PAYERCHIN
Payerchin is an associate editor for Medical Economics®.

Adolescents and older adults abusing opioids could benefit from medications to treat addiction—but they aren’t getting the needed treatments, according to a new study.1

Investigators cited evidence of the effectiveness of the medications methadone, buprenorphine, or naltrexone. But estimates indicate low access to those drugs for young people, pregnant women, rural residents, adults in the criminal legal system, and racial and ethnic minorities.

“Medication for OUD [opioid use disorder] is associated with reductions in opioid use and disorder, longer treatment retention, and substantially reduced opioid-related mortality. Despite the strong evidence base, access to MOUD is limited by low facility and clinician uptake and persistent stigma surrounding OUD and medication,” wrote the authors, led by Pia M. Mauro, PhD, of Columbia University in New York, New York.

The investigation is the first to estimate past-year medication for opioid use disorder (MOUD).

The investigators used data from the National Survey on Drug Use and Health, maintained by the Substance Abuse and Mental Health Services Administration of the federal Department of Health and Human Services.

In a sample of more than 2.2 million people with treatment need, 27.8% reported past-year MOUD. Those using MOUD included no adolescents ages 12 to 17 and only 13.2% of adults age 50 or older.

The investigators noted buprenorphine is the only medication approved to treat OUD in adolescents.

“Gaps in access could be worsened by specialty facilities with adolescent treatment programs being less likely to provide MOUD than facilities serving adults,” the authors wrote. “Our findings support calls for additional MOUD engagement and retention strategies tailored for youths.”

For older adults, misconceptions regarding substance abuse in older age and lower screening and assessment rates may contribute to lower treatment rates.

“Insurance was the main enabling resource associated with treatment status,” with 35.2% of people with public insurance receiving MOUD, compared with 21% of people with private insurance and 16.8% of those with no public or private insurance.

Medicaid was an important characteristic among those receiving MOUD.

“However, our study shows that substantial gaps remain even among publicly insured people, which composed more than half of our sample,” the study said.

Those needing MOUD reported contacts with the health care and criminal legal systems, but most did not receive the treatment, “highlighting systemic gaps and continued missed opportunity increase MOUD uptake.”

REFERENCE

Keywords: opioid use disorder, public insurance, Medicare, Medicaid

Dr. Demirjian on prediction model for acute kidney injury after cardiac surgery

In this video, Sevag Demirjian, MD, shares additional insights from the recent JAMA study, “Predictive Accuracy of a Perioperative Laboratory Test-Based Prediction Model for Moderate to Severe Acute Kidney Injury After Cardiac Surgery,” for which he served as first author. Demirjian is a nephrologist at Glickman Urological & Kidney Institute at Cleveland Clinic in Ohio.
**ORGOVYX** achieved sustained testosterone suppression\(^1\)

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

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

![Sustained testosterone suppression rate graph]

**STUDY DESIGN**
Results from the HERO study, a multinational, randomized, open-label, phase 3 trial in 934 men with advanced prostate cancer. Patients were randomized 2:1 to receive ORGOVYX (360 mg on the first day followed by daily doses of 120 mg orally \([n=624]\)) or leuprolide acetate (22.5 mg injection or 11.25 mg \(^6\) in Japan and Taiwan per local guidelines) subcutaneously every 3 months \([n=310]\) for 48 weeks.\(^{1,3}\)

Please see key study enrollment criteria at ORGOVYXHCP.COM

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

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**

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

**Embryo-Fetal Toxicity:** The safety and efficacy of ORGOVYX have not been established in females. Based on findings in animals and mechanism of action, ORGOVYX can cause fetal harm and loss of pregnancy when administered to a pregnant female. Advise males with female partners of reproductive potential to use effective contraception during treatment and for 2 weeks after the last dose of ORGOVYX.

**Laboratory Testing:** Therapy with ORGOVYX results in suppression of the pituitary gonadal system. Results of diagnostic tests of the pituitary gonadotropic and gonadal functions conducted during and after ORGOVYX may be affected. The therapeutic effect of ORGOVYX should be monitored by measuring serum concentrations of prostate-specific antigen (PSA) periodically. If PSA increases, serum concentrations of testosterone should be measured.
ORGOVYX offers an injection-free option for testosterone control1-3

- **RAPID TESTOSTERONE SUPPRESSION WITHOUT A SURGE:** 56% of men treated with ORGOVYX achieved testosterone suppression to <50 ng/dL on Day 4
  - 0% of men treated with leuprolide had testosterone levels <50 ng/dL on Day 4
- **PROFOUND TESTOSTERONE SUPPRESSION:** 95% of men treated with ORGOVYX achieved profound testosterone suppression to <20 ng/dL on Day 29
  - 57% of men treated with leuprolide had testosterone levels <20 ng/dL on Day 29
- **90-DAY TESTOSTERONE RECOVERY:** in a substudy, 55% of the 137 men treated with ORGOVYX had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after treatment discontinuation
  - 3% of 47 men treated with leuprolide had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after discontinuation

BRIEF SUMMARY

ORGOVYX® (relugolix) tablets, for oral use

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

1 INDICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 QT/QTc Interval Prolongation

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

5.2 Embryo-Fetal Toxicity

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

5.3 Laboratory Testing

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

6 ADVERSE REACTIONS

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

• QT/QTc Interval Prolongation.

6.1 Clinical Trials Experience

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

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

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

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

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

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

Table 1 summarizes the adverse reactions in HERO.

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

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>ORGOVYX N = 622</th>
<th>Leuprolide Acetate N = 308</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot flush</td>
<td>54</td>
<td>0.6</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal pain*</td>
<td>30</td>
<td>1.1</td>
</tr>
<tr>
<td>General</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue*</td>
<td>26</td>
<td>0.3</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea*</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>Constipation</td>
<td>12</td>
<td>0</td>
</tr>
</tbody>
</table>

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

Clinically relevant adverse reactions in < 10% of patients who received ORGOVYX included increased weight, insomnia, gynecomastia, hyperhidrosis, depression, and decreased libido.

Table 2 summarizes the laboratory abnormalities in HERO.

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

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>ORGOVYX</th>
<th>Leuprolide Acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3-4 (%)</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose increased</td>
<td>44</td>
<td>2.9</td>
</tr>
<tr>
<td>Triglycerides increased</td>
<td>35</td>
<td>2</td>
</tr>
<tr>
<td>ALT increased</td>
<td>27</td>
<td>0.3</td>
</tr>
<tr>
<td>AST increased</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>28</td>
<td>0.5</td>
</tr>
</tbody>
</table>

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

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ORGOVYX

P-gp Inhibitors

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

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

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

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

Combined P-gp and Strong CYP3A Inducers

Co-administration of ORGOVYX with a combined P-gp and a strong CYP3A inducer decreases the AUC and Cmax of relugolix, which may reduce the effects of ORGOVYX. Avoid co-administration of ORGOVYX with combined P-gp and strong CYP3A inducers.

If co-administration is unavoidable, increase the ORGOVYX dose. After discontinuation of the combined P-gp and strong CYP3A inducer, resume the recommended dose of ORGOVYX once daily.
8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary
The safety and efficacy of ORGOVYX have not been established in females. Based on findings in animals and mechanism of action, ORGOVYX can cause fetal harm and loss of pregnancy when administered to a pregnant female. There are no human data on the use of ORGOVYX in pregnant females to inform the drug-associated risk. In an animal reproduction study, oral administration of relugolix to pregnant rabbits during organogenesis caused embryo-fetal lethality at maternal exposures that were 0.3 times the human exposure at the recommended dose of 120 mg daily based on AUC (see Data). Advise patients of the potential risk to the fetus.

Data

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

8.2 Lactation

Risk Summary
The safety and efficacy of ORGOVYX at the recommended dose of 120 mg daily have not been established in females. There are no data on the presence of relugolix in human milk, the effects on the breastfed child, or the effects on milk production. Relugolix and/or its metabolites were present in milk of lactating rats (see Data).

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

8.3 Females and Males of Reproductive Potential

Contraception

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

Infertility

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

12.3 Pharmacokinetics

Specific Populations
No clinically meaningful differences in the pharmacokinetics of relugolix were observed based on age (45 to 91 years), race/ethnicity (Asian [19%], White [71%], Black/African American [6%]), body weight (41 to 193 kg), mild to severe renal impairment (creatinine clearance [CrCl] 15 to 60 mL/min, as estimated by the Cockcroft-Gault equation), or mild to moderate hepatic impairment (Child-Pugh A or B). The effect of end-stage renal disease with or without hemodialysis or severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of relugolix has not been evaluated.

Drug Interaction Studies

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

Combined P-gp and Strong CYP3A Inducer: Co-administration with rifampin (P-gp and strong CYP3A inducer) decreased the AUC and Cmax of relugolix by 95% and 23%, respectively.

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

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

Transporter Systems: Relugolix is a substrate of P-gp, but not a substrate of BCRP. Relugolix is an inhibitor of BCRP and P-gp, but not an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2-K, or BSEP.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

13.2 Animal Toxicology and/or Pharmacology

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

17 PATIENT COUNSELING INFORMATION

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

QT/QTc Interval Prolongation

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

Androgen Deprivation

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

Embryo-Fetal Toxicity

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

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

Infertility

• Inform patients that ORGOVYX may cause infertility.

Manufactured by Bushu Pharmaceuticals, Ltd, Kawagoe, Saitama, Japan
Manufactured for Myovant Sciences, Inc., Brisbane, CA 94005
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Can one choose a cancer diagnosis code without tissue?

Pathologic tissue confirmation is usually the best practice

Q. My provider performed a laparoscopic radical nephrectomy (90-day global procedure) on a patient with a renal mass worrisome for kidney cancer. I was told not to use a “kidney cancer” diagnosis until cancer was proven, so I used a “renal mass” ICD-10 code. The final pathology report confirmed kidney cancer. My provider wants to bill for the post-op visits within 90 days saying billable because the patient now has a diagnosis of cancer that they did not have before the surgery. Can we bill those visits?

A. The short answer is no. But it may be best to explain why. Let’s start with the diagnosis code portion. The International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10 CM) guidelines instruct the clinician to choose a diagnosis code that accurately describes a patient’s clinical condition or reason for visit. Additionally, the guidelines instruct the coder supporting the clinician to check the appropriate code selection with the clinician when there is a question. In short, the clinician has the final say regarding which ICD-10-CM code should be used.

It is likely there are clinicians who would argue that based upon imaging alone, they are comfortable making a diagnosis of cancer without a biopsy or tissue diagnosis, especially with more modern imaging. However, we believe that it remains best practice to only use a cancer diagnosis code in patients with pathologic tissue confirmation with rare exceptions (such as with cancer recurrence or metastasis and those who need treatment and tissue cannot be obtained). In addition to the medical implications of a cancer diagnosis, many such diagnoses will affect patient insurability and potential employment. From a coding perspective, diagnoses assigned prior to confirmation may result in the bundling of care that should be separately payable. That being said, at times a clinician needs to use their best clinical judgment when caring for an individual patient, as some patients may not be eligible for certain therapies without the corresponding diagnosis codes being chosen. However, in the case of the renal mass mentioned above, most providers will use a “renal mass” diagnosis code instead of a “kidney cancer” code.

Now, let’s get to the question about whether visits within 90 days after laparoscopic radical nephrectomy are billable if a patient now has a definitive diagnosis of kidney cancer. The global surgical package is set up in a way such that payment has already been made to include all the necessary services normally furnished by a surgeon before, during, and after a procedure. That means that all hospital and outpatient visit that occur within that global period have been paid, unless an exception exists. According to Medicare, services such as evaluation and management (E/M) visits that are not included in the global payment package and are separately payable within a global period include:

1. Visits unrelated to the diagnosis for which the surgical procedure is performed, unless the visits occur due to complications of the surgery.
2. Treatment for the underlying condition or an added course of treatment that is not part of normal recovery from surgery.

Charging for visits during the postoperative period for planning and follow-up of cancer will depend on documentation and payer processing.

In this particular case, the intent of the surgery was for the treatment of a known or suspected kidney cancer, whether or not a kidney cancer diagnoses code was used or was confirmed before the procedure. Had the physician not suspected that the patient had cancer, the patient would likely not have undergone the nephrectomy. A computer may require and allow for an E/M code to be reported with a different diagnosis than used for the surgery and modifier –24 (Unrelated Evaluation and Management Service by the Same Physician During a Postoperative Period), which states that the “physician may need to indicate that an evaluation and management service was performed during a postoperative period for a reason(s) unrelated to the original procedure.” However, the definition of the modifier is not specific to the diagnosis code but instead focuses on “reason(s) unrelated to the original procedure,” nor is the Medicare rule limited to a specific diagnosis—“visits unrelated to the diagnosis for which the original surgical procedure is performed.” Therefore, billing for the visits based solely on a change in diagnostic code is not appropriate, as noted in point 1 above.
The visits are clearly related to the reason(s) for which the surgical service was performed, regardless of the ICD-10-CM code reported for the surgical service. On the other hand, the second point above would warrant additional consideration.

Chemotherapy care provided for the systemic treatment of cancer is not related to the recovery from surgery. Instead, it is targeted to treatment of the underlying disease and is an added course of treatment not considered a part of normal recovery from surgery. Under this exception, the services related to the treatment for kidney cancer are payable.

The visits for planning and follow-up during the global period are not as clear cut. In reviewing multiple charts, it is common for a physician to discuss with the patient, prior to laparoscopic radical nephrectomy, the potential for kidney cancer and the need for further treatment after surgery, including chemotherapy. As this discussion is common for surgery, it is harder to support the position that this planning is not a normal part of the recovery from surgery. If there is no suspicion of cancer and the laparoscopic partial nephrectomy is performed with a discovery of cancer during or after surgery, the argument that the cancer treatment planning and follow-up for cancer is not a part of normal recovery is supported. Even with that differentiation, we have to remember that relative value units and rules are developed not for the individual case but instead for the average case.

In summary, charging for visits during the postoperative period for planning and follow-up of cancer will depend on documentation and payer processing. In general, similar to the discussion of stone prevention during the postoperative period of an extracorporeal shock wave lithotripsy, payment may be warranted in some cases but may be difficult to obtain.

Q. Is it appropriate to use 0649T (quantitative magnetic resonance for analysis of tissue composition [eg, fat, iron, water content], including multiparametric data acquisition, data preparation and transmission, interpretation and report, obtained with diagnostic MRI examination of the same anatomy [eg, organ, gland, tissue, target structure]; single organ [list separately in addition to code for primary procedure]) as an add-on code to multiparametric MRI of the prostate?

A. Code 0649T was accepted as an “investigational” (category III) code at a Current Procedural Terminology (CPT) meeting last year, using this seemingly proprietary liver imaging test as the justification. The Federal Register mentions its use specifically with this particular liver scan.1

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If the service is indeed justified and supported, we would recommend checking with the payer prior to submitting code 0649T.

However, the CPT code, as is typical for CPT codes, was written to address the technology more broadly than referencing a particular test or service. As published, it does appear to leave the door open to be used in other organs such as the prostate (72197), and there is no list of primary codes that would restrict its use as an add-on for code 72197.

However, neither the American Urological Association nor Physician Reimbursement Systems have been made aware that it could or would be used for the prostate. Radiologists have been reading prostate MRIs using 72197 for around a decade without discussion that another add-on code would be needed or appropriate. We are unaware of the efficacy related to the service or whether the analysis is additional or included relative to code 72197.

Codes 0648T and 0649T were designed to report Quantitative Multiparametric MR for analysis of tissue composition. They were designed to be used in any organ or tissue in the body. However, the key word is quantitative, meaning an actual quantitative analysis must be performed. That requires actual reporting of quantitative values related to tissue properties, not just a qualitative assessment. There are many examples of quantitative sequences being qualitatively interpreted and that would not meet the threshold of coding 0648T or 0649T. Currently, the most common use for these new codes is in the liver, but research is ongoing for their use in other organs. In our experience thus far, this type of quantitative assessment and reporting is not typically being performed in conjunction with prostate MRI.

Coverage as noted in the Federal Register at this time appears to be restricted to the liver scan. If the service is indeed justified and supported, we would recommend checking with the payer prior to submitting code 0649T. •

REFERENCE

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Send coding and reimbursement questions to Jonathan Rubenstein, MD, and Mark Painter c/o Urology Times®, at UTEditors@mjhlifesciences.com.

Questions of general interest will be chosen for publication. The information in this column is designed to be authoritative, and every effort has been made to ensure its accuracy at the time it was written. However, readers are encouraged to check with their individual carrier or private payers for updates and to confirm that this information conforms to their specific rules.

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Differences in operative autonomy among men and women urology trainees

In this video, Kate H. Kraft, MD, discusses the main points of her presentation, “Closing the Gap: The effect of Gender on Operative Autonomy in Urology Training,” which was presented at the Society of Women in Urology Annual Clinical Mentoring Conference. Kraft is an associate professor and residency program director in the Department of Urology at the University of Michigan in Ann Arbor.
Leuprolide tops urology spending for Medicare Part B drugs

Urologists are the principal drivers of utilization for 14 drugs

Physicians in many specialties continue to derive substantial revenue from administering drugs reimbursed by Medicare Part B, commonly referred to as “buy and bill.” Under current rules, physicians are reimbursed based upon the average sales price of a drug plus 6%, adjusted for sequestration. In November 2021, the Centers for Medicare & Medicaid Services (CMS) formally rescinded a proposed rule—the Most Favored Nation Model—for Medicare Part B drugs and biologicals that would have indexed payments for Part B drugs to the reduced amounts paid by peer countries and tested a flat add-on fee to replace the current model of average sales price plus a percentage.

The policy concerns that led to this (now canceled) proposed measure still exist: growth in drug costs, growth in drug utilization, and a perception that the current reimbursement model encourages the use of more expensive drugs and overutilization. The top specialties paid under part B in 2019 were ophthalmology, hematology-oncology, rheumatology, internal medicine, family practice, neurology, and urology. In this article, I update the spending and costs for Medicare Part B Drugs commonly used by urologists in the office setting and explain why the information should matter to you.

CMS recently released detailed Part B drug spending data for 2016 to 2020, and total Medicare spending by provider and specialty for 2019.1 “Spending” in this context includes the estimated total costs, including deductible, coinsurance, and Medicare spending. Total spending in 2020 for 603 Part B drugs was $38.5 billion, up 3.4% from 2019; this is a much slower growth rate than from 2018 to 2019 which may be explained in part by reduced demand for services during the pandemic. One drug—pembrolizumab (Keytruda)—accounted for $3.5 billion (9.1%) of all spending in the program in 2020. Spending on any drug may increase because of increased utilization, increased price, or both.

According to the 2019 data, drug administration accounted for 13.9% of total Part B Medicare revenue in urology, and the specialty ranks 10th in percentage of Medicare revenue from Part B drugs. The top specialties earning revenue from buy-and-bill drugs in 2019 (Medicare revenue %) were hematology-oncology (61%), hemato poetic cell transplantation and cellular therapy (50%), hematology (49%), ophthalmology (43%), gynecological oncology (34%), and allergy/immunology (28%; Table). Twenty-one drugs commonly used by urologists account for less than 7% of total Medicare Part B drug spending, and spending in 2020 was down almost 3% for this subset of drugs compared with 2019. Of these 21 drugs commonly used in the urology office for Medicare beneficiaries, the drug with the largest 2020 total spend—as in 2019—was denosumab (Xgeva) ($1.63 billion); in 2020, utilization for denosumab actually decreased by 3% but spending per unit (price) increased 4.6%, resulting in higher overall spending. Denosumab spending has increased 4.1% per year over the last 5 years. The dominant specialty for denosumab is hematology-oncology, and urologists accounted for an estimated 4.5% of denosumab spending (eighth-ranked specialty).

Using estimates based on 2019 specialty data, the largest spend for urology in 2020 was leuprolide ($232 million) followed by sipuleucel-T (Provenge; $113 million), denosumab ($73 million), degarelix acetate ($15 million), and onabotulinumtoxinA (Botox; $14 million). Urologists were the principal specialty reimbursed by Medicare Part B in 2019 for all the androgen deprivation therapies as well as sipuleucel-T, BCG, dimethyl sulfoxide, and most of the testosterone replacement therapies. These are the drugs to watch.

Among the drugs used to treat non–muscle-invasive bladder cancer in 2020, mitomycin in combination therapy dropped 21% from 2019 and the price dropped 38%, resulting in total spending of $8.5 million, down 51% from the prior year. Gemcitabine utilization was down 3.4%, the price was down 22%, and total spending down 24.5% compared with the previous year. Valrubicin spending was down 29%, driven entirely by decreased utilization. The price of BCG was relatively unchanged from 2019, and other year-on-year comparisons are not possible because the new Healthcare Common Procedure
In the androgen deprivation therapy market, leuprolide acetate was still the most commonly administered drug, with spending in 2020 of $285 million (down 5.5% from 2019). Utilization was down for all the drugs in this class except goserelin acetate (up 2.2%). Collective spending on these 5 drugs was $326 million, down 4.6% from the previous year.

In general, among these 21 drugs, those with 1 or 2 manufacturers have seen higher annual growth in spending per dose (a surrogate for price) and those with 3 or more manufacturers have seen lower or negative annual growth. Goserelin acetate and gentamicin have been notable exceptions to this rule over the past 5 years, with 10% annual growth over 5 years despite apparent competition among 3 or more manufacturers. BCG has a single manufacturer unable to meet current demand, yet the price has barely changed in the last 2 years.

THE BOTTOM LINE AND WHY IT MATTERS

Urology practices continue to derive substantial revenue from administering “buy-and-bill” drugs, including from the Medicare Part B program (14% of revenue). Of 21 Part B drugs commonly used by urologists, total spending in 2020 increased for 5 drugs and decreased for 16 drugs over the previous year. Urologists were the principal prescribers for 14 of 21 common drugs they administer. Urologists should understand that spending in the Part B program continues to attract the attention of CMS and other payers; although reimbursement to the specialty is still only a fraction (1.5%) of the total Part B drug spend by CMS, urologists are the principal drivers of utilization for 14 drugs, including some expensive agents.

REFERENCES


2019 CMS data adapted by Robert A. Dowling, MD

* Indicates multiple brand and/or generic names for a specific Healthcare Common Procedure Coding System code.

2020 CMS data adapted by Robert A. Dowling, MD
Rising interest rates could affect your investments

Diversification is key to mitigate impact of rising rates

Earlier this month, the Federal Reserve (Fed) announced they will start taking actions to raise interest rates and end their quantitative easing policy to halt rising inflation. With inflation currently around 7.00%, businesses and consumers are feeling the pinch of higher prices. The Fed’s actions are designed to reduce the inflation rate to a more comfortable 2.00% to 3.00%. To accomplish this, the Fed will raise its Federal Funds rate. The Federal Funds rate is the rate at which banks can borrow and lend from each other so they can continue to provide loans to businesses and individuals. They will also end their policy of quantitative easing. Quantitative easing is a monetary policy that allows the Central Bank to purchase long-term securities from the open market. The policy increases the amount of money in the money supply, encourages lending and investment, and lowers interest rates. By raising interest rates and ending quantitative easing, the Fed hopes to reduce the amount of the money in the money supply and bring inflation rates down to more comfortable levels.

What could be the impact of rising interest rates on your investments? Bond prices typically move in the opposite direction of interest rates, meaning rising interest rates generally cause formerly issued bond prices to fall. This is commonly known as interest rate risk. When the yield on newly issued bonds is higher than the yield on older bonds, the newly issued bonds have more value. If you own an older bond, you must sell that bond at a discount in order to entice someone to buy it, otherwise they would just purchase a new bond. Thus, the value of old bonds decreases when interest rates increase.

Additionally, with higher yields available with new bonds, many investors tend to sell their current bonds to purchase the higher-paying ones. Heavy selling causes the prices of old bonds to fall even more.

The best way to manage interest rate risk is with a diversified portfolio, including international and domestic bonds with short to intermediate maturities, as they may be less affected by rate hikes. The sooner a bond matures, the sooner with short to intermediate maturities, as they may be less affected by rate hikes. The sooner a bond matures, the sooner.

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The best way to manage interest rate risk is with a diversified portfolio, including international and domestic bonds with short to intermediate maturities, as they may be less affected by rate hikes. The sooner a bond matures, the sooner.

What is the overall takeaway? Diversification is key. The more diversified your stock and bond holdings, the less affected you are likely to be by rising interest rates. To take that one step further, the more diversified you are, the less affected you are likely to be by any event that negatively affects one specific type of investment.
Please review the instructions for use for a complete listing of indications, contraindications, warnings, precautions, potential adverse events and directions for use. The Optilume DCB is indicated for use in patients with obstructive urinary symptoms associated with anterior urethral stricture. It is designed to be used in adult males for urethral strictures of ≤3cm in length. The Optilume DCB is contraindicated for patients with known hypersensitivity to paclitaxel or structurally related compounds and patients with urologic implants such as penile implants or artificial urinary sphincters. Paclitaxel may be present in semen after treatment with the Optilume DCB. The risks associated with paclitaxel in semen and the impact on sperm and spermatogenesis are unknown. Men should abstain or use a condom for 30 days and men with partners of child-bearing potential should use highly effective contraceptive and avoid fathering children for 6 months after treatment. Monitor for signs of anaphylaxis or hypersensitivity to paclitaxel. Potential risks can include, but are not limited to, the following: blood in the urine (hematuria), painful urination (dysuria), urinary tract infection (UTI), urinary retention, and stricture recurrence.


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Inquiries may be directed to: Mark Plante, MD, FRCS(C), FACS, Division Chief, melisa.garcia@hphmg.org

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Affidavits of merit and why they matter

Most states require affidavits for malpractice cases to proceed

To reduce the number of medical malpractice lawsuits, more than half of US states have enacted laws that require a plaintiff to file an affidavit of merit, sometimes called a certificate of merit, showing a claim’s validity before the case can move forward. The underlying goal of implementing such laws was to reduce the financial burden that medical malpractice claims impose on the health care industry.

WHAT ARE AFFIDAVITS OF MERIT?
An affidavit of merit is a sworn statement by a qualified expert affirming that the plaintiff has a legitimate claim. Each state has its own requirements as to what must be included in the affidavit. Generally speaking, the affiant must be familiar with the standard of care for the defendant, have reviewed the relevant facts of the case, and be able to opine that the defendant’s conduct fell short of the appropriate medical standard of care. In other words, a qualified expert must be able to attest to the merits of the claim for each medical provider named as a defendant.

Additionally, the expert must have an adequate foundation to testify to the standard of care applied to each defendant. For example, in most cases a nurse practitioner cannot file an affidavit opining that a doctor’s breach caused the plaintiff’s injury. Similarly, a chiropractor cannot opine against an emergency department surgeon, unless the chiropractor can show they have a background, education, training, and practice similar to those of an emergency department surgeon. Some courts have held that the affidavit must specifically identify which defendant or defendants breached the standard of care.

Outside of the context of a lawsuit, requiring affidavits of merit may not appear to have an impact on the day-to-day lives of medical professionals. However, when states enacted this requirement, legislators specifically had day-to-day effects in mind. Affidavits of merit are a product of tort reform efforts; in other words, efforts to reduce the amount of litigation in the United States. The underlying policy was to force prospective plaintiffs to substantiate any potential medical claims by showing that there was a true issue of liability before filing. The primary goal was to weed out frivolous medical malpractice claims. Further, states wanted to:

• reduce the amount of settlement money paid toward questionable claims
• limit decisions based upon fear of a potential lawsuit instead of professional judgment
• limit the types, amount, and cost of liability insurance

Therefore, the idea was that this requirement would cause medical malpractice insurance premiums to decrease because insurance companies would not have to waste money defending meritless claims. Additionally, it was hoped the requirement would enable health care providers to provide medical care and treatment based solely on their professional judgment, which would in turn improve health care quality.

Opponents of affidavits of merit argue that there is little evidence that medical malpractice claims have much effect on insurance premiums.

HAVE AFFIDAVITS OF MERIT SHOWN THEIR MERIT?
Since gaining popularity, the affidavit of merit has stirred debate. Practically speaking, opponents argue that the requirement has not produced the desired goals. Specifically, they argue that when some courts apply their state’s law, frivolous claims are still allowed to proceed, resulting in more litigation expenses. Additionally, opponents argue that there is little evidence that medical malpractice claims have much effect on insurance premiums.

In many cases, the affidavit is composed of conclusory statements that do not identify the specific acts of malpractice or provide an explanation of the basis of the opinion. Often, the courts in many states are lenient in demanding that the requirement be fully honored; furthermore, the requirement adds an extra step in the litigation process. This inevitably means that there are more issues to dispute, which can potentially draw out the process and therefore make the litigation more expensive. Many cases have had to go through the appeals process solely to determine when an expert is needed and who qualifies as an expert.

Still, the amount of medical malpractice cases has decreased since states began enacting this reform measure. As state courts continue to interpret their own state’s requirements, legislators will have to continue to analyze whether they need to enact updates to meet their goals in improving the health care system more effectively.
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