INDICATION
Natesto is indicated for replacement therapy in adult males for conditions associated with a deficiency or absence of endogenous testosterone.

• Primary hypogonadism (congenital or acquired), testicular failure due to conditions such as cryptorchidism, bilateral torsion, cryptorchidism, vanishing testes syndrome, orchectomy, Klinefelter syndrome, chemotherapy, or toxic damage from alcohol or heavy metals. These men usually have low serum testosterone concentrations and gonadotropins (follicle-stimulating hormone [FSH], luteinizing hormone [LH]) above the normal range.
• Hypogonadal (hypogonadotrophic) hypogonadism (congenital or acquired), gonadotropin or luteinizing hormone-releasing hormone (LHRH) deficiency or pituitary-hypothalamic injury from tumors, trauma, or radiation. These men have low testosterone serum concentrations but have gonadotropins in the normal range.

Limitations of use:
• Safety and efficacy of Natesto in men with "age-related hypogonadism" (also referred to as "late-onset hypogonadism") have not been established.
• Safety and efficacy of Natesto in males less than 18 years old have not been established.

IMPORTANT SAFETY INFORMATION
CONTRAINDICATIONS
Natesto is contraindicated in:
• Men with carcinoma of the breast, or known or suspected carcinoma of the prostate.
• Women who are or who may become pregnant, or who are breastfeeding.
• Men with carcinoma of the breast, or known or suspected carcinoma of the prostate.
• Natesto may cause serious adverse reactions in nursing infants. Exposure of a fetus or nursing infant to androgens may result in varying degrees of virilization. If a pregnant woman is exposed to Natesto, she should be apprised of the potential hazard to the fetus.

WARNINGS AND PRECAUTIONS
Nasal Adverse Reactions and Limited Long-Term Information on Nasal Safety
• Nasal adverse reactions, including rhinorrhea, rhinosis, rhinorrhagia, nasal dryness, nasal discomfort, and nasal irritation were reported in the clinical trial experience with Natesto. All nasal adverse reactions except a single case of upper respiratory infection were reported as mild or moderate in severity. To date, long-term clinical trial data on nasal safety is available in a limited number of subjects. Patients should be instructed to report any nasal symptoms or signs to their healthcare professional. In that circumstance, healthcare professionals should determine whether further evaluation or discontinuation of Natesto is appropriate.

Use in Patients with Chronic Nasal Conditions and Alterations in Nasal Anatomy:
Natesto is not recommended for use in patients with a history of nasal disorders; history of nasal or sinus surgery; history of nasal fracture within the previous 6 months; or nasal fracture that caused a deviated anterior nasal septum, nasal septal perforation, septal hematoma, or sinonasal surgery.

Natesto may cause serious adverse reactions in nursing infants. Exposure of a fetus or nursing infant to androgens may result in varying degrees of virilization. If a pregnant woman is exposed to Natesto, she should be apprised of the potential hazard to the fetus.

GIVE HIM A DIFFERENT TYPE OF T THERAPY
Natesto is an innovative intranasal therapy for testosterone (T) deficiency, designed to safely restore T levels to therapeutic range while allowing his hypothalamic-pituitary-gonadal (HPG) axis to remain active.1-5
Venous Thromboembolism: Postmarketing reports of venous thromboembolic events (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), have been reported in patients using testosterone products such as Natesto. Evaluate patients who report symptoms of pain, edema, warmth, and redness in the lower extremities for DVT and those who present with sudden shortness of breath for PE. If a VTE is suspected, discontinuation treatment with Natesto is recommended.

Cardiovascular Risk: Long-term clinical safety trials have not been conducted to assess the cardiovascular outcomes of testosterone replacement therapy in men. Some studies, but not all, have reported an increased risk of major adverse cardiovascular events (MACE), such as non-fatal myocardial infarction, non-fatal stroke, and cardiovascular death in association with use of testosterone replacement therapy in men. Patients should be informed of this possible risk when deciding whether to use or to continue to use Natesto.

Abuse of Testosterone and Monitoring of Serum Testosterone

Concentrations: Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication and in combination with other anabolic androgenic steroids. Testosterone-related adverse effects can lead to serious cardiovascular and psychiatric adverse reactions. If abuse is suspected, check testosterone levels to ensure they are within therapeutic range. However, testosterone concentrations may be in the normal range in men abusing synthetic testosterone derivatives. Counsel patients concerning the serious adverse reactions associated with abuse of testosterone and anabolic androgenic steroids. Conversely, consider the possibility of testosterone- and anabolic androgenic steroid abuse in suspected patients who present with serious cardiovascular or psychiatric adverse events.

Use in Women: Due to lack of controlled studies in women and potential virilizing effects, Natesto is not indicated for use in women.

Potential for Adverse Effects on Sperrmato genesis: At large doses of exogenous androgens, including Natesto, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH) that could lead to adverse effects on semen parameters, including sperm count.

Hepatic Adverse Effects: Prolonged use of high doses of orally active androgens (methylntestosterone has been associated with serious hepatic adverse events), hepatic neoplasms, and jaundice. Prolonged use can be a life-threatening or fatal complication. Long-term therapy with testosterone enanthate has been associated with hepatic abnormalities. Natesto is not known to cause these adverse effects.

Cardiovascular: Testosterone and corticosteroids concurrently may increase fluid retention and require careful monitoring, particularly in patients with cardiac, renal, or hepatic disease.

Ovulatory: A 25% decrease in mean 24-hour bioavailability of testosterone and 26.6% decrease in mean maximal observed concentration of total testosterone (sustained release) is observed in women with concomitant use of the oral contraceptive pill. Natesto is not known to impact ovulation in these patients. combines with testosterone in the presence of the enzyme aromatase to form estradiol (i.e., estradiol). If these occur, promptly discontinue Natesto until the level is evaluated.

Edema: Androgens, including Natesto, may promote retention of sodium and water. Edema, with or without congestive heart failure, may be a serious complication in patients with pre-existing cardiovascular, renal, or hepatic disease. In addition to discontinuation of the drug, diuretic therapy may be required.

Gynecomastia: Use of testosterone and corticosteroids concurrently may increase fluid retention and require careful monitoring, particularly in patients with cardiac, renal, or hepatic disease.

Sleep Apnea: The treatment of hypogonadism with exogenous androgens has been associated with exacerbation of sleep apnea in patients being treated with androgens, including Natesto, for hypogonadism.

Hypertension: Androgens, including Natesto, should be used with caution in patients at risk of hyperten sion (such as obesity and chronic lung disease).

Lipids: Changes in the total lipoprotein profile, particularly after starting testosterone therapy, changes in serum lipid profiles may require discontinuation of testosterone therapy.

Hyperglycemia: Androgens, including Natesto, should be used with caution in patients with diabetes mellitus, especially in those with risk factors such as obesity and chronic lung disease.

Cirrhosis: Changes in the total lipoprotein profile, particularly after starting testosterone therapy, changes in serum lipid profiles may require discontinuation of testosterone therapy.

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Interest grows for focal therapy in treating prostate cancer

BLADDER CANCER
Neoadjuvant pembrolizumab regimen shows benefit in MIBC

OVERACTIVE BLADDER/INCONTINENCE
Surgical center size is significant in reoperation risk after sling surgery

BENIGN PROSTATIC HYPERPLASIA
5-year Rezum study results show low rates of ED and ejaculatory dysfunction

SEXUAL DYSFUNCTION
Studies highlight costs, risks with direct-to-consumer men’s health products

KIDNEY STONES
Narcotics-free ureteroscopy: Anatomy of an ERAS protocol
XTANDI is available in a tablet formulation*

40 mg  80 mg

Not actual size of tablets.

For more information, visit XtandiTablets.com or scan this QR code

*Please specify “XTANDI 40 mg tablets” or “XTANDI 80 mg tablets” when prescribing XTANDI to your patients.
Interest grows for focal therapy in treating prostate cancer

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I t was a surreal but positive experience pivoting from the American Urological Association (AUA) Annual Meeting right into the European Society for Medical Oncology (ESMO) Virtual Congress this year. Both meetings had programs chock-full of compelling research, which, in the case of AUA, you’ll find in this issue of Urology Times®. (Look for ESMO coverage next month. Of course, you can find all of our latest news and meeting coverage at www.urologytimes.com.) Both programs did excellent jobs with their virtual-only formats, although, as I wrote here last month, the hope is certainly for there to be in-person meetings again soon. I’m already looking forward to the 2022 AUA annual meeting in New Orleans in May!

This issue of Urology Times® has plenty of AUA 2021 coverage; highlights include reports on new data for the prostate cancer treatment darolutamide (Nubeqa), as well as coverage of studies of benign prostatic hyperplasia treatments such as Rezum and the prostate urethral lift (UroLift). In addition, in Journal Article of the Month, Badar M. Mian, MD, examines a recent study that evaluated men who converted from active surveillance (AS) to active treatment for prostate cancer.1 “This large cohort study confirms the safety of AS, as shown in the low rate of metastasis or death, including those who subsequently converted to treatment,” Mian writes.

Our clinical content this month also includes several insightful Q&A interviews. In one of these, Ardeeshir (Art) Rustinehad, DO, gives an in-depth overview of the burgeoning field of focal therapy for prostate cancer. In addition, we spoke with Nicole L. Miller, MD, FACS, who breaks down her institution’s protocol for narcotics-free ureteroscopy.

Finally, Kevin T. McVary, MD, FACS, discusses 5-year data on erectile and ejaculatory function in men undergoing treatment with Rezum.2 Leading off our columns this month is Coding and Reimbursement, in which Jonathan Rubenstein, MD, and Mark Painter provide an update on new urology-related Current Procedural Terminology codes coming in January 2022.

In Practice Matters, Robert A. Dowling, MD, examines a Centers for Medicare & Medicaid Services document that provides compelling insights into the composition of urology practices in the US. As Dowling writes in his column, the file “provides interesting food for thought.” In Money Matters, Jeff Witz, CFP, writes about the importance of long-term disability insurance for physicians. “Disability insurance is important, as it protects your most valuable asset—your ability to practice medicine and earn income in your specialty field,” Witz writes.

We close this month’s issue with Speak Out, in which 3 urologists discuss how the resurgence of the COVID-19 pandemic has affected their practice. “Pandemic 2 is far worse. The only good news is that we planned for this originally, so we have options for delivering care. Our intensive care unit [ICU] is 100% full, so we turned our recovery room into another ICU. Luckily, we hadn’t had to go to the next level and set up a ward in the auditorium,” says Nina Davis, MD, FACS. Stay safe, and thanks for reading. •

+ MIKE HENNESSY SR Mike Hennessy Sr is chairman and founder of Urology Times® parent company, MJH Life Sciences®.
**FDA authorizes artificial intelligence–based software for prostate cancer detection**

The FDA has authorized the marketing of Paige Prostate, an artificial intelligence–based software platform to help pathologists identify prostate cancer when they review slide images from prostate biopsies.1

The standard biopsy review process involves the pathologist examining digitally scanned slide images from prostate biopsies to find areas that are suspicious for cancer. Paige Prostate provides a supplementary assessment of the image and locates the area with the highest probability of harboring cancer. The pathologist can then examine this specific area further if they did not identify it on their initial assessment.

In making its decision to authorize the marketing of Paige Prostate, the FDA reviewed the results of a clinical study involving 16 pathologists who assessed 527 slide images of prostate biopsies. The images had been digitized with a scanner and included 171 with cancerous tissue and 356 with benign tissue. All pathologists performed 2 assessments of each slide image, 1 with the assistance of Paige Prostate and 1 without.

The results showed that detection of cancer on individual slide images was improved by an average of 7.3% with the assistance of Paige Prostate versus the pathologists’ unassisted reads. There was no impact on the assessment of the benign slide images. Of note, the impact of Paige Prostate on final patient diagnosis was not an end point of the study, as that is typically determined following multiple biopsies.

The FDA noted that false-negative and false-positive results are potential risks with Paige Prostate. However, the agency maintained that these risks are mitigated by the fact that the device is only a supplementary tool used to assist pathologists who are able to provide their own independent evaluation that accounts for a broad spectrum of relevant clinical information. The risk of false negatives/positives also is mitigated by the pathologists’ capacity to conduct additional laboratory studies on the biopsy samples before making a final diagnosis.

Paige Prostate, which is marketed by Paige.AI, was reviewed by the FDA through its de novo premarket review pathway, which is specifically for novel devices that are considered by agency to be low to moderate risk.

**REFERENCE**


**NCCN guidelines add PSMA-PET imaging modalities for prostate cancer**

The National Comprehensive Cancer Network (NCCN) has added Ga 68- and F 18-based prostate-specific membrane antigen (PSMA)-PET imaging modalities to its clinical practice guidelines for prostate cancer.

“The updated guidelines will encourage clinicians to use PSMA-PET as a primary imaging modality in patients and will deliver the benefit of a more streamlined approach. We look forward to having access to this functional form of imaging as new products come into the market,” A. Oliver Sartor, MD, the Bernadine Laborde Professor of Cancer Research at Tulane University School of Medicine and medical director of Tulane Cancer Center in New Orleans, Louisiana, said in a news release from Telix pharmaceuticals, a manufacturer of PSMA-PET imaging products.

Lantheus Holdings Inc, manufacturer of piflufolastat F 18 (Pylarify) injection, also commented on the announcement in a separate news release.2

“We are extremely pleased that the NCCN panel of prostate cancer experts, who are dedicated to high-quality, high-value, patient-centered cancer care, have added PSMA-targeted PET imaging with piflufolastat F 18 in unfavora-

**REFERENCES**


**Olaparib plus abiraterone significantly delays progression in frontline mCRPC**

Adding olaparib (Lynparza) to standard frontline abiraterone acetate (Zytiga) significantly improved radiographic progression-free survival (PFS) vs abiraterone alone in patients with metastatic castration-resistant prostate cancer (mCRPC), regardless of homologous recombination repair (HRR) gene mutation status, according to findings from the phase 3 PROpel trial (NCT03732820).1

The results, which came from an interim analysis of the study, also showed a trend toward improved overall survival (OS) with the combination of the PARP inhibitor and novel hormonal agent; however, the data remain immature and the OS analysis remains ongoing. There were no new safety or tolerability signals with either agent compared with the toxicity profiles of either agent established in prior trials. No specific data have been released yet, with the findings targeted to be presented at a future medical conference.

Overall, the double-blind, multicenter phase 3 PROpel trial assessed the efficacy and safety of frontline abiraterone plus either olaparib or placebo in patients with mCRPC who had no prior chemotherapy or treatment with a novel hormonal agent in the frontline mCRPC setting. Patients in both arms also received prednisone or prednisolone twice daily.

The study enrolled an all-comer population of patients with or without HRR gene mutations. Prior docetaxel was allowed if it was administered in a dis-

**REFERENCE**

The heart of the matter

Unquestionably, the mainstay of therapy for men with advanced and metastatic prostate cancer is androgen deprivation therapy (ADT). The beneficial effect of ADT on controlling prostate cancer has been evident for more than 70 years following the pioneering work of Huggins and Hodges.1 Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of noncancer death in men with prostate cancer, and many men with advanced prostate cancer harbor cardiovascular risk factors.2

Although the benefits of ADT are not disputed and the risk of ASCVD is acknowledged, there is controversy surrounding the relative cardiovascular safety of gonadotropin-releasing hormone (GnRH) antagonists compared with the GnRH agonists in men with prostate cancer and ASCVD treated with these agents.

To highlight this controversy, 2 important clinical trials recently published are worthy of mention. In the PRONOUNCE trial (NCT02663908), an international multicenter prospective study, men with prostate cancer and ASCVD were randomized to receive the GnRH antagonist degarelix or the GnRH agonist leuprolide for 12 months.3 The primary outcome was the time to first major adverse cardiovascular event (MACE). The study was terminated early because of the slower than projected enrollment and fewer than anticipated primary outcome events. Overall, there was no difference in MACE at 1 year between patients assigned to degarelix and those who received leuprolide (5.5% vs 4.1%, respectively; P = .534). The authors concluded that the relative cardiovascular safety of GnRH antagonists and agonists remains unresolved.

In contrast, in the phase 3 HERO study (NCT03085095), patients with advanced prostate cancer were randomly assigned 2:1 to receive relugolix (Orgovyx), an oral GnRH antagonist, or leuprolide for 48 weeks.4 The primary end point was sustained testosterone suppression to castrate levels through 48 weeks, and the study met this end point. Of men who received relugolix, 96.7% maintained castration through 48 weeks compared with 88.8% of men receiving leuprolide. Among all patients, incidence of MACE was 2.9% in the relugolix group and 6.2% in the leuprolide group. The authors concluded that relugolix achieved rapid, sustained suppression of testosterone levels that was superior to that with leuprolide, with a 54% lower risk of MACE.

So what explains the difference between these 2 studies? One possibility is that the theoretical differences in safety between these agents is not as clinically meaningful in routine practice. There could also be differences in injectable vs oral GnRH antagonists. Another possibility is that in the PRONOUNCE study, in which the patients had known cardiovascular risk factors, cardiovascular events might have been lower because of better awareness and attention to cardiovascular risk control.

In contrast, although patients who experienced MACE within 6 months before trial initiation were excluded in the HERO trial, presumably routine cardiovascular risk control would not have been so closely scrutinized. At a minimum, better attention to the cardiovascular risk factors among men with advanced prostate cancer, including those treated with ADT, will improve outcomes and reduce MACE. And perhaps there is another Nobel Prize waiting to be had if we could reduce the cardiovascular effect of ADT and unlock the answer to the controversy surrounding the comparative safety and impact on cardiovascular health between GnRH agonists and antagonists.

Perhaps there is another Nobel Prize waiting to be had if we could reduce the cardiovascular effect of ADT and unlock the answer to the controversy surrounding the comparative safety and impact on cardiovascular health between GnRH agonists and antagonists.

REFERENCES

H ave feedback?

Send your comments to Cookson, c/o Urology Times®, at UTEditors@mjlifesciences.com.

UrologyTimes.com
Neoadjuvant pembrolizumab shows benefit in MIBC

More than a third of patients had complete regression

JASON M. BRODERICK, Associate Editorial Director, Urology Times

Neoadjuvant treatment with pembrolizumab (Keytruda) plus gemcitabine and cisplatin showed promise in patients with muscle-invasive bladder cancer (MIBC), according to findings from a phase 2 study published in the Journal of Clinical Oncology.1,2

The study enrolled patients with clinical T2-4aN0/XM0 MIBC who were eligible for radical cystectomy. Overall, 56% of patients had pathologic downstaging (< pT2N0) and 36% of patients had a pathologic complete response (pCR; pT0N0M0).

The study included 39 patients with a median age of 66 years (range, 45-82). Eighty-two percent of patients were male and 18% were female. Ninety-seven percent of patients were White and 3% were Black. Eighteen percent of patients were current smokers, 67% were former smokers, and 15% were never smokers. The clinical stage at enrollment was T2 for 72% of patients, T3 for 23% of patients, and T4a for 5% of patients.

Eighteen percent of patients had previous non–muscle-invasive bladder cancer, 79% of patients did not, and prior status was unknown for 3%. Five patients had prior BCG. Seventy-two percent of patients had an ECOG performance score of 0 and 28% had a score of 1. Regarding histology, 28 patients had pure urothelial disease; 7 had urothelial with squamous cell disease; and 1 each had urothelial with micropapillary, sarcomatoid, signet ring, and glandular and squamous.

Overall, 22 (56%) patients reached < pT2N0 with the triplet regimen and 14 (36%) reached a pCR at pT0N0. PD-L1 status did not have a significant effect on pathologic downstaging. There was a numerical, but not a statistically significant, difference in the downstaging rate between PD-L1–positive and –negative patients (67% vs 47%, respectively; P = .25).

“More than a third of the patients saw a complete regression of their cancer and ultimately may not require surgical bladder removal,” lead author Tracy Rose, MD, MPH, assistant professor at the UNC School of Medicine, UNC Lineberger Comprehensive Cancer Center, in Chapel Hill, North Carolina, said in a news release. “More studies will need to be done to identify who can safely avoid surgery. Several ongoing trials are investigating this bladder-sparing approach.”

The most common adverse events (AEs) across all grades were thrombocytopenia (74%), anemia (69%), neutropenia (67%), and hypomagnesemia (67%). New-onset type 1 diabetes mellitus with ketocidosis considered to be related to pembrolizumab occurred in 1 patient. Steroids for immune-related AEs were not required for any of the patients.

“Optimal management of MIBC is a huge unmet need,” UNC Lineberger’s Matthew Milowsky, MD, the paper’s corresponding author and the George Gabriel and Frances Gable Villere Distinguished Professor of Bladder and Genitourinary Cancer Research, said in the news release. “We think that the combination treatment used in our trial may improve outcomes compared with chemotherapy alone, with the aim of ridding micrometastatic disease so that even a modest improvement in response rates translates to higher cure rates.”

REFERENCES

UrologyTimes.com
Long-term follow-up of UTUC treatment yields promising results

Patients’ chances of maintaining a complete response are “quite high,” expert says

Patients with low-grade upper tract urothelial carcinoma (LG UTUC) usually receive treatment in the form of radical nephroureterectomy, an endoscopic procedure associated with high recurrence rates. Recent studies have found that UGN-101 (Jelmyto) is a new efficacious treatment for this condition that mitigates the risk of recurrence. In a study presented at the 2021 American Urological Association (AUA) Annual Meeting,1 senior author Karim Chamie, MD, and coauthors further examined the long-term results of UGN-101 for patients with LG UTUC given the favorable outcomes of the initial OLYMPUS trial (NCT02793128). Chamie is an associate professor of urology and director of the Urologic Oncology Fellowship and the Bladder Cancer Program at the University of California, Los Angeles.

Q. Please discuss the background for this study.
A. The background of this study really hinges on the OLYMPUS trial, which was a registrational study conducted by UroGen to evaluate the efficacy and safety of UGN-101. It’s a reverse hydrogel polymer that is liquid in cold temperatures and solid at body temperature. Essentially, you can mix it with mitomycin C at cold or room temperature and then inject it directly into the kidney, whereby the gel solidifies in the collecting system of the kidney. Over 6 to 7 hours, it starts to dissolve. Meanwhile, the tumor that’s located up in the renal pelvis is exposed to the chemotherapy for that period of time.

The purpose of doing this study, which was presented as a late-breaking abstract at the [2021] AUA, was to look at long-term follow-up. The reason that’s important is that if you look at published data from the best of hands, the incidence of recurrence of upper tract urothelial carcinoma, even for low and intermediate risk, is still very high. So, if you follow patients out for 3.5 years, you’ll see that 65% of patients still recur despite endoscopic therapies like laser and fulguration. These are authors who are proud of the results and published it. And what we found in this OLYMPUS trial was that the recurrence rate was significantly lower than what we would find with pooled analyses of standard endoscopic therapy. The OLYMPUS trial examined 1-year data. The purpose of this study was to quantify longer-term follow-up, so 2 to 3 years.

Q. What were some of the notable findings from this study? Were any of them surprising to you and your coauthors?
A. The fact that you’re seeing durability of this agent speaks volumes. These patients have a high chance of recurrence. Remember that the cohort in the OLYMPUS trial was composed of nearly half of patients that had already recurred at least once. We have historically attributed the high recurrence rates to the concept of the entire urothelium being diseased—like a ticking time bomb. We are actively monitoring our patients, anxiously waiting for the next tumor to show up—at least that’s what we used to think. It’s entirely possible that the problem with what we’ve done in the past was that (A); we didn’t see all of the tumor, and those are the areas where tumors came back, or (B); we were potentially seeding the urothelium with tumors. So you go up there with the laser fiber and you start ablating the tumor, and you end up seeding the cancer cell throughout the urothelial lining. To have the durability and efficacy rate that is seen with UGN-101 that high is very surprising.

I was also a coauthor on a separate paper that examined the Mayo Clinic series of patients with upper tract urothelial carcinoma. What they found was that patients that had tumors in the upper urinary tract where the urologist ureteroscoped and lasered the tumor—versus up-front nephroureterectomy without manipulating the tumor—their recurrence rate was much higher. It’s entirely possible that as urologists we may be seeding tumors when we start to laser the lesion. Maybe the less we manipulate the better.

Q. How does this study build on previous research on UGN-101?
A. The prior study, which was published in Lancet Oncology, looked at the complete response rate and the durability up to a year. This study builds on that and shows that in patients that have a complete response, the chances of maintaining that complete response are really quite high—much higher than we’d anticipate with endoscopic therapies.

Q. What is the significance of these findings for patients with low-grade UTUC?
A. I think this is very significant for patients who have low-grade upper tract urothelial carcinoma because this will eventually be the standard of care. I wouldn’t be surprised to see urologists switching from endoscopic ablation to chemoablation of tumors. This may be a paradigm shift when you see that the recurrence rates are that low.

The take-home message is that patients who have low-grade upper tract urothelial carcinoma develop a complete response to UGN-101, and the probability of maintaining that complete response is quite high. And it’s durable; up to 2 years or even longer.

REFERENCES

UrologyTimes.com
THE FIRST AND ONLY FDA-APPROVED TREATMENT FOR LOW-GRADE UPPER TRACT UROTHELIAL CANCER (UTUC) IN ADULT PATIENTS

CHEMOABLATE NOW SPARE THE KIDNEY FOR TOMORROW

In the OLYMPUS Study, JELMYTO demonstrated complete response (CR) in 58% (95% CI: 45, 69) and durability of response in 82% (95% CI: 66, 91) of patients.

At the 12-month assessment of durability (n=41):
- 23 patients remained in CR
- 8 patients had disease recurrence
- 10 patients were invaluable
- Median duration of response was not reached, with a range of 0-18.8 months
- Patients had treatment-naïve or recurrent low-grade non-invasive UTUC with at least one measurable papillary tumor 5 to 15 mm
- Kaplan-Meier analysis estimates probability of durable response. It does not represent an actual percentage of patients. In the OLYMPUS trial, at the time of the 12-month assessment for durability, not all patients had a recurrence (patients may have still been in CR, died, or discontinued). The KM analysis accounts for these missing data. The analysis has potential limitations: the sample size was small (n=41) and median duration of response was not reached due to the limited number of recurrences (n=8); this may be reflective of a short follow-up time (12 months).
- The most common adverse reactions in ≥ 20% of patients treated with JELMYTO were ureteric obstruction, urinary tract infection, hematuria, flank pain, nausea, dysuria, renal dysfunction, vomiting, fatigue, and abdominal pain.

Indications and Usage
JELMYTO (mitomycin) for pylecalyceal solution is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC).

Important Safety Information
Contraindications
JELMYTO is contraindicated in patients with perforation of the bladder or upper urinary tract.

Ureteric Obstruction
Ureteric obstruction, including ureteral stenosis and hydroprothesis, occurred in patients receiving JELMYTO. Monitor patients for signs and symptoms of ureteric obstruction, including flank pain, and fever, and for changes in renal function. Patients who experience obstruction may require transient or long-term ureteral stents or alternative procedures. Withhold or permanently discontinue JELMYTO based on the severity of ureteric obstruction.

Bone Marrow Suppression
The use of JELMYTO can result in bone marrow suppression, particularly thrombocytopenia and neutropenia. The following tests should be obtained prior to each treatment: Platelet count, white blood cell count differential and hemoglobin. Withhold JELMYTO for Grade 2 thrombocytopenia or neutropenia. Permanently discontinue for Grade 3 or greater thrombocytopenia or neutropenia.

Embryo-Fetal Toxicity
Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise females of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO.

Common Adverse Reactions
The most common adverse reactions in ≥ 20% of patients treated with JELMYTO were ureteric obstruction, urinary tract infection, hematuria, flank pain, nausea, dysuria, renal dysfunction, vomiting, fatigue, and abdominal pain.

Additional Adverse Reactions Information
Selected clinically relevant adverse reactions in < 10% and ≥ 2% of patients who received JELMYTO include urinary tract inflammation, bladder spasm, urosepsis, hypersensitivity, and instillation site pain.

Use in Specific Populations
Lactation
Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with JELMYTO and for 1 week following the last dose.

Preparation and Administration Information
JELMYTO is for pylecalyceal use only and not for intravenous use, topical use, or oral administration. JELMYTO must be prepared and administered by a healthcare provider. To ensure proper dosing, it is important to follow the preparation instructions found in the JELMYTO Instructions for Pharmacy and administration instructions found in the JELMYTO Instructions for Administration.

JELMYTO may discolor urine to a violet to blue color following the instillation procedure. Advise patients to avoid contact with urine for at least six hours post-instillation, to void urine sitting on a toilet, and to flush the toilet several times after use.

JELMYTO is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Please see Brief Summary of Prescribing Information for JELMYTO on the following pages.

References:

Learn more at JELMYTO.com/hcp

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JELMYTO®
(mitomycin) for pyelocalyceal solution

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

Please refer to the JELMYTO Package Insert for Full Prescribing Information, including instructions for preparation and administration.

INDICATIONS AND USAGE

JELMYTO® is indicated for the treatment of adult patients with low-grade Upper Tract Urothelial Cancer (LG-UTUC).

DOSAGE AND ADMINISTRATION

Important Administration Instructions

See the Instructions for Administration provided separately. JELMYTO is for pyelocalyceal use only. JELMYTO is not for intravenous use, topical use, or oral administration. Advise patients that JELMYTO may discolor urine to a violet to blue color following the instillation procedure. Advise patients to avoid contact with urine for at least six hours post-instillation, to void urine sitting on a toilet, and to flush the toilet several times after use.

Preparation and Handling - See the Instructions for Pharmacy preparation provided separately. JELMYTO is a cytotoxic drug. Follow applicable special handling and disposal procedures. JELMYTO must be instilled as a chilled solution using a Uroject® Lever, a Luer lock syringe, and a ureteral catheter with molded Luer lock connector. Once chilled at -3°C to 5°C (27°F to 41°F), JELMYTO will convert to a viscous liquid for instillation and is stable for up to 1 additional hour. Reconstituted JELMYTO must be instilled within 1 hour after it is converted to a viscous liquid.

CONTRAINDICATIONS

JELMYTO is contraindicated in patients with perforation of the bladder or upper urinary tract.

WARNINGS AND PRECAUTIONS

Ureteric Obstruction - Ureteric obstruction, including ureteral stenosis and hydronephrosis, occurred in patients receiving JELMYTO. In the OLYMPUS study, ureteric obstruction was reported in 58% (n=49) of patients receiving JELMYTO, including 17% (n=12) of patients who experienced Grade 3 obstruction. The median time to first onset was 72 days (range: 15-482). Interventions in the 41 patients experiencing ureteric obstruction included ureteral stent placement (88%), balloon dilatation (29%), and nephroureterectomy (4.9%). In the 36 patients who required ureteral stent placement, the median duration of indwelling stents was 52 days (range: 1-292). Ureteric obstruction did not resolve or resolved with sequelae in 44% (n=18) of these patients. Of the 41 patients who experienced ureteric obstruction, 17% (n=7) experienced Grades 1-2 increase in serum creatinine. In the 42 patients who only received JELMYTO during the treatment phase (no maintenance therapy), ureteric obstruction was reported in 40% (n=17). Monitor patients for signs and symptoms of ureteric obstruction, including flank pain, and fever, and for changes in renal function. Patients who experience obstruction may require transient or long-term ureteral stents or alternative procedures. Withhold or permanently discontinue JELMYTO based on the severity of ureteric obstruction.

Bone Marrow Suppression - The use of JELMYTO can result in bone marrow suppression, particularly thrombocytopenia and neutropenia. In the OLYMPUS study, Grade 3 thrombocytopenia occurred in three patients, Grade 3 anemia in one patient, and Grade 3 neutropenia in one patient. Gross extravasation of JELMYTO via urinary tract perforation or impaired mucosa was not observed in these patients. The following tests should be obtained prior to each treatment: Platelet count, white blood cell count differential and hemoglobin. Withhold JELMYTO for Grade 2 thrombocytopenia or neutropenia. Permanently discontinue for Grade 3 or greater thrombocytopenia or neutropenia.

Embryo-Fetal Toxicity - Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise females of reproductive potential to use effective contraception during treatment with JELMYTO and for 6 months following the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with JELMYTO and for 3 months following the last dose.

ADVERSE REACTIONS

Clinical Trials Experience - The safety of JELMYTO was evaluated in OLYMPUS, an open-label, single-arm study in 71 patients with LG-UTUC. For the 71 patients treated with JELMYTO during the treatment period, the median number of instillations was 6 (range: 3-8). Following initial treatment, 29 patients were treated with up to 11 doses of maintenance instillations, with a median of 6 instillations (range: 0-11). Serious adverse reactions occurred in 39% of patients who received JELMYTO. Serious adverse reactions in > 3% of patients included ureteric obstruction (including ureteric stenosis and hydronephrosis), flank pain, and urosepsis. Two deaths occurred due to cerebrovascular accident and failure to thrive. JELMYTO was permanently discontinued due to an adverse reaction in 17 (24%) patients, including 11 patients who discontinued during the treatment phase and 6 who discontinued during the maintenance phase. Adverse reactions resulting in study drug discontinuation of JELMYTO in > 3% of patients who received JELMYTO included ureteric obstruction. Dosage interruptions due to an adverse reaction occurred in 37% of patients who received JELMYTO. Adverse reactions requiring dosage interruption in > 3% of patients who received JELMYTO included renal dysfunction, ureteric obstruction, urinary tract infection, and flank pain. The most common adverse reactions (≥ 20%) reported were ureteric obstruction, urinary tract infection, hematuria, flank pain, nausea, dysuria, renal dysfunction, vomiting, fatigue, and abdominal pain.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>JELMYTO* (n=71)</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Grades</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory Abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>28</td>
<td>2.8</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>34</td>
<td>4.2</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>21</td>
<td>2.8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>21</td>
<td>2.8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21</td>
<td>2.8</td>
</tr>
<tr>
<td>All Grades (expressed as percentage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laboratory Abnormality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>17</td>
<td></td>
</tr>
</tbody>
</table>

*Percentages may not total 100% due to rounding.
Table 1 summarizes the adverse reactions in OLYMPUS.

Table 1: Adverse Reactions (≥ 10% All Grades) in Patients Who Received JELMYTO in OLYMPUS

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>JELMYTO* (n=71)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade ≥ 3 (%)</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ureteric Obstruction</td>
<td>58</td>
<td>17</td>
</tr>
<tr>
<td>Ureteric stenosis</td>
<td>44</td>
<td>9</td>
</tr>
<tr>
<td>Hydronephrosis</td>
<td>18</td>
<td>6</td>
</tr>
<tr>
<td>Urinary tract obstruction</td>
<td>7</td>
<td>1.4</td>
</tr>
<tr>
<td>Pelvi-ureteric obstruction</td>
<td>6</td>
<td>1.4</td>
</tr>
<tr>
<td>Ureteric obstruction</td>
<td>2.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Obstructive uropathy</td>
<td>1.4</td>
<td>0</td>
</tr>
<tr>
<td>Flank pain</td>
<td>41</td>
<td>2.8</td>
</tr>
<tr>
<td>Hematuria</td>
<td>34</td>
<td>2.8</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>34</td>
<td>4.2</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>25</td>
<td>2.8</td>
</tr>
<tr>
<td>Dysuria</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Pollakiuria</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>1.4</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>28</td>
<td>1.4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>20</td>
<td>4.2</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>27</td>
<td>1.4</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>13</td>
<td>1.4</td>
</tr>
<tr>
<td>Chills</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>14</td>
<td>1.4</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10</td>
<td>4.2</td>
</tr>
</tbody>
</table>

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5). Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available.

Selected clinically relevant adverse reactions in < 10% and ≥ 2% of patients who received JELMYTO in OLYMPUS include urinary tract inflammation, bladder spasm, urosepsis, hypersensitivity, and instillation site pain.

Table 2 summarizes the laboratory abnormalities in OLYMPUS.

Table 2: Select Laboratory Abnormalities (≥ 10%) Worsening from Baseline in Patients Who Received JELMYTO in OLYMPUS

<table>
<thead>
<tr>
<th>Laboratory Abnormality*</th>
<th>JELMYTO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>38</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>21</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
</tr>
<tr>
<td>Estimated Glomerular Filtration Rate (eGFR)*</td>
<td>38</td>
</tr>
<tr>
<td>Creatinine Increased</td>
<td>34</td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>28</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>16</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>16</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>13</td>
</tr>
<tr>
<td>Hypernatremia</td>
<td>11</td>
</tr>
</tbody>
</table>

*Graded per National Cancer Institute Common Terminology Criteria for Adverse Events. Version 5.0 (NCI CTCAE v5). Each test incidence is based on the number of patients who had both baseline and at least one on-study laboratory measurement available.

**eGFR calculated per MDRD (Modification of Diet in Renal Disease) equation**

**USE IN SPECIFIC POPULATIONS**

**Pregnancy** - Risk Summary - Based on findings in animals and mechanism of action, JELMYTO can cause fetal harm when administered to a pregnant woman. There are no available data on JELMYTO use in pregnant women to inform the drug-associated risk. In animal reproduction studies, administration of mitomycin resulted in teratogenicity. Advise pregnant women of the potential risk to a fetus.

**Lactation** - Risk Summary - There are no data on the presence of mitomycin in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment with JELMYTO and for 1 week following the last dose.

**Females and Males of Reproductive Potential** - Pregnancy Testing - Verify pregnancy status in females of reproductive potential prior to initiating JELMYTO.

**Geriatric Use** - Of the total number of patients in the OLYMPUS trial, 75% (53 patients) were 65 years of age and over and 37% (26 patients) were 75 years of age and over. Clinical studies of JELMYTO did not include sufficient numbers of younger patients less than 65 years old to determine whether they respond differently from older patients.

**Renal Impairment** - No data are available in patients with severe renal impairment. Avoid use of JELMYTO in patients with a Glomerular Filtration Rate of < 30 mL/min.

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Princeton, NJ 08540
U.S. Patent Nos. 9,040,074 and 9,950,089
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Surveillance for prostate cancer is generally safe, study results show

Active surveillance (AS) for the management of low-risk prostate cancer is slowly becoming the de facto standard of care. Although the adoption of AS has been increasing, still too many patients with low-risk prostate cancer appear to be undergoing active treatment. A frequently voiced concern by patients and physicians alike is the risk of disease progression and the need for active treatment. These issues were addressed in the study by Cooley et al of a large, multicenter cohort of men converting from AS to active treatment.1

The investigators evaluated the clinical and pathologic parameters associated with the time to conversion from AS to treatment in the pooled cohort of 7279 patients from 28 institutions between 1991 and 2018. They also evaluated the association of germline genetic variants to conversion to treatment in a subset of patients. The primary question to be addressed was the time from prostate cancer diagnosis to conversion to treatment. Those men followed without a strict AS protocol were analyzed in the same manner as those on AS.

The patients were stratified into risk groups. Low-risk patients were Gleason grade group (GG) 1 (Gleason score 3+3) and had prostate-specific antigen (PSA) level lower than 10 ng/mL, clinical-stage cT1, and 2 or fewer positive biopsy cores. Intermediate-risk patients were GG2 (Gleason 3+4) and had PSA level 10 to 20 ng/mL, stage cT2, or 3 positive biopsy cores of any Gleason grade. High-risk patients were GG3 or higher and had cT3 or 4 positive cores of any GG.

The investigators compared low-volume GG1, high-volume GG1 (≥ 4 biopsy cores involved), intermediate-risk, and high-risk patients. Also, exploratory subgroup analysis including self-reported race and genetically inferred ancestry was performed for time to conversion. The genetic inference was obtained from patient data of uncorrelated single nucleotide polymorphisms that were available for a subset of patients. Of the 6775 men meeting the inclusion criteria, median PSA level was 5.0 ng/mL, and GG1 was noted in 91.6%, stage cT1 in 79.5%, 1 to 2 positive biopsy cores in 77.6% of patients. There were 882 men (13.0%) who had some higher-risk features such as GG at least 3 (12.2%), cT3 (0.7%), or 4 or more positive cores of any GG (11.3%).

The median follow-up was 6.7 years, during which 33.4% of men converted to treatment. The median time to conversion was 6.8, 6.1, and 7.0 years for low-, intermediate-, and high-risk/high-volume disease, respectively. The most common reasons for conversion were grade reclassification alone (48.8%), PSA progression (8.5%), tumor volume progression (7.2%), anxiety (5.0%), and other (9.0%). Of the men who died, less than 1% died of prostate cancer, whereas 1.3% died of other competing causes.

Multivariable analysis, including the self-reported race, demonstrated that higher GG, PSA, clinical tumor stage, number of positive biopsy cores, and more recent year of diagnosis were significantly associated with earlier time to conversion. Men with high-volume, 4 or more GG1 cores were more likely than those with 3 or fewer GG1 cores to convert to treatment (63.6% vs 26.0%). Further, the conversion rate was higher than those with intermediate-risk disease (63.6% vs 38.3%), but similar to men with other higher-risk features (63.6% vs 65.7%). Men with high-volume GG1 converted to treatment sooner than patients with low-volume GG1 (aHR, 3.46; 95% CI, 2.92-4.10).

Age, race, and a positive family history of prostate cancer were not associated with the time to conversion. There was no difference in the time to conversion between Black and White men across various risk groups. Further, none of the genetic ancestry groups had a shorter time to conversion to treatment. Conversion to treatment was noted in 2260 men (1107 prostatectomy, 565 radiotherapy, and 588 other treatments), of whom 124 (5.5%) subsequently developed a PSA recurrence, 29 (1.3%) developed metastasis, and 11 (< 1%) died of prostate cancer.

The higher rate of conversion to treatment for men with 4 cores of GG1 than those with 3 or fewer cores GG1 or intermediate-risk prostate cancer is not surprising. When starting at a higher volume of cancer, one is likely to arrive at the arbitrary threshold (PSA, grade, volume) for intervention earlier. The most common triggers for treatment in this AS cohort were changes in Gleason grade or PSA or positive cores. It is important to consider that conversion to treatment (based on higher tumor volume or PSA) is not necessarily the biologic destiny of these cancers but likely an epiphenomenon related to the treating urologists’ understanding or concern over those changes.

This large cohort study confirms the safety of AS, as shown in the low rate of metastasis or death, including those who subsequently converted to treatment. The 33% rate of conversion to treatment (for any reason) is not a failure of the AS strategy, but rather a success because two-thirds of patients were safely spared any treatment for over 7 years. Now, with the incorporation of prostate MRI or genomic tests, patients and urologists can feel more confident in the use of AS to safely avoid unnecessary treatment.

REFERENCE
Darolutamide significantly delays time to HRQOL deterioration in nmCRPC

Benjamin P. Saylor
Managing Editor, Urology Times

The androgen receptor inhibitor darolutamide (Nubeqa) significantly delayed time to locally invasive procedures and time to deterioration in health-related quality of life (HRQOL) measures in patients with nonmetastatic castration-resistant prostate cancer (nmCRPC), investigators reported at the American Urological Association's 2021 Annual Meeting.1

The investigators evaluated the effect of darolutamide on local symptom control. Specifically, they examined incidence and time to first prostate cancer–related invasive procedures, time to deterioration in HRQOL measures, and incidence of urinary and bowel treatment-related adverse events and their correlation with prostate-specific antigen (PSA) level decline from baseline to week 16 in patients receiving darolutamide.

Time to deterioration in HRQOL measures was assessed using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Prostate Cancer Module and the Functional Assessment of Cancer Therapy-Prostate (FACT-P) prostate cancer subscale.

In assessing incidence and time to first locally invasive procedures, “the results of these analyses showed that fewer patients receiving darolutamide, 4.7%, underwent locally invasive procedures, compared with patients receiving placebo, 9.6%,” said first author Neal D. Shore, MD, FACS, medical director for the Carolina Urologic Research Center in Myrtle Beach, South Carolina. The most common procedures included catheterization, transurethral resection of the prostate, nephrostomy, and surgical excisions and resections.

Darolutamide also significantly prolonged the time to first prostate cancer–related locally invasive procedure compared with placebo (HR, 0.42; 95% CI, 0.28-0.62).

“For the EORTC urinary symptom subscale, darolutamide significantly delayed the time to deterioration in quality of life for total urinary symptoms and for each individual question about urinary symptoms versus placebo,” Shore said.

The 4 factors that contributed most to the delay in time to deterioration of HRQOL with darolutamide were:

• Urinate frequently during the day (HR, 0.764; 95% CI, 0.648-0.902)
• Urinate frequently at night (HR, 0.664; 95% CI, 0.539-0.790)
• Pain when urinating (HR, 0.569; 95% CI, 0.441-0.734)
• Urinary problems interfere with daily activities (HR, 0.748; 95% CI, 0.614-0.910).

Darolutamide was also found to significantly delay the time to deterioration of total bowel symptoms vs placebo (HR, 0.781; 95% CI, 0.664-0.918).

Regarding the FACT-P prostate cancer subscale, darolutamide significantly delayed time to deterioration for total urinary symptoms as well as for each of the 3 urinary symptom questions. The time to deterioration in trouble moving bowels was not significantly affected by treatment with darolutamide, however (HR, 1.089; 95% CI, 0.862-1.376).

In the overall study population, urinary retention occurred in 36 patients (3.8%) in the treatment arm vs 41 patients (7.4%) in the placebo arm. Dysuria occurred in 25 patients (2.6%) in the treatment arm vs 29 patients (5.2%) in the placebo arm.

In addition, for patients treated with darolutamide, greater PSA response was associated with a lower incidence of urinary retention and dysuria.

Specifically, patients receiving darolutamide who had a PSA level decline of 90% or greater from baseline to week 16 had incidences of urinary retention and dysuria of 2.2% and 0.5%, respectively, compared with 5.1% for urinary retention and dysuria in patients with a PSA response of less than 50%. ●

REFERENCE

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Interest grows for focal therapy in treating prostate cancer

Focal therapy confers myriad advantages in prostate cancer treatment but is currently limited to the clinical trial setting. In this interview, Ardeshr (Art) Rastinehad, DO, discusses the current state of focal therapy in prostate cancer, the role of fusion biopsy in pushing the treatment forward, and what institutions looking to implement focal therapy should know.

Rastinehad is system director for prostate cancer at Northwell Health and vice chair at the Smith Institute for Urology at Lenox Hill Hospital in New York, New York.

Q. What is the current state of focal therapy in prostate cancer?
A. It’s still considered investigational. Most of the work being done around the world is done in trials and through registries to track outcomes. There are limited long-term data supporting the use of focal therapy, but it is an area of extreme interest.

When taking a high-level look at prostate cancer, there are several questions that arise. First, are we finding the best patients that actually need treatment and also identifying patients that would be best served by active surveillance? A recent survey presented at this year’s American Urological Association Annual Meeting found that less than 55% of patients with low-risk prostate cancer are being offered active surveillance. Second, once we determine which patients need treatment, we need to determine which treatment is best suited for them, taking into account their goals of treatment, such as quality of life and oncologic control.

Next, how do we risk-stratify these patients to different treatment options, including active surveillance? In some cases, patients will have focal disease that we’re able to identify through high-quality MRI imaging of the prostate, biomarkers, or germline- or somatic-mutation testing. After a thorough diagnostic work-up of patients with localized prostate cancer, 20% to 40% may be candidates for focal therapy. The cornerstone of today’s approach to focal therapy rests on high-quality multiparametric MRIs of the prostate and MR/US (magnetic resonance/ultrasound) fusion-guided prostate biopsy. After this approach, we may be able to better identify men that don’t have to have their prostate removed or radiated and help them avoid the risks of incontinence and erectile dysfunction.

In the past 5 years, focal therapy as a research topic has really exploded. Almost every major urologic organization is featuring programs on focal therapy. In 2019, to meet this demand, the focal therapy group collaborated with the Endourological Society and created the Focal Therapy Society with Thomas Polascik, MD, as the president. That has helped to bring every single major research group and academic clinician, and even private researchers, under 1 umbrella. That’s what’s really been exciting. In the beginning, a lot of the groups were segmented or isolated by technology and vendor. Now, everyone is under 1 organization working together with a common goal of researching and investigating the use of focal therapy.

In that spirit, we have also created the Focal Therapy Registry, which is an international collaborative to look at postmarket approval of
An expert outlines his advice for institutions looking to implement the novel treatment in their practice.

We found that it takes about 8 to 12 weeks for a patient to be given a diagnosis. At our institution, Smith Institute for Urology, an MRI is ordered on every patient with a suspected or elevated PSA (prostate-specific antigen) level or suspicion of prostate cancer. From that, they go through what is called the rapid diagnostic pathway, which is a quick, streamlined approach so every step is clearly outlined, and patients aren’t wondering what’s going to happen next. We try to make it easier because we found that it takes about 8 to 12 weeks for a man to go through the diagnostic process and maybe find out the PSA was elevated due to some other reason than prostate cancer. We at the Smith Institute for Urology at Lenox Hill, Northwell Health felt that this timeline wasn’t acceptable, so we collaborated with some of our colleagues in the United Kingdom, including Hashim Ahmed, PhD, BM, BCh, at Imperial College London, England, and we’re rolling out the Northwell Health Rapid Diagnostic Pathway. This approach decreases wait times, helps better stratify a patient’s prostate cancer level of disease, and can help us identify men for focal therapy. Our flagship research project was in nanomedicine, with nanoparticle-directed ablation for prostate tumors, which has been published in *PNAS (Proceedings of the National Academy of Sciences of the United States of America)* and other publications. That trial is moving forward very well and it’s in at least 6 sites around the country.

We are also a research site for Philips Healthcare; our collaboration at Northwell Health started in 2012 and has been very productive. We were the first site in the world to validate the original MR/US fusion technology developed at the [National Institutes of Health]. Currently, through our collaboration with Sam Coons’ research team from Philips Healthcare, we’ve developed MR/US fusion ablation-planning software, which is reaching FDA approval within the month. What’s nice about this is that the expertise in 3D-guided focal therapies that I have developed over my career is not needed when you can use this software application to help physicians visualize a 3D-treatment plan and perform ablations. This technology is agnostic, which means it can work with multiple treatment modalities.

In some cases, if a patient has a recurrence, we can treat the spot again, which is similar to our history with renal focal therapy, which is considered a part of the standard of care today. We’re 1 of 2 test sites in the world developing this technology. The technology was borne out of Peter Pinto, MD [investigator and faculty member, Urologic Oncology, National Cancer Institutes of Health, NIH, Bethesda, Maryland] and Brad Wood [MD; chief, Center for Interventional Oncology and chief of Interventional Radiology, NIH, Bethesda, Maryland], work with the NIH in 2008. We developed a platform so a urologist without an intense imaging background or experience can pick up focal therapy and provide it to their patients and perform trials in their local hospitals. We’ve done that trial for cryoablation with Philips Healthcare using UroNav guidance technology. As for other modalities, we also offer high-intensity focused ultrasound (HIFU) for hemiablation and focal ablation of prostate tissue. Finally, most recently, we’re in collaboration with AngioDynamics and the Society of Urologic Oncology to offer irreversible electroporation of prostate tissue.

To create a strong focal therapy program, you must have an expert at every level that collaborates well. We have dedicated prostate imaging—specialized radiologists, pathologists, MR technologists, and urologists trained in focal therapy at Northwell Health.

**Q.** How has the increasing use of fusion biopsy pushed focal therapy forward?  
**A.** As I mentioned before, fusion biopsy really was developed with the idea of using multi-parametric MRI to risk-stratify patients for prostate cancer. If you can’t see it, how are you going to sample it? In the past, people used to try to use their mind’s eye (cognitive biopsy) to sample the area of the prostate in that region. We know that it’s not as effective as using a targeting technology. The first targeting technology was developed out of the NIH with Pinto and Wood’s group, which I was a part of, as well as Peter Choyke [MD; investigator and chief, Molecular Imaging, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, Maryland] and Baris Turkbey [MD; chief, Molecular Imaging, Center for Cancer Research, National Cancer Institute, NIH, Bethesda, Maryland]. That was the core group of people that really helped launch this technology. We had the first publication in the field on this.

We can sample an area of the prostate and go back and resample it if we had to. The system creates a 3D map that can help guide us to those areas as well as know the exact area of the prostate sampled on biopsy. This helps us assess how well we are interpreting MRIs of the prostate. The next obvious question is: Can we use that same information to plan a treatment? Can we put a needle there that would facilitate the treatment? Can we guide the ablation technology to destroy that specific area of the prostate and then use that information from those treatments to confirm that we did it later on? That’s why you have patients that are now very familiar with fusion biopsy technology. Patients ask...
the question, “If you can biopsy the area, why can’t you just treat the spot? Why do I have to have my entire prostate removed or radiate the whole thing?” Yes, we know that prostate cancer is a multifocal disease. However, the implication is that a cohort of patients could have a focal treatment and we can observe the rest of the prostate for new disease arising with the use of imaging and biopsy if needed. Essentially, they are in a modified active-surveillance plan. Patients are interested in the concept of focal therapy because they hope to avoid the adverse events of typical whole-gland therapy, which are erectile dysfunction and stress urinary incontinence. Those are the things that challenge patients today.

If you look at the literature, 40% of patients have treatment regret after being treated for prostate cancer because they feel like their quality of life was affected so much that the treatment was not worth it. I really feel patients are going to drive this work forward. But as surgeon-scientists, we have to critically evaluate this new approach and do these things on trial. Some people do this off trial. I’m not here to critique that; we’re just trying to work hard to identify and make sure we know who those patients are. No man wants to get his cancer treated and not have high quality erections or leak urine. We’re trying to find that “middle path,” as Mark Emberton, MD, FRCS, would say, between whole-gland therapy and active surveillance. Early on, a lot of providers were treating Gleason 6 disease and calling that focal therapy. We know in the history of prostate cancer that true Gleason 6 prostate cancer is not a malignant disease that’s going to progress. It’s just, unfortunately, with the technology we have today, we’re not able to always identify that disease subset as optimally as we would want to.

Q. Please discuss the advantages of focal therapy.
A. Everything has really changed for us in medicine because of COVID-19. I think focal therapy fits in well because it’s a same-day outpatient procedure. Patients don’t stay in a hospital; they don’t have multiple touch points like radiation. Some are even treated without the need for a urinary catheter; add to that fewer adverse events. But what are you giving up when you say, “fewer adverse events”? Maybe oncologic control long-term, but no one really knows. When you’re looking at the incidence of metastatic disease, it’s 3% to 5% for Gleason 7 prostate cancer at 15 years and cancer death rates less than 5%. That means 95% of patients will be fine over the long term. We don’t have that data for focal therapy; that’s just looking at long-term prostatectomy data. We can compare the gene signatures for similar patients that are undergoing focal therapy and compare that to prostatectomy. So we may have some idea what the outcome should be, and if there’s a deviation from expected events, we can understand that maybe focal therapy was not the ideal choice for that type of patient.

Probably more than 90% of patients will be served fine long-term with focal therapy. We’re just trying to work hard to identify and make sure we know who those patients are. No man wants to get his cancer treated and not have high quality erections or leak urine. We’re trying to find that “middle path,” as Mark Emberton, MD, FRCS, would say, between whole-gland therapy and active surveillance. Early on, a lot of providers were treating Gleason 6 disease and calling that focal therapy. We know in the history of prostate cancer that true Gleason 6 prostate cancer is not a malignant disease that’s going to progress. It’s just, unfortunately, with the technology we have today, we’re not able to always identify that disease subset as optimally as we would want to.

Q. What would you say are the barriers to implementing focal therapy, and how are they overcome?
A. There’s a hardware issue, and there’s a skills issue. The first barrier is: How do you identify patients? That has to be done with high-quality multiparametric MRI imaging. The problem is that not all prostate MRI is created equal. That’s a challenge we deal with on a regular basis. It takes time. Time is money. The longer your scan is, the higher the cost to your institution will be because everyone’s paid the same amount for a good scan or a bad scan from a reimbursement point of view, which is a challenge. Hopefully, the American College of Radiology will come up with new minimum standards for prostate MRI specifically, but we haven’t seen that to date. It’s been talked about, but it hasn’t been implemented. So first is how we screen more efficiently and effectively identify men that need a biopsy. If you have a biomarker, risk-stratify the patient that it can help. But at the end of the day, if you’re going to perform a focal therapy treatment or a hemi-gland ablation, you need high-quality imaging for the planning. You can’t get around that fact.

The second part is targeted biopsy. Cognitive biopsy is not going to cut it because you’re not going to have a record of exactly where each core was. It’s a learning process; you have to have this feedback loop that goes into critiquing your technique. No one’s perfect. Not every biopsy will come out perfect. Sometimes, a standard biopsy will find cancer that was not visualized on the MRI, and you have to go back and ask yourself, “Was it my technique? Was it the interpretation of the MRI? Or was it the technique or the MRI quality that led us to miss this specific area?” Then you can develop a treatment plan based on these 3D data with high-quality multiparametric MR imaging of the prostate. Those are the first 2 major hurdles.

I think what we need a clinician to understand is that there has to be a complete care-cycle database tool created for men at risk for prostate cancer and those diagnosed, treated, and their long-term oncologic outcomes. We are working with industry, Philips Healthcare, to create such a full care-cycle platform and feel that it will improve patient outcomes and also be able to assess the full cost of prostate cancer care for a health system. This may be very useful in the value-based reimbursement space. It’s exciting to see this rolled out. Fourth, and finally, what technology do you pick? Each technology has its pros and cons. But even inside the same technology, the data you look at—how they use the technology—can affect their patient-specific outcomes and oncologic control.
We're not curing cancer. No one really cures prostate cancer; we just control it, because there's always a risk of biochemical recurrence, and it's high regardless of the disease state. Or did we just control cancer to hopefully decrease the risk of progression to metastatic disease, which could affect our patients?

Implementing the technology, you must have the key skill set. I have completed 2 IR [interventional radiology] fellowships to help implement these new therapies. My second fellowship was with Wood's team at the NIH. This is where I learned this technology. We teach this today; we have a fellowship in interventional urology here at Northwell Health, which is exciting. We're training the next generation of surgeons to be able to use these technologies. There are other focal therapy fellowships around the world, which is also very exciting. Imperial College London and University College London have them. UCLA has one as well. But a deficit that we see is people's ability as a urologist or a person using this technology to be able to span the gamut of oncology, and diagnostic radiology. When I came out of training, this was so new. In 2011, I realized that I had to have all 3 skill sets. That's why I spent every week learning how to read an MRI from Turkbey and Choyke. I spent time with Wood and Pinto helping develop the fusion biopsy technology, which is actually the foundation for the majority of the focal therapy technology imagery that we have today. And of course, completing a Society of Urologic Oncology fellowship at the National Cancer Institute helped me understand the biology of cancer.

**Q. What advice do you have for practices or institutions that would like to provide focal therapy for patients?**

**A.** They have to create that multidisciplinary team that must include a dedicated radiologist that comes to the treatments. The radiologists need to understand their role in the treatment of these patients. When we launched the nanoparticle trial, I spoke to the principal investigators at different sites. I told them, “Your radiologist has to come see these procedures to understand the implications of what they do and the impact on patient outcomes.” A lot of times, I don’t think radiologists really get that experience because they’re just reading films. Once they show up and they see a couple of procedures, they realize the impact of what they’re doing and why their role in it is so crucial to the team’s success.

Number 2 is you have to figure out how to critically evaluate yourself. Are you doing the right thing on a consistent basis? That’s a challenge, and understanding the technology and having a mechanism to create a feedback loop to complete the evaluation is key. To pick an ablation technology, you have to pick one that you feel offers a good safety profile, and good oncologic outcomes, as well as one that is not cost prohibitive. How much does it cost to implement? A lot of this stuff is not reimbursed. It can be sponsored by industry or your institution, or others charge cash. Cryoablation is covered by insurance, and that is probably the easiest one to start with. It’s the one that urologists have the most experience with. You can actually see what you’re doing, because the ice ball is easily visualized on ultrasound, and since most fusion technology is guidance based on ultrasound, it makes an easy starting point. No one technology fits all. You need to have a recipe book where you pull out one technology for a location of a tumor in one area versus another.

**Q. Is there anything else you feel our audience should know about this topic?**

**A.** I want people to get involved. Join the society, come to the meetings, talk to people. We have a mentoring system where you can have the opportunity to speak to leaders in the field to help start your own program. Our next meeting will be in June 2022. The Focal Therapy Society has a hands-on meeting run by Arvin George, MD, but due to COVID-19, it was postponed this year. George’s meeting is more of a community-based approach with hands-on courses teaching these new technologies. By supporting the society, it helps grow the whole field.
Olaparib/pembrolizumab, focal therapy, and ultrasonic propulsion of stones: AUA 2021 highlights

BY JANELLE HART, JASON HARRIS, BRITTANY LOVELY, JASON M. BRODERICK, AND BENJAMIN P. SAYLOR

FOR THE SECOND STRAIGHT YEAR, the American Urological Association (AUA) held its annual meeting in a virtual format only. As with last year’s online-only event, AUA 2021 offered attendees a wide range of scientific content, including poster and podium presentations, guideline updates, lectures, and much more. To access all our written, video, and podcast coverage of the meeting, go to www.urologytimes.com. Here we present just some of the key research from this year’s meeting.

OLAPARIB PLUS PEMBROLIZUMAB CONTINUES TO SHOW ANTITUMOR ACTIVITY

Combination treatment with the PARP inhibitor olaparib (Lynparza) and the immunotherapy pembrolizumab (Keytruda) continued to demonstrate antitumor activity in postdocetaxel metastatic castration-resistant prostate cancer (mCRPC), according to the latest results from the ongoing phase 1b/2 KEYNOTE-365 trial.1

“With a minimum of 11.4 months follow-up, pembrolizumab plus olaparib demonstrated antitumor activity and an acceptable safety profile for men with molecularly unselected, docetaxel-pretreated mCRPC,” said author Luke T. Nordquist, MD, FACP, urologic medical oncologist and CEO of the Urology Cancer Center and GU Research Network, Omaha, Nebraska.

The KEYNOTE-365 trial (NCT02861573) was launched to assess the efficacy and safety of the olaparib/pembrolizumab regimen in patients with mCRPC. Prior results shared from cohort A showed promising clinical activity in molecularly unselected patients who had previously received docetaxel.1,11

“Cohort A of KEYNOTE-365 examined specifically the safety and efficacy of the combination of pembrolizumab and olaparib in molecularly unselected patients with mCRPC,” Nordquist said.

Patients were enrolled if they had molecularly unselected, docetaxel-pretreated mCRPC that had progressed within 6 months of screening. They also must have been treated previously no more than once with chemotheraphy for mCRPC and no more than twice with second-generation hormonal therapies.

Of the 104 patients who enrolled, 102 were treated and 92 discontinued their treatment, mainly because of disease progression (51%). Median age of enrolled patients was 69.5 years (range, 47-84), 29 patients (28.4%) were PD-L1 positive, 34 (33.3%) had visceral disease, and 58 (56.9%) had measurable disease. Twenty-four patients (23.5%) had previously been treated with abiraterone (Zytiga) only, 24 (23.5%) had previously been treated with enzalutamide (Xtandi) only, and 46 patients (45.1%) had previously been treated with both.

Prostate-specific antigen (PSA) response rate in all patients with a PSA measure at baseline (n = 102) was 14.7% (95% CI, 8.5%-23.1%) and in the 58 patients who had measurable disease, confirmed objective response rate was 6.9% (95% CI, 1.9%-16.7%; 4 partial responses).

Additionally, investigators found the median time to PSA progression was 4 months (range, 3.0-4.9), the median duration of response was not reached (range, 7.2+ to 37.8+), the disease control rate was 26.5% (95% CI, 18.2%-36.1%), the median radiographic progression-free survival was 5.2 months (range, 4.1-6.5) and the median overall survival was 14.4 months (range, 10.4-17.9).

There were high rates of treatment-related adverse events (TRAEs), which occurred in 49 patients (48.0%). Six patients (5.9%) died of AEs, and 2 deaths were treatment related.

ExAblate MR-guided focal therapy using real-time MR thermometry preserves urinary incontinence and sexual function and it’s effective for grade 2 and 3 prostate cancer cancers based on 2-year biopsy outcomes,” said lead author Behfar Ehdai, MD, MS, a urologic surgeon at Memorial Sloan Kettering Cancer Center. “ExAblate MR-guided focused ultrasound may enable men to consider a tissue preserving approach and defer or avoid radical therapy.”

Final results from a phase 2b study (NCT01657942) of MRgFUS showed that at 24 months, 88% of men had no evidence of grade group 2 or 3 prostate cancer in the treatment area according to targeted prostate biopsy. Additionally, 60% of men had no evidence of grade group 2 or 3 disease anywhere in the prostate gland, including outside the treatment area. Serum PSA levels decreased by almost 50% after treatment and stabilized after 6 months. Ehdai said investigators recorded no serious AEs. Most minor or moderate AEs self-resolved by 90 days. Two patients had ejaculation disorder and 1 had hematospermia beyond 90 days.

Erectile function scores were slightly worse at 24 months compared with baseline (HR, –3.5; 95% CI, –5.4 to –1.6). Ten patients (11%) reported no sexual activity and 81% of patients achieved erections adequate for intercourse.

MR-GUIDED FOCAL THERAPY EMERGES AS ALTERNATIVE TO RADICAL THERAPY

In some men with intermediate-risk prostate cancer, magnetic resonance (MR)-guided focused ultrasound (MRgFUS) focal therapy may be an effective alternative to radical therapy that improves quality-of-life measures such as sexual function and urinary incontinence.4

“ExAblate MR-guided focal therapy using real-time MR thermometry preserves urinary incontinence and sexual function and it’s effective for grade group 2 and 3 prostate cancer cancers based on 2-year biopsy outcomes,” said lead author Behfar Ehdai, MD, MS, a urologic surgeon at Memorial Sloan Kettering Cancer Center. “ExAblate MR-guided focused ultrasound may enable men to consider a tissue preserving approach and defer or avoid radical therapy.”

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NADOFARAGENE FIRADENOVEC EFFICACY BIOMARKER EMERGES

Investigators may have found an efficacy biomarker for nadofaragene firadenovec in patients with BCG–
unresponsive non-muscle-invasive bladder cancer (NMIBC), a population in which the novel agent has already demonstrated strong clinical activity.1

Investigators conducted a secondary analysis of a phase 3 study (NCT02773849), hypothesizing that antiadenoviral antibody levels and fold change metrics could be novel predictors of durable response to nadofaragene firadenovec. Based on response to the intravesical gene therapy, patients with peak titer levels that were greater than 800 and peak fold changes greater than 8 were determined to be favorable for response. Patients who did not meet both criteria were designated as unfavorable.

At month 12 following the first treatment with nadofaragene firadenovec, 47 patients were responsive to treatment and a total of 44 patients were nonresponders. On-treatment peak titer levels greater than 800 were reached in 89.4% of responders compared with 59.1% of nonresponders (P = .001). Regarding peak fold change, 51.1% of responders had a peak fold change of at least 8 compared with 27.3% of nonresponders (P = .020).

Further, the combination of markers was noted in 46.8% and 18.2% of responders and nonresponders, respectively (P = .004).

“[Peak titer levels] were associated with the highest sensitivity, accuracy, and negative predictive value,” said Anirban P. Mitra, MD, PhD, a urologic oncology fellow at The University of Texas MD Anderson Cancer Center in Houston. “In addition, when we looked at peak fold changes with a cutoff of 8, this was also able to significantly distinguish between responders and nonresponders such that we then classified patients as ‘favorable’ if they had a combination of peak titer greater than 800 and a peak fold change greater than 8.”

Mitra added that the marker combination was associated with the highest sensitivity and positive predictive value.

**ULTRASONIC PROPULSION DEVICE CLEARRESIDUAL STONE FRAGMENTS**

A novel, handheld ultrasonic propulsion device effectively facilitated the clearance of chronic residual stone fragments, according to a case study from an ongoing randomized controlled trial.6

The overall goal of the ongoing trial is to validate a “handheld, ultrasound-based system in a single platform that we use on awake subjects to image and reposition stones and fragments to facilitate natural clearance of stones,” according to lead study investigator Mathew Sorensen, MD, an associate professor in the Department of Urology at the University of Washington.

The study is enrolling adult patients who have residual fragments that are visible on imaging following treatment for stones. The recruitment goal for the trial is 66 patients.

For the trial, patients receive a screening ultrasound with the investigational study device and, if the investigators are able to see the fragments and the patient meets the other study criteria, the patient is randomized 1:1 to the treatment or control arm. Patients in the control arm receive nothing beyond the screening ultrasound.

In the treatment arm, the patient receives the procedure, in which investigators attempt to reposition the fragments with the device. The individuals in the control arm also get a series of pain assessments before and through the procedure, as well as weekly phone calls for 3 weeks to follow up on the passage of fragments and/or any AEs.

The study treatment of ultrasonic propulsion is delivered in a session that lasts a maximum of 10 minutes. According to Sorensen, the treatment uses low negative pressure with a peak of 2.4 MPa, a short pulse duration of 25 milliseconds, 20 Hz, and each push is a maximum of 3 seconds. He also noted that ultrasound provides real-time guidance on the movement of fragments. Investigators are allowed to repeat the propulsion every 4 or more weeks up to a maximum of 4 total sessions per side.

“Patients with low urinary tract symptoms (LUTS) frequently complain of sexual dysfunction and sometimes even urinary incontinence (UI),” the authors wrote in their abstract.

**URINARY INCONTINENCE IS LINKED TO WORSE SEXUAL FUNCTION**

Worse urinary incontinence appears to be associated with worse sexual function in patients presenting with lower urinary tract symptoms (LUTS).7

“Patients with low urinary tract symptoms (LUTS) frequently complain of [sexual dys-
Study focuses on mechanism of olaparib resistance in prostate cancer

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

Research shared during the 2021 American Urological Association Annual Meeting provided insight on the cellular mechanisms of resistance to the PARP inhibitor olaparib (Lynparza) and offered a potential solution to overcoming this resistance.1

“PARP inhibitors represent the dawn of precision medicine in prostate cancer,” said Alan Lombard, PhD, of the University of California, Davis. “The PARP inhibitors olaparib and rucaparib (Rubraca) were both approved by the FDA [for prostate cancer] in 2020 and have been shown to be highly effective in biomarker-selected patients. Several ongoing trials are exploring additional PARP inhibitors, various combinations, and varying disease stages.”

Despite this progress, Lombard said key questions about PARP inhibitors remain regarding how to optimize the use of these agents in prostate cancer. Specifically, he noted that the mechanism of action of PARP inhibition is not fully understood and, “the questions of how do PARP inhibitor–sensitive prostate tumor cells respond to treatment and what mechanisms will drive resistance to these drugs need to be addressed.”

For their study, Lombard and his coinvestigators sought to address these questions by modeling PARP inhibitor treatment and resistance in prostate cancer.

Through their modeling process, Lombard et al first determined that the LNCap and C4-2B cell lines are sensitive to olaparib, which they determined was likely due to a BRCA2 mutation. Next, through chronic olaparib exposure of these 2 cell lines, the investigators developed the olaparib-resistant cell lines LN-OlapR and 2B-OlapR.

“Cell growth assays demonstrated that both OlapR cell line models are robustly resistant to olaparib. We additionally found that both LN-OlapR and 2B-OlapR are cross-resistant to the additional PARP inhibitors rucaparib, niraparib (Zejula), and talazoparib (Talzenna). Altogether, these results suggest that OlapR cells are models of pan–PARP inhibitor resistance,” said Lombard.

The investigators then conducted Western blot testing which provided insight on why OlapR cells are resistant to PARP inhibition. Specifically, the DNA double-strand break marker gamma-H2AX demonstrated that olaparib induces DNA damage in the sensitive LNCap and C4-2B cells, but it does not induce this damage in OlapR cells.

Western blotting “for cleaved-PARP showed that olaparib leads to cell death in sensitive [LNCap and C4-2B] cells, but not resistant cells,” said Lombard. “Interestingly, we also observed that a significant proportion of treated sensitive [LNCap and C4-2B] cells appear to undergo cryostasis and exhibit a flattened morphology reminiscent of senescence. We did not observe this in OlapR cells.”

Lombard and coinvestigators also found through flow cytometry that treatment with olaparib activates the G2/M checkpoint and this leads to significant arrest of cell growth in the sensitive LNCap and C4-2B cells, but not in resistant OlapR cells.

Further it was observed that β-galactosidase activity is greatly increased in LNCap and C4-2B cells, “suggesting entry into senescence,” Lombard explained, adding that a similar degree of heightened β-galactosidase activity did not occur in OlapR models.

“Taken together, these data suggest that OlapR cells override the G2/M checkpoint and may re-emerge from senescence during acquisition of resistance,” said Lombard.

The PARP inhibitor research also revealed that expression of the CDK inhibitor p21 was significantly augmented in LNCap and C4-2B cells but in OlapR cells, “thus providing a putative mechanism which may drive senescence,” noted Lombard.

The investigators examined the combined impact of olaparib and inhibition of p21 and discovered there was significantly reduced cellular viability, with increased DNA damage and cell death.

“These data suggest that blocking growth arrest and entry into senescence may promote cell death in the context of high levels of DNA damage. Thus, targeting PARP inhibitor–induced senescence may be a means to enhance PARP inhibitor efficacy,” said Lombard.

He added that, “Comparing gamma-H2AX levels in OlapR cells to respective sensitive cells indicates that resistant cells harbor increased levels of intrinsic DNA damage, which may suggest that resistance may depend on enhancing DNA repair activity to manage persistent stress.”

Prior research in the literature and their own observations on the impact of CDK inhibition, led the investigators to evaluate whether CDK1 inhibition could help reverse olaparib resistance and sensitize OlapR cells to the PARP inhibitor.

The investigators’ hypothesis was confirmed as the modeling showed that knockdown of CDK1 resulted in a higher incidence of DNA damage and cell death in both LN-OlapR and 2B-OlapR cells, and when combined with olaparib further reduced cellular viability.

Lombard et al also found that BMS-265246, a small molecule inhibitor of CDK1, produced this same effect when used in combination with olaparib.

“PARP inhibitor resistance can be overcome through CDK inhibition. Development of this strategy may enhance and/or prolong PARP inhibitor utility,” said Lombard. “CDK1 may be an attractive strategy for enhancing olaparib clinical efficacy.”

REFERENCE
Surgical center size is significant in reoperation risk after sling surgery

Investigators observe a 55% reduction in reoperation risk with higher-volume centers

Patients who received midurethral slings (MUSs) at higher-volume medical centers had a lower risk of reoperation, according to findings from a retrospective cohort study published in the *Journal of Urology.*

The results showed that at 9 years, there was a 55% reduction (HR, 0.45; *P* <.01) in reoperation risk for patients treated at higher-volume centers, defined as those performing more than 58 MUSs per year. The reoperation rate at 9 years was 4.9% vs 9.8% at higher- vs lower-volume centers, respectively. Similarly, the reoperation rate at 9 years for recurrent stress urinary incontinence (SUI) was lower at higher-volume centers, at 4% vs 9.1%, respectively (P <.01).

“Midurethral slings, the gold standard surgical treatment of SUI, are performed 250,000 times annually in the United States. As the population ages, it is estimated that these procedures will increase in utilization….Given that the goal of the MUS is to improve the quality of life of women with SUI, it is vital to understand modifiable risk factors that could reduce surgical morbidity and improve efficacy,” wrote the investigators, led by Alexander A. Berger, MD, MPH.

From 2005 to 2016, 13,404 women received primary MUS at 11 centers. Each center had a range of 12 to 345 MUSs performed each year with a mean surgical center volume of 128. Lower-volume centers (≤58 MUS per year) performed 7% of surgeries (999 of 13,404, 17% of all operations) and higher-volume centers (>58 MUS per year) performed the other 93% (12,405 of 13,404) of the MUSs.

The mean age of women in the study was 56.4 and 54.7 years for lower- and higher-volume centers, respectively. Most patients identified as Hispanic (55% and 52% in the lower- and higher-volume arms, respectively) or Caucasian (34% and 40%, respectively). The rest were Asian/Pacific Islander, African American, or other/unknown.

Beyond the primary outcome of MUS reoperation rate, secondary outcomes included specific reoperation rates for surgical failure and complications, excluding intraoperative complications. The investigators assessed the following types of reoperations: urinary retention, mesh exposure, pain, bleeding, infection, nerve injury, retropubic hematoma, bladder/urethral injury, and bowel injury.

“Our large managed care organization includes a diverse group of patients operated on at multiple surgical centers. We examined all MUSs over greater than a decade of time. A wide range of MUS approaches and MUS synthetic mesh implants were used, representing typical practice patterns and enhancing generalizability. Implants were linked to patient electronic medical records, thus enhancing internal validity,” the investigators wrote.

Patients operated on at higher-volume centers had a lower rate of repeat MUS, at 1.8% vs 5.7% at lower-volume centers. Overall, the rates of MUS mesh sling removal/revision were comparable between the higher- and lower-volume study arms. There was no difference between the 2 types of centers in terms of mesh removal/revision reoperation for urinary retention/urethrolysis, pain, or bleeding. There were no reported incidents of MUS mesh sling removal/revision for nerve injury, retropubic hematoma, bladder, urethral, or bowel injury.

Given the results of the study, the investigators have created specialized pelvic floor centers in their large managed care organization with higher-volume surgical centers. They believe this development “will continue to improve surgical efficacy and safety” among patients with SUI.

REFERENCE

Staskin discusses counseling patients on vibegron for OAB

In this video, David Staskin, MD, discusses the takeaways associated with the findings from the study, Vibegron for the treatment of patients with dry overactive bladder: A subgroup analysis from the EMPOWUR trial, presented at the 2021 American Urological Association annual meeting.
In the SPARTAN study, cerebrovascular events occurred in 4.7% of patients treated with ERLEADA® and 2% of patients treated with placebo. Across the SPARTAN and TITAN studies, 5 patients (0.5%) treated with ERLEADA® and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

Cerebrovascular and ischemic cardiovascular events, including seizures, occurred in 3% of patients treated with ERLEADA® and 3% of patients treated with placebo. In the TITAN study, cerebrovascular events occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

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

Fractures — In a randomized study (SPARTAN) of patients with mCSPC, fractures occurred in 12% of patients treated with ERLEADA® and in 7% of patients treated with placebo. In a randomized study (TITAN) of patients with mCSPC, fractures occurred in 9% of patients treated with ERLEADA® and in 6% of patients treated with placebo. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents.

Laboratory Abnormalities — All Grades (Grade 3-4)

- Hematology — In the TITAN study: white blood cell decreased ERLEADA® 27% (0.4%), placebo 19% (0.6%). In the SPARTAN study: anemia ERLEADA® 70% (0.4%), placebo 64% (0.5%); leukopenia ERLEADA® 47% (0.3%), placebo 29% (0%); lymphopenia ERLEADA® 41% (2%), placebo 21% (2%).
- Chemistry — In the TITAN study: hypertriglyceridemia ERLEADA® 17% (9%), placebo 12% (2%). In the SPARTAN study: hypercholesterolemia ERLEADA® 70% (0.1%), placebo 49% (0%); hyperuricemia ERLEADA® 70% (2%), placebo 59% (1%); hyperglycemia ERLEADA® 67% (2%), placebo 49% (0.8%); hyperkalemia ERLEADA® 52% (2%), placebo 22% (0.1%).
START EARLY WITH ERLEADA®
TO PUSH BACK ON PROGRESSION

UPDATED RESULTS: OVERALL SURVIVAL FOR TITAN FINAL ANALYSIS

TITAN study*:
FIRST AND ONLY
therapy to achieve a 35% reduction in the risk of death in a registration trial in mCSPC
(ERLEADA® + ADT vs placebo + ADT; median OS: NR vs 22.2 months; HR=0.65; 95% CI: 0.53, 0.79; P<0.0001).

SPARTAN study*:
FIRST AND ONLY
AR inhibitor to improve median MFS by 2 YEARS in nmCRPC
(ERLEADA® + ADT vs placebo + ADT 40.5 months vs 16.2 months; HR=0.28; 95% CI: 0.23, 0.35; P<0.0001).

SPARTAN study*:
FIRST AND ONLY
therapy to improve median OS by 14 MONTHS in nmCRPC
(ERLEADA® + ADT vs placebo + ADT 73.9 months [6.2 years] vs 59.9 months [5 years]; HR=0.78; 95% CI: 0.64, 0.96; P=0.0169).

Rash — In 2 randomized studies (SPARTAN and TITAN), rash was most commonly described as macular or maculopapular. Adverse reactions of rash were 21% with ERLEADA® vs 8% with placebo. Grade 3 rashes (defined as covering >30% body surface area [BSA]) were reported with ERLEADA® treatment (6%) vs placebo (0.5%). The onset of rash occurred at a median of 83 days. Rash resolved in 78% of patients within a median of 78 days from onset. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA®.

Hypothyroidism — In 2 randomized studies (SPARTAN and TITAN), hypothyroidism was reported for 8% of patients treated with ERLEADA® and 2% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 3 or 4 adverse reactions. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted.

Drug Interactions
Effect of Other Drugs on ERLEADA® — Co-administration of a strong CYP2C8 or CYP3A4 inhibitor is predicted to increase the steady-state exposure of the active moieties. No initial dose adjustment is necessary; however, reduce the ERLEADA® dose based on tolerability [see Dosage and Administration (2.2)].

Effect of ERLEADA® on Other Drugs

CYP3A4, CYP2C9, and CYP2C19, and UGT Substrates — ERLEADA®, a CYP3A4, CYP2C9, and UGT inhibitor, is recommended when possible or evaluate for loss of activity if medication is continued. Concomitant administration of ERLEADA® with medications that are substrates of UGT- glucuronyltransferase (UGT) can result in decreased exposure. Use caution if substrates of UGT must be co-administered with ERLEADA® and evaluate for loss of activity.

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

ADT — androgen deprivation therapy; ALH — androgen receptor ligand; CT — computed tomography; CTN — goserelin-containing releasing hormone; HR — hazard ratio; mCSPC — metastatic castration-sensitive prostate cancer; MFS — metastasis-free survival; NE = non-estimable; nmCRPC — non-metastatic castration-resistant prostate cancer; OS — overall survival; PSA — prostate-specific antigen; rPFS — radiographic progression-free survival; SPARTAN — Selective Prostate Androgen Receptor Targeting with ARN-509; TITAN — Targeted Investigational Treatment Analysis of Novel Androgens.

Study Design: TITAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with mCSPC. Patients had previously been diagnosed with mCSPC or relapsed metastatic disease after an initial diagnosis of localized disease. Patients with severe (ie, lung or liver) metastases or as the only sites of metastases were excluded. Patients were randomized 2:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the TITAN trial received a concurrent GnRH analog or had a prior bilateral orchiectomy. The primary end points were overall survival and rPFS.1,4

All patients who enrolled in the TITAN study started ADT for mCSPC 6 months prior to randomization.1,4

Study Design: SPARTAN was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of patients with nmCRPC (n=1,627). Patients had a PSA doubling time ≤10 months and serum testosterone levels ≤50 ng/mL. All patients enrolled were confirmed to be non-metastatic by blinded central imaging review. Patients with a history of severe, predosing factors for anorexia, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. Patients were randomized 2:1 to receive ERLEADA® 240 mg orally once daily or placebo orally once daily. All patients in the SPARTAN trial received a concurrent GnRH analog or had a bilateral orchiectomy. The primary end point was metastasis-free survival (MFS), defined as the time from randomization to the time of first evidence of blinded independent central review confirmed distant metastases, defined as new bone or soft tissue lesions or enlarged lymph nodes above the iliac bifurcation, or death due to any cause, whichever occurred first.

Secondary endpoints were time to progression, progression-free survival, time to symptomatic progression, overall survival, and time to initiation of cytotoxic chemotherapy.1,2

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References:
Brief Summary of Prescribing Information for ERLEADA® (apalutamide)

ERLEADA® (apalutamide) tablets, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE

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

CONTRAINdications

None.

WARNINGS AND PRECAUTIONS

Cerebrovascular and Ischemic Cardiovascular Events

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

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

In the SPARTAN study, cerebrovascular events occurred in 4.7% of patients treated with ERLEADA and 0.8% of patients treated with placebo [see Clinical Trials Experience]. In the TITAN study, cerebrovascular events occurred in 9% of patients treated with ERLEADA and 2.1% of patients treated with placebo. Across the SPARTAN and TITAN studies, 3 patients (0.2%) treated with ERLEADA, and 2 patients (0.2%) treated with placebo died from a cerebrovascular event.

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

Fractures

Fractures occurred in patients receiving ERLEADA. Evaluate patients for fracture risk. Monitor and manage patients at risk for fractures according to established treatment guidelines and consider use of bone-targeted agents. In a randomized study (SPARTAN) of patients with non-metastatic castration-resistant prostate cancer, fractures occurred in 12% of patients treated with ERLEADA and in 7% of patients treated with placebo. Grade 3 fractures occurred in 3% of patients treated with ERLEADA and in 1% of patients treated with placebo. The median time to onset of fracture was 314 days (range: 20 to 953 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the SPARTAN study.

In a randomized study (TITAN) of patients with metastatic castration-sensitive prostate cancer, fractures occurred in 8% of patients treated with ERLEADA and in 6% of patients treated with placebo. Grade 3-4 fractures were similar in both arms at 2% each. The median time to onset of fracture was 56 days (range: 2 to 111 days) for patients treated with ERLEADA. Routine bone density assessment and treatment of osteoporosis with bone-targeted agents were not performed in the TITAN study.

Fails

Fails occurred in patients receiving ERLEADA with increased frequency in the elderly [see Use in Specific Populations]. Evaluate patients for fall risk. In a randomized study (SPARTAN), fails occurred in 16% of patients treated with ERLEADA compared to 9% of patients treated with placebo. Fails were not associated with loss of consciousness or seizure.

Seizure

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

In two randomized studies (SPARTAN and TITAN), five patients (0.5%) treated with ERLEADA and one patient treated with placebo (0.1%) experienced a seizure. Seizure occurred from 159 to 650 days after initiation of ERLEADA. Patients with a history of seizure, predisposing factors for seizure, or receiving drugs known to decrease the seizure threshold or to induce seizure were excluded. There is no clinical experience in re-administering ERLEADA to patients who experienced a seizure.

Embryo-Fetal Toxicity

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

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Cerebrovascular and Ischemic Cardiovascular Events [see Warnings and Precautions].
- Fractures [see Warnings and Precautions].
- Fails [see Warnings and Precautions].
- Seizure [see Warnings and Precautions].

Clinical Trial Experience

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

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

Metastatic Castration-sensitive Prostate Cancer (mCSPC)

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

Ten patients (2%) who were treated with ERLEADA died from adverse reactions. The reasons for death were ischemic cardiovascular events (n=3), acute kidney injury (n=2), cardiac-respiratory arrest (n=1), sudden cardiac death (n=1), respiratory failure (n=1), cerebrovascular accident (n=1), and large intestinal ulcer perforation (n=1). ERLEADA was discontinued due to adverse reactions in 8% of patients, most commonly from rash (2%). Adverse reactions leading to dose interruption or reduction of ERLEADA occurred in 23% of patients; the most frequent (>1%) were rash, fatigue, and hypertension. Serious adverse reactions occurred in 20% of ERLEADA-treated patients and 20% in patients receiving placebo.

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

Table 1: Adverse Reactions in TITAN (nmCSPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse reaction</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>17</td>
<td>0.4</td>
<td>15</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>28</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pruritus</td>
<td>11</td>
<td>&lt;1</td>
<td>5</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hot flush</td>
<td>23</td>
<td>0</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>19</td>
<td>8</td>
<td>16</td>
<td>9</td>
</tr>
</tbody>
</table>

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

Includes rash, rash maculo-papular, rash generalized, urticaria, rash pruritic, rash macular, conjunctivitis, erythema multiforme, rash papular, skin exfoliation, genital rash, rash erythematous, stomatitis, drug eruption, mouth ulceration, rash pustular, blister, papule, pemphigoid, skin erosion, dermatitis, and rash vesicular.

Additional adverse reactions of interest occurring in 2%, but less than 10% of patients treated with ERLEADA included diarrhea (8% versus 6% on placebo), muscle spasm (3% versus 2% on placebo), dysgeusia (3% versus 1% on placebo), and hypothyroidism (4% versus 1% on placebo).

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>All Grades</th>
<th>Grade 3-4</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematology</td>
<td>White blood cell decreased</td>
<td>27</td>
<td>0.4</td>
<td>19</td>
</tr>
<tr>
<td>Chemistry</td>
<td>Hypertriglyceridemia</td>
<td>17</td>
<td>3</td>
<td>12</td>
</tr>
</tbody>
</table>

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

Non-metastatic Castration-resistant Prostate Cancer (nmCRPC)

SPARTAN, a randomized (2:1), double-blind, placebo-controlled, multi-center clinical study, enrolled patients who had nmCRPC. In this study, patients received either ERLEADA at a dose of 240 mg daily or a placebo. All patients in the SPARTAN study received a concomitant gonadotropin-releasing hormone (GnRH) analog or had a bilateral orchiectomy. The median duration of exposure was 33 months (range: 0.1 to 75 months) in patients who received ERLEADA and 11 months (range: 0.1 to 37 months) in patients who received placebo.

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

Table 3 shows adverse reactions occurring in ≥10% on the ERLEADA arm in SPARTAN that occurred with ≥2% absolute increase in frequency compared to placebo. Table 4 shows laboratory abnormalities that occurred in ≥15% of patients, and more frequently (≥5%) in the ERLEADA arm compared to placebo.

Table 3: Adverse Reactions in SPARTAN (nmCRPC)

<table>
<thead>
<tr>
<th>System/Organ Class</th>
<th>Adverse reaction</th>
<th>All Grades</th>
<th>Grade 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatiguea</td>
<td>39</td>
<td>1</td>
</tr>
<tr>
<td>Muscle and connective tissue disorders</td>
<td>Arthralgia</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>12</td>
<td>0.1</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Fallb</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Fracture</td>
<td>Weight decreaseda</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>25</td>
<td>14</td>
</tr>
<tr>
<td>Hot flush</td>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>18</td>
<td>0</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>ERLEADA N=803</th>
<th>Placebo N=398</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>70</td>
<td>0.4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47</td>
<td>0.3</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>41</td>
<td>2</td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemiaa</td>
<td>76</td>
<td>0.1</td>
</tr>
<tr>
<td>Hypertglycemiaa</td>
<td>70</td>
<td>2</td>
</tr>
<tr>
<td>Hyperturicemiaa</td>
<td>67</td>
<td>2</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>32</td>
<td>2</td>
</tr>
</tbody>
</table>

*Does not reflect fasting values

Rash

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, rash associated with ERLEADA was most commonly described as macular or maculo-papular. Adverse reactions of rash were reported for 26% of patients treated with ERLEADA versus 8% of patients treated with placebo. Grade 3 rashes (defined as covering > 30% body surface area [BSA]) were reported with ERLEADA treatment (6%) versus placebo (0.5%).

The onset of rash occurred at a median of 83 days of ERLEADA treatment. Rash resolved in 78% of patients within a median of 78 days from onset of rash. Rash was commonly managed with oral antihistamines, topical corticosteroids, and 19% of patients received systemic corticosteroids. Dose reduction or dose interruption occurred in 14% and 28% of patients, respectively. Of the patients who had dose interruption, 59% experienced recurrence of rash upon reintroduction of ERLEADA.

Hyperthyroidism

In the combined data of two randomized, placebo-controlled clinical studies, SPARTAN and TITAN, hyperthyroidism was reported for 6% of patients treated with ERLEADA and 2% of patients treated with placebo based on assessments of thyroid-stimulating hormone (TSH) every 4 months. Elevated TSH occurred in 25% of patients treated with ERLEADA and 7% of patients treated with placebo. The median onset was at the first scheduled assessment. There were no Grade 4 or adverse reactions. Thyroid replacement therapy was initiated in 5% of patients treated with ERLEADA. Thyroid replacement therapy, when clinically indicated, should be initiated or dose-adjusted (see Drug Interactions).

Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of ERLEADA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Respiratory, Thoracic and Mediastinal Disorders: interstitial lung disease

Drug Interactions

Effect of Other Drugs on ERLEADA

Strong CYP2C8 or CYP3A4 Inhibitors

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

Effect of ERLEADA on Other Drugs

CYP3A4, CYP2C9, CYP2C19 and UGT Substrates

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary
The safety and efficacy of ERLEADA have not been established in females. Based on findings from animals and its mechanism of action, ERLEADA can cause fetal harm and loss of pregnancy when administered to a pregnant female (see Clinical Pharmacology (12.1) in Full Prescribing Information). There are no available data on ERLEADA use in pregnant women to inform a drug-associated risk. In an animal reproduction study, oral administration of apalutamide to pregnant rats during and after organogenesis resulted in fetotoxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 2, 4 and 6 times, respectively, the AUC in patients.

Animal Data
In a pilot embryo-fetal developmental toxicity study in rats, apalutamide caused developmental toxicity when administered at oral doses of 25, 50 or 100 mg/kg/day throughout and after the period of organogenesis (gestational days 6-20). Findings included embryo-fetal lethality (resorptions) at doses ≥50 mg/kg/day, decreased fetal anogenital distance, misshapen pituitary gland, and skeletal variations (unossified phalanges, supernumerary short thoracolumbar rib(s), and small, incomplete ossification, and/or misshapen hyoid bone) at ≥25 mg/kg/day. A dose of 100 mg/kg/day caused maternal toxicity. The doses tested in rats resulted in systemic exposures (AUC) approximately 2, 4 and 6 times, respectively, the AUC in patients.

Lactation

Risk Summary
The safety and efficacy of ERLEADA have not been established in females. There are no data on the presence of apalutamide or its metabolites in human milk, the effect on the breastfed child, or the effect on milk production.

Females and Males of Reproductive Potential

Contraception
Males
Based on the mechanism of action and findings in an animal reproduction study, advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of ERLEADA. (see Use in Specific Populations).

Infertility
Males
Based on animal studies, ERLEADA may impair fertility in males of reproductive potential (see Nonclinical Toxicology (13.1) in Full Prescribing Information).

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

Geriatric Use
Of the 1327 patients who received ERLEADA in clinical studies, 19% of patients were younger than 65 years, 41% of patients were 65 years to 74 years, and 40% were 75 years and older. No overall differences in effectiveness were observed between older and younger patients. Of patients treated with ERLEADA (n=1073), Grade 3-4 adverse reactions occurred in 39% of patients younger than 65 years, 41% of patients 65-74 years, and 49% of patients 75 years or older. Falls in patients receiving ERLEADA with androgen deprivation therapy was elevated in the elderly, occurring in 8% of patients younger than 65 years, 10% of patients 65-74 years, and 19% of patients 75 years or older.

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

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information). Cerebrovascular and Ischemic Cardiovascular Events
• Inform patients that ERLEADA has been associated with cerebrovascular and ischemic cardiovascular events. Advise patients to seek immediate medical attention if any symptoms suggestive of a cardiovascular or a cerebrovascular event occur (see Warnings and Precautions).

Falls and Fractures
• Inform patients that ERLEADA is associated with an increased incidence of falls and fractures (see Warnings and Precautions).
5-year Rezum study results show low rates of ED and ejaculatory dysfunction

Erectile and ejaculatory dysfunction are prominent postoperative symptoms in men who are treated for benign prostatic hyperplasia (BPH) with traditional prostate surgeries, such as transurethral resection of the prostate (TURP). New treatment methods, like Rezum or prostatic urethral Lift (PUL), aim to reduce those symptoms.

In a recent study presented at the American Urological Association (AUA) 2021 Annual Meeting, Kevin T. McVary, MD, FACS, and coauthors assessed the 5-year outcomes of Rezum water vapor thermal therapy in patients with BPH, specifically focusing on erectile and ejaculatory function. McVary is a professor of urology and director of the Center for Male Health at Loyola University Medical Center, Maywood, Illinois.

Q. Please discuss the background for this study.

A. The basis of the study was to look at the sexual function aspect of the 5-year Rezum study, the pivotal study that looked at lower urinary tract symptom improvement in men with BPH who had convective water vapor therapy Rezum treatment. We published those pivotal results concerning LUTS [lower urinary tract symptoms] improvement about 6 months ago. It had a marked improvement in lower urinary tract symptoms that were durable for 5 years. Prospectively, in this trial we measured various aspects of sexual function. The purpose of this particular manuscript, which is under review and was presented at this year's AUA [meeting], was specifically focused on aspects of sexual function over 5 years following a Rezum treatment. It's an ancillary study to the pivotal study of Rezum treatment, but with this investigation we're focused entirely on male sexual health.

Q. What were some of the notable findings? Were any of them surprising?

A. I think there are a couple of very important aspects of this study that are worth mentioning. By way of review, men had a significant and durable improvement in lower urinary tract symptoms and flow rates over the 5-year period. And that is represented in our previous published paper this past year. There are several ways of addressing sexual function. A very common way is to track it with the use of sexual function questionnaires. It's considered a quantitative, more objective evaluation of sexual function. One of those is called the SHIM, the Sexual Health Inventory for Men. It's a measurement of their assessment of erection quality over time. In this study, we focused on the men who are in the trial and sexually active, measuring their erectile function. In this you see a very stable response to erection measurement over the 5-year period of time. Rezum does not appear to affect erection, which again confirms what we saw at 3 months, at 1 year, and at 2, 3, 4, and now at 5 years at the end of the report, so that's good.

Similarly, we measured ejaculatory function. If you look at the questionnaire data, it's basically a straight and stable line across time and with very narrow confidence intervals, meaning ejaculatory function doesn't change much either.

Additionally, if you look at men who reported a history of sexual dysfunction compared with men that had good sexual function at the beginning of the study, both groups had an equal response to improvement in their lower urinary tract symptoms. So there isn't an influence of sexual function on response to Rezum. That's 1 message that you can tell patients.

There are 2 other important things, 1 of which was unexpected. First, the unexpected one: If, at the beginning of the trial, in addition to doing the standard questionnaires, we also asked men about their previous sexual history—questions like “Have you ever had an alteration in sexual function prior to enrollment in the study?”—a man could say, “Yes, I've had sexual dysfunction in the past, but I'm still sexually active” or “No, I've had no problems in the past.” When you follow those sexually active men with no sexual dysfunction in their past and men who reported sexual complaints in the past, you note they diverge. Men that had no history of sexual dysfunction had absolutely no change in their erectile function over time, but men who say, “Yes, I've had episodes” actually have a slight decline over time, which is very consistent with what we saw in a previous trial—the MTOPS trial (NCT00021814), where we followed sexual function in a placebo group of men with BPH for 5 years. What does that mean? Well, that means it's still important to ask patients, face-to-face, “How is erection? How is ejaculation?” because they can give you a clue to their sexual function may be performing going forward. The fact that the questionnaires go straight across is one thing, but the fact that the history can help you differentiate who might have a slight decrease over time and who can be very beneficial for a physician to counsel patients. They can gauge expectations. No one's ever done that before. In my own view, this new finding should really make a difference in the way we do clinical trials in the future. You still have to stick to the NIH [National Institutes of Health] consensus conference of 1990, where it said questionnaire data is important, but you have to talk to men to fully gauge their sexual function. It turns out that same process occurs in men who say that they had an ejaculatory complaint. They also track a little bit different from men who say there was no history of ejaculatory problems. They're not substantial decreases, but they're different than men who say, “No, I've never had a problem in the past.”

The other is a reassurance point that I'm grateful doesn't surprise me. It's that if we rate men at baseline, no sexual dysfunction, mild ED [erectile dysfunction], moderate ED, or severe ED, you'll see over the 5-year period that no one changes their level of sexual function category. If you start with no ED, no history of ED, good sexual function, you remain there over the 5 years of the trial. If you're in the mild category, you remain there over the 5 years of the trial. Your score can alter a little bit, but you don't do a categorical shift. If a guy says, “Yeah, I have a little problem now and then,” then you can say, “Well, that's not getting better. It's not getting categorically worse.” Again, the ability to reassure the patients on that is another finding from this study.
Q. How do these data build on previous research of Rezum?
A. It tells us there is a good impact on BPH outcomes, lower urinary tract symptom improvement, and urinary flow rates. It confirms that, as well as the fact that sexual function doesn't seem like it influences that. Second is that you have stable sexual function over a 5-year period of time. You don't do a categorical shift. However, if you do have a history of ED, you actually track differently than men that say, “No, I've been perfect my whole life.”

Q. With so many options available, please describe your patient selection process for BPH procedures.
A. As cochairman of the AUA BPH clinical guidelines, my comments dovetail with the BPH guidelines. The first approach is if a man has LUTS, he needs to be informed of his options: medicine and surgery. If he is not responding to medicine and surgery. If at the start a man is not interested in medications, then it's totally legitimate to proceed directly into an intervention once he understands the range of options. The choice of intervention is based in part on prostate size—how severe and how big is the prostate.

The other factor is his willingness to accept risk. That means if we have a man whose prostate size is, let's say, 50 g, and you say, “We have a minimally invasive option versus a more traditional surgical option, like bipolar TURP or PVP [photoselective vaporization of the prostate],” you can discern choice by asking him about his proclivity for wanting to preserve sexual function.

If the man says, “Sexual function is very high on my particular balance beam of motivation,” then choosing a minimally invasive therapy might be a better choice for that guy because it is known that current minimally invasive surgeries do a better job at preserving sexual function. For a man like that, I would encourage him to proceed in that direction. If the man said, “Those days are past. Sexual function is not really a motivation for me,” then many times the discussion turns to durability of procedure. What we can say about MIST, minimally invasive surgical treatment, and in the current guidelines, the real players are Rezum and UroLift; there are reliable data to 5 years but not beyond. And we know about retreatment rates within 5 years. Surgical retreatment rates in terms of Rezum at 5 years is 4.4%, relatively low. In prostatic urethral lift, surgical retreatment rates are much higher. If you add medication retreatments as another way to fail, then both are a little bit worse. The discussion is a review of durability of response, and we can only say durability to 5 years because that's the furthest the data go.

When we look at bipolar TURPs or PVPs, then the durability data are more extensive because the procedures are more well established. Some men will say, “I want the procedure with the best durability that you know of,” and I'd say, “Well, there are some unknowns with the MIST, so perhaps it might be better for you to choose a laser procedure or a bipolar TURP.”

The other aspect is level of invasiveness, regardless of sexual function. There's no question that the MISTs are much easier for men to undergo and recover from. There's no hospital stay. There's no general anesthesia. That is attractive to men with or without sexual dysfunction. If that is a big deal, then MIST is going to be a better approach for that patient. It has to be individualized to the motivations of the patient and also what I call his phenotype. How big is his prostate? How bad is his problem? What is his tolerance for adverse effects?

Q. What is the message for the practicing urologist?
A. Rezum is a durable therapy for lower urinary tract symptoms, secondary to BPH. The adverse event profile is quite favorable, the impact on sexual function is minimal, and retreatment rates are exceedingly low with this therapy.

Q. Is there anything else you feel our audience should know?
A. I think that summarizes where we’re going to be because the pivotal trial is over. Looking forward to comparisons of minimally invasive surgery versus medical therapy is, at this point, untapped. It's something that we think we have insight into, but we really don't have good data. We have done some modeling in that regard, where minimally invasive surgery compares favorably to medication, as seen in the MTOPS cohort, but that is a modeling investigation.4 That is not the same as a randomized control trial.

Another area is utilities, quality of life. How do patients rate these types of therapies as impactful in the quality of their life? This is done quantitatively looking at risk trade-offs: “I will accept this amount of adverse effect if I can have this amount of quality years in my lifetime,” called utility or quality-of-life years. And that's not been done, other than some projects that we're doing right now to address that. It's very exciting.

The other is cost benefit. There's a health policy issue here. We're doing these procedures, and there is an expense to our society and our health care system. What are we getting as a nation in return? Are we getting men with a sustained benefit? Are we spending a lot of money for procedures that may or may not be durable? Cost-effectiveness evaluation is also a thing that we need to look forward to. And then there is the question “Has anyone really compared these MISTs to more traditional surgeries?” The answer is yes and no. Rezum has not done that. It's a newer therapy. UroLift has done that—not in the U.S. There was a European trial looking at TURP versus UroLift, and TURP seem to beat UroLift in most important aspects, except the patient softer measures about time to recovery, sexual function, and those types of things. Regardless, those are additional health policy questions that really need to be addressed.

REFERENCES
NOW ENROLLING

The CONTACT•02 study is designed to explore the safety and efficacy of an investigational drug combination—cabozantinib with atezolizumab—for patients with metastatic castration-resistant prostate cancer (mCRPC).

CONTACT•02 is recruiting patients who have or have had*:

- mCRPC (measurable visceral disease or measurable extrapelvic adenopathy)
- Progressive disease as defined by prostate-specific antigen (PSA) progression or soft tissue progression
- Prior treatment with one, and only one, novel hormonal therapy (NHT) for locally advanced or metastatic castration-sensitive prostate cancer (mCSPC), M0 CRPC, and/or mCRPC
- Radiographic progression or rising PSA on prior NHT
- No prior non-hormonal therapy for mCRPC; prior taxane-based chemotherapy for locally advanced or metastatic CSPC allowed
- ECOG performance status of 0 or 1

*Patients must meet additional eligibility criteria to enroll.

Learn more at contact02study.com or clinicaltrials.gov and search for NCT04446117, or contact Exelixis Medical Information at 1-888-EXELIXIS (1-888-393-5494) or druginfo@exelixis.com.

THE COMBINATION OF CABOZANTINIB AND ATEZOLIZUMAB IS NOT APPROVED FOR THE USE UNDER INVESTIGATION IN THIS TRIAL. SAFETY AND EFFICACY HAVE NOT BEEN ESTABLISHED.

The CONTACT clinical program is a collaboration between Exelixis and Roche-Genentech to evaluate cabozantinib in combination with atezolizumab in multiple solid tumors. CONTACT•02 is sponsored by Exelixis.
A large real-world analysis of retreatment and return procedures found that the prostatic urethral lift (PUL; UroLift) has the lowest complications and that Rezum has the highest retreatment rate, when comparing these procedures along with GreenLight and transurethral resection of the prostate (TURP).1

The results were presented at the American Urological Association’s 2021 Annual Meeting by Steven A. Kaplan, MD, professor of urology and director of the Men’s Wellness Program, Mount Sinai Health System, and professor, Icahn School of Medicine at Mount Sinai, New York, New York. Kaplan and coinvestigator Daniel Rukstalis, MD, sought to compare real-world rates and calculated hazards for surgical retreatment and return procedures following treatment with minimally invasive surgical treatments or traditional surgery. Real-world data were derived from a patient-level longitudinal, observational analysis of Medicare and commercial outcomes claims data from 2015 to 2019. Multivariate Cox proportional hazard models were used for calculating HRs for encountering a surgical retreatment or a postoperative return procedure, accounting for potential differences in treatment populations. A return procedure was defined as a postoperative procedure performed during a return visit to an outpatient setting as identified by a Current Procedural Terminology or International Classification of Diseases ninth or 10th edition code. Surgical retreatment was defined as a second benign prostatic hyperplasia (BPH) procedure (Rezum, GreenLight, TURP, PUL, or holmium laser enucleation of the prostate).

Of the men included in the study, 19,507 underwent TURP, 10,173 underwent GreenLight, 5228 underwent PUL, and 935 underwent Rezum.

“At 365 days, the rate of return procedures was lowest for the UroLift. The rate of return procedures was higher after Rezum vs UroLift,” Kaplan said. Specifically, the rates of return for the 4 procedures were 23% for Rezum, 22% for GreenLight, 21% for TURP, and 17% for PUL.

Looking at the hazard model for return procedures and after adjusting for population variables, the investigators found a lower risk of experiencing a return procedure after PUL vs GreenLight, Rezum, and TURP. There was a 24% higher hazard for TURP vs PUL, 35% higher hazard for GreenLight vs PUL, and 41% higher hazard for Rezum vs PUL.

In addition, at 1 year, the rate of surgical retreatment was similar between GreenLight, TURP, and PUL but was higher for Rezum vs PUL (P = .04). Rates of retreatment at 1 year were 7.2% for Rezum, 5.4% for PUL, 5.3% for TURP, and 5.2% for GreenLight.

Upon examining the hazard model for retreatment, risk of retreatment within 1 year was similar for GreenLight, TURP, and PUL, the highest risk for retreatment being seen with Rezum. There was a 36% higher hazard for Rezum vs PUL, 40% higher hazard for Rezum vs TURP, and 43% higher hazard for Rezum vs GreenLight.

“At 365 days, the rate of return procedures was lowest for the UroLift. The rate of return procedures was higher after Rezum vs UroLift.”

STEVEN A. KAPLAN, MD

REFERENCES

Real-world data point to low complication rate for urethral lift

Highest retreatment rate is observed with Rezum procedures, data indicate

Benign Prostatic Hyperplasia

CLINICAL UPDATES

Kaplan discusses patient selection for BPH treatments

In this video, Steven A. Kaplan, MD, discusses his patient selection process for BPH treatments and shares the take-home message of the study, UroLift PUL compared to Rezum, TURP and GreenLight PVP: US Medicare and commercial claims analysis reveals lowest complications for PUL and highest retreatment for Rezum, presented at the 2021 American Urological Association annual meeting.
LEARN MORE AT APCRisks.com

Patients with advanced prostate cancer are at risk for other serious conditions, such as cardiovascular disease, diabetes, and osteoporosis—risks that may increase with androgen deprivation therapy.1–5


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A group of studies presented at the 2021 American Urological Association Annual Meeting illustrate the costs and risks inherent to seeking care for men’s health-related conditions online and/or from nonurologists.

The studies were presented in a press briefing moderated by Petar Bajic, MD, of the Center for Men’s Health at the Glickman Urological and Kidney Institute in Cleveland, Ohio.

SHOCK WAVE THERAPY
Results of the first study, which evaluated shock wave therapy for erectile dysfunction in 7 major US cities, were presented by James Weinberger, MD, MBA.1

“Shock wave therapy has emerged as a restorative therapy for referrals for erectile dysfunction in the second-line setting. The shock wave therapy market segment has largely been dominated by GAINSWave, a practitioner database and direct-to-consumer advertising platform that has promoted the efficacy of shock wave therapy for erectile dysfunction, despite limited evidence supporting its claim,” said Weinberger, a urology resident at the David Geffen School of Medicine at the University of California, Los Angeles, working with Sriram Eleswarapu, MD, PhD, and colleagues.

The investigators used Google search to identify shock wave therapy providers across 7 major metropolitan areas: Atlanta, Georgia; Boston, Massachusetts; Dallas, Texas; Los Angeles, California; New York, New York; Philadelphia, Pennsylvania; and Washington DC. Search terms used included “shockwave therapy for erectile dysfunction in [city], shockwave therapy for ED in [city], and GAINSWave in [city].” Clinics had to explicitly advertise shock wave therapy and be located within the boundaries of 1 of the metropolitan areas to be included in the analysis. The investigators obtained information via phone, specifically inquiring about providers administering treatment, pricing, and duration of treatment. Clinics were excluded from the analysis after 3 failed attempts at contact.

Sixty clinics that offered shock wave therapy for erectile dysfunction were identified, 60% of which offered comprehensive information about providers, pricing, and duration.

The average price was $3559 per treatment course (range, $650-$10,800). Across the 7 metropolitan areas, an average of 10% of providers were trained in urology, and 13% were nonphysician providers.

“Level 1 data on shock wave therapy for ED [are] still pending. It should not be marketed as having such. Importantly, erectile dysfunction can portend significant morbidities. If patients are exploring treatment in the second-line setting, they should really be evaluated by [a] urologist, who can perform a formal men’s health evaluation,” Weinberger said.

PRESCRIPTION COSTS FOR PDEIS
A second study sought to compare costs of phosphodiesterase inhibitor (PDEi) prescriptions when obtained from online direct-to-consumer (DTC) companies vs a traditional physician visit.2

Investigators examined pricing for 90-day supplies of sildenafil (Viagra), 20 mg and 100 mg, and tadalafil (Cialis), 5 mg and 20 mg. The analysis included 2 DTC companies, 2 compounding pharmacies, 3 Canadian pharmacies, and 16 local American pharmacy chains in 5 zip codes. Direct communication was used to obtain DTC and compounding and Canadian pharmacies pricing.

Pricing for local pharmacies was obtained through GoodRx with an online coupon. Price for a physician visit was determined based on 2020 Centers for Medicare & Medicaid Services reimbursement.

“We found that physician visit with a local pharmacy prescription with the coupon consistently produced the lowest available prices. Online direct-to-consumer consistently provided the most expensive option for fulfilling PDEi prescriptions. These effects were most pronounced at higher doses and with tadalafil compared with sildenafil,” said first author Dennis Schneider, BS, a fourth-year medical student at the University of California, Irvine, working with Faysal A. Yafi, MD, FRCSC, and colleagues.

The price difference between online DTC and a physician visit with a local pharmacy was $54.55 for sildenafil 20 mg, $762.84 for sildenafil 100 mg, $594.20 for tadalafil 5 mg, and $2719.00 for tadalafil 20 mg, according to Schneider.

MALE INFERTILITY SUPPLEMENTS
In the third study, which explored supplements related to male infertility, the investigators queried the online marketplaces Amazon, Google Shopping, and Walmart for currently available male infertility supplements.1 They collected customer reviews and data regarding costs, ingredients, and advertised claims. Then they compared the active ingredients to the current literature of randomized controlled trials of supplements.

The investigators analyzed 30 distinct supplements and found 73 total ingredients. Zinc (57%), folic acid (53%), L-carnitine (50%), and selenium (50%) were the most common active ingredients identified.

“The majority of these ingredients—almost 60% of them—were not studied in human trials. I thought that was one of our most important findings,” said first author Igor Inoyatov, MD, urology resident at Renaissance School of Medicine at Stony Brook University in New York, working with Yefim R. Sheynkin, MD, FACS, and colleagues.

In addition, 70% of the products claimed to improve sperm motility, 63%, to increase sperm count; and 12%, to increase chance of conception. However, only zinc and vitamin E have been shown to improve fertility rates, Inoyatov said.

The average 30-day cost per product was $35.10. “While they’re relatively less expensive than artificial reproductive technology, these ingredients are not backed up by proven clinical efficacy,” Inoyatov said.

REFERENCES
Narcotics-free ureteroscopy: Anatomy of an ERAS protocol

Opioid abuse continues to be a problem in the US, with 14,139 deaths involving prescription opioids reported in 2019. One way health care providers are addressing this issue is by treating pain from surgical procedures differently. In this interview, Nicole L. Miller, MD, FACS, discusses her institution’s enhanced recovery after surgery (ERAS) protocol for ureteroscopy, which eliminates the use of opioids in patients undergoing this common procedure. Miller is a professor of urology at Vanderbilt University Medical Center, in Nashville, Tennessee.

Q. How did you come to identify ureteroscopy as a procedure for which to create a narcotics-free protocol?
A. Patients with kidney stones have a painful condition that’s typically recurrent, so they visit emergency rooms and acute care clinics regularly. At every point of care, there is the potential that they will be prescribed pain medications, and opioids have traditionally been used for this type of pain. We felt this patient population had an opportunity not only for increased opiate use but also for repeated exposure. Studies have shown that the risk of persistent use in opioid-naive patients following ureteroscopy is 6.2%, or 1 in every 16 patients.

When patients with kidney stones need surgery, we typically put in a ureteral stent after the procedure. Many patients tell us that the stent is the most uncomfortable part of the operation. Traditionally, we thought that we needed opioids to control pain related to the stent. But the opioid crisis in the US made us begin to question whether this was true. As we evaluated our prescribing practices, it became more evident that much of it was based on habit rather than need.

Ureteroscopy seemed like the obvious procedure to test the hypothesis that we could reduce or even eliminate opioids because we could evaluate these patients during the short time during which the stent was in place and record adverse events, symptoms, presentations, and acute care visits.

Q. Please briefly walk through the narcotics-free protocol for ureteroscopy.
A. Vanderbilt as an institution has implemented ERAS protocols for many different operations. These are intended to be patient-centered, evidence-based, multidisciplinary team-developed protocols to optimize physiologic function and facilitate patient recovery. I’m making a distinction between protocol and enhanced recovery after surgery to emphasize our desire to not only decrease opiate exposure postoperatively but also to examine every phase of care to improve the entire operative experience.

Patients undergoing ureteroscopy with ureteral stent placement are given acetaminophen (650-1000 mg) and gabapentin (100-300 mg) in the preoperative holding area. Gabapentin, which acts on the nociceptive processes involved in central sensitization, has been shown to reduce postoperative pain and opioids use during the first 24 hours after surgery.

In the operating room, the patient is given a belladonna and opium suppository per rectum to treat stent-related bladder discomfort and the nonsteroidal anti-inflammatory medication Ketorolac. Typically, we give 30 mg of Ketorolac intravenously if the patient has normal renal function. We will reduce it to 15 mg if renal function is at all compromised. In randomized trials, nonsteroidal anti-inflammatory drugs have been shown to be superior to opiates for renal colic, so if you had a choice between giving patients in the emergency room ketorolac or morphine, they actually did better and required less pain medication with the nonsteroids. Using Ketorolac intraoperatively allows us to target the prostaglandin-mediated pain pathway that’s involved in kidney and ureteral stent-related pain.

The anesthesia team gives minimal or often zero intraoperative opioids, and in the recovery room opioids are only given if the patient has breakthrough pain. In that case, a single IV dose of hydromorphone 0.25 mg or an oral dose of oxycodone 5 mg may be given.

Many of the published studies on opiate reduction in kidney stone patients have focused on postoperative prescribing. We used to standardly prescribe a 5- to 7-day course of opiates to last until the ureteral stent was removed. Considering these medications are typically taken every 6 hours, these prescriptions could be 20 to 28 pills at minimum.

A real problem is what happens to unused opioid medications, many of which are consumed by someone other than the patient, are sold for profit, or result in accidental exposure to children. The postoperative portion of our ERAS protocol is certainly where we have made the most change. For most patients, no opioids are prescribed. We use a 4-medication regimen as our standard protocol. Patients are instructed to take acetaminophen 1000 mg every 8 hours, alternating with ibuprofen 800 mg every 8 hours. We want them to alternate between the Tylenol and the ibuprofen so that there’s something they can take for pain every 6 to 8 hours. Two additional medications, tamsulosin and
oxycodone, are meant to combat the stent-related discomfort. In a randomized controlled trial, tamsulosin was shown to improve stent pain and oxycodone to decrease bladder spasms. Patients are prescribed tamsulosin 0.4 mg daily and oxycodone XL 10 mg until stent removal. In choosing these 4 medications, we are providing multimodal analgesia. We are targeting different pain pathways to improve the patient experience, decrease pain, and reduce opioid exposure.

**Q. What effects have you seen by introducing the ERAS pathway at your institution?**

**A.** One thing that’s been incredibly positive is improved communication among providers because everyone is focused on the same outcome, which is for the patient to have the best experience, but also to understand we’re implementing these protocols in order to decrease opioid prescribing and to combat the crisis in this country. We now understand that the risk of developing persistent use is associated with how much we prescribe. There have been multiple studies showing that the more opiates we give patients at the time we prescribe them, the more likely they are to be at risk for persistent use. I think everyone understands that, and so among the nursing team, the anesthesia team, and the surgery team, there’s much better collaborative management and ownership of patient outcomes. We are all working from the same protocol and have the same goals.

**Q. What sorts of challenges were involved in implementing this pathway?**

**A.** Many patients have had kidney stone surgery before, and they remember that when they had a stent, they had pain. When you tell them that you’re not going to prescribe opiates, patients often worry that they will have uncontrolled pain. Educating the patient and all the care providers is crucial. We explain to the patient that our goal is not to make them pain-free, but rather to control their pain so that they’re able to perform the activities of daily living.

**“We explain to the patient that our goal is not to make them pain-free, but rather to control their pain so that they’re able to perform the activities of daily living.”**

NICOLE L. MILLER, MD, FACS

**Q. What advice would you give to other practices that might like to implement this sort of pathway?**

**A.** I would say do it and don’t look back. It will require some commitment and collaboration. The first step is to know your prescribing data; you need to know where you’re starting from. It could be that you’re prescribing opioids based on what you’ve always done rather than what is actually needed. It’s also important to see what variations you have in prescribing opioids and whether they are appropriate. One of the things the literature has shown is that we don’t often prescribe based on the procedure we’re performing. Ureteroscopy is a fairly minimally invasive procedure, and yet some patients have been prescribed as much opioid as they would if they had had a more invasive, open surgery. I’m not saying we should never prescribe opioids, but I do think that we need to be thoughtful about prescribing.

Once you know your prescribing data and implement prescribing changes, you have to follow the outcomes. I highly recommend doing that because I think the fear when you institute a protocol like this is that acute patient visits and episodes of care will increase, putting a strain on providers, clinics, and institutions. We have not really seen that. Once you know your prescribing data, make the change, and monitor the outcome, you can feel very comfortable that your efforts will be successful. In addition, the American Urological Association has recently released a position statement on opioid use that is an excellent resource for clinicians.

**Q. Is there anything else that you feel our audience should know?**

**A.** It’s really important to know what is going on in your state. You need to understand what legislative measures are being taken; you need to know whether there is a controlled-substances monitoring database. If there is, you should be using it to monitor your patients. Another thing we’ve seen and published on at Vanderbilt is that patients often get narcotics from more than one prescriber, which has been described as postoperative “doctor shopping.” So you may not be giving opioids to your patients, but someone else might be. You have to look at the patient as a whole. Here is where controlled-substances monitoring databases are really useful. And make sure that everyone is aligned to the same goal: the patient undergoing the procedure, the anesthesia team giving medications intraoperatively, the nursing staff treating patients and reporting their pain scales. Everyone needs to be communicating well with one another. If you can do that, this can be incredibly successful. I think education of the entire care team as well as the patient is the most crucial factor.

**REFERENCES**

Watch for these urology-related CPT codes this January

New and updated codes encompass balloon continence devices, hypospadias

Current Procedure Terminology (CPT) codes are continuously being updated. New and updated Category I and III codes will become active on January 1, 2022. In addition, some other Category III codes may be released on July 1 of the calendar year, prior to the release of the new CPT code book. For a discussion about how to report Category III codes, please see our previous article on this subject. Here are new and updated CPT codes that may be of interest to urologists.

**CPT Codes for Hypospadias Repair**

- **54340**: repair of hypospadias complication(s) (eg, fistula, stricture, diverticula); by closure, incision, or excision, simple
- **54344**: requiring mobilization of skin flaps and urethroplasty with flap or patch graft
- **54348**: requiring extensive dissection and urethroplasty with flap, patch, or tubed graft, including urinary diversion, when performed
- **54352**: revision of prior hypospadias repair requiring extensive dissection and excision of previously constructed structures including rerelease of chordee and reconstruction of urethra and skin brought in as flaps or grafts. (Do not report 54352 in conjunction with 15275, 15574, 15740, 53235, 53410, 54300, 54336, 54340, 54344, 54348, or 54360.)

**Discussion**: CPT code 54352 describes a revision of prior hypospadias repair of ultimate complexity that requires work above that of a flap, patch, or graft but also including excision of previously constructed structures. The code is mainly an editorial change because the previously used code had an outdated term that could be interpreted as offensive. The new terminology more accurately describes the work performed.

**CPT Codes for Balloon Continence Devices**

- **53451**: periurethral transperineal adjustable balloon continence device; bilateral insertion, including cystourethroscopy and imaging guidance. (Do not report 53451 in conjunction with 52000, 53452, 53453, 53454, or 76000.)
- **53452**: unilateral insertion, including cystourethroscopy and imaging guidance. (Do not report 53452 in conjunction with 52000, 53451, 53453, 53454, or 76000.)
- **53453**: removal, each balloon. Do not report 53453 in conjunction with 53451, 53452, or 53454.
- **53454**: percutaneous adjustment of balloon(s) fluid volume. (Report only once per patient encounter. Do not report 53454 in conjunction with 53451, 53452, or 53453.)

**Discussion**: The new year will bring 4 new Category I CPT codes that describe the insertion, removal, or fluid adjustment of periurethral balloon continence devices. These codes will replace Category III codes 0548T, 0549T, 0550T, and 0551T, which are currently used to report these procedures. The reason for the change was that the maturation of data and use of these procedures met the American Medical Association’s criteria to achieve a Category I status. It is important to be aware of the code change and use the new codes to report these procedures starting January 1. The 4 codes include descriptions of the work of the code along with the exclusions and reporting instructions, which are listed in the associated parentheticals beneath each code.

**CPT Codes for Female Bladder Neck Remodeling**

- **0672T**: endovaginal cryogen-cooled, monopolar radiofrequency remodeling of the tissues surrounding the female bladder neck and proximal urethra for urinary incontinence

**Discussion**: Category III code 0672T describes a technology to treat female stress urinary incontinence with a novel dual-energy procedure, described as endovaginal cryogen-cooled, monopolar radiofrequency remodeling of the tissue surrounding the female bladder neck and proximal urethra for urinary incontinence. The device itself is not yet approved by the FDA.
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prostate tissue, including transrectal imaging guidance, with magnetic resonance-fused images or other enhanced ultrasound imaging. (Do not report 0655T in conjunction with 52000, 76376, 76377, 76872, 76940, 76942, or 76998.)

**Discussion:** This CPT code should be used for reporting transperineal focal laser ablation of malignant prostate tissue. Imaging guidance is included and should not be reported separately.

As you update your systems and charge communication platforms for 2022, it is important to avoid using new CPT codes until they become effective on January 1, 2022. We are expecting the release of the final rule from Medicare with relative value units for the Category I codes in early November. Coverage for new codes may take some time for Medicare and other payers to develop, but all HIPAA-compliant entities are required to adopt the new CPT codes on January 1, 2022. CPT and Medicare coding conventions require reporting the most accurate code available. Private payers may require special reporting of new services if covered and are encouraged to obtain any special instructions in writing, if possible.

**ICD-10 International Classification of Diseases, Tenth Revision (ICD-10) coding changes for 2022**

Became effective on October 1, 2021. Each office is encouraged to review the changes for ICD-10 as soon as possible for any changes relevant to its practice. All ICD-10 changes can be found in the 2022 Addendum file at the following link: https://go.cms.gov/3EYc39S.

A summary of the minor changes to ICD-10 for 2022 considered relevant to urology includes minor changes in Excludes notes for codes N16 (renal tubulointerstitial disorders in diseases classified elsewhere) and N39 (other disorders of urinary system).

**ADDED CODES**

- R35.81 Nocturnal polyuria
- R35.89 Other polyuria

**Z92.85 Personal history of cellular therapy**

**Z92.850 Personal history of chimeric antigen receptor T-cell therapy**

**Z92.858 Personal history of other cellular therapy**

**Z92.859 Personal history of cellular therapy, unspecified**

**Z92.86 Personal history of gene therapy**

Additional Z code changes for patient status relative to food insecurity and homelessness may be relevant to some practices but were not included as urology specific for this article.

**REFERENCE**


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**ONC: App integration with EHR systems is on the rise**

By Keith A. Reynolds

The Office of the National Coordinator for Health Information Technology (ONC) says that more apps are integrating with EHRs.1 According to a blog post from ONC, the entity has released research analyzing apps that were discoverable in app galleries managed by EHR developers such as Allscripts, athenahealth, Cerner Corporation, and Epic Systems Corporation as well as the SMART App Gallery. It found that there has been a 20% rise in the number of apps that integrate EHRs as the health care industry continues to adopt the digital tools.

The goal of the research was to understand growth in the app market, the various app functions, how they connect to EHRs, and if they Health Level Seven (HL7) Fast Healthcare Interoperability Resources (FHIR) standard prior to finalization and implementation of the ONC Cures Act final rule, according to the post.

The total number of unique apps saw an increase during 2020 with administrative apps that handled scheduling, check-in, and billing making up 42% of available apps. Other common apps include clinical apps with 38%, care management apps with 31%, patient engagement apps with 20%, and research with 5%, the post says.

Meanwhile, the number of FHIR-enabled apps has remained near constant despite more apps supporting FHIR as there has not been a statistically significant increase in the proportion of FHIR-enabled apps among all apps.

The post says that the modest growth may be tied to the prevalence of administrative apps that typically do not support FHIR, as well as the fact that FHIR apps are typically developed around specific use cases.

**REFERENCE**

Telemedicine and telehealth services were growing before the COVID-19 pandemic, and demand has soared since the March 2020 shutdown as patients and providers alike recognized the efficiencies and convenience of delivering care remotely. However, along with the surge in demand for virtual care comes higher risk of malpractice claims for health care professionals.

Misdiagnosis risk. One of the biggest risks in the act of practicing medicine virtually involves the challenges of virtual examinations: reviewing diagnostics, communicating with the patient, and loss of contextual clues, among other factors. Physicians conducting a telemedicine appointment must rely on a patient’s description and interpretation of their symptoms to try to make a diagnosis without the benefit of testing and physical examination, as at an in-person clinical visit. That could more easily lead to misdiagnosis, missed symptoms or physical clues, prescription of the wrong medication, and the potential consequence of prescribing medication across state lines without conducting an in-person examination (a criminal offense in some states).

Security & technology concerns. Virtual health care can also be prone to security and technology threats. Privacy breaches, software malfunctions, cyber security threats, ransomware, and other issues could result in noncompliance with regulations. Something as simple as a poor internet connection or an older computer with a low-quality camera lens could play a role in misdiagnosis or miscommunication between patient and provider.

Protect yourself. Despite these risks, the standard of care test remains the same for virtual medicine: acceptable medical treatment provided by reasonably prudent health care professionals under like or similar circumstances. Providers who choose to offer virtual care can reduce their risk by implementing best practices and recommendations from the American Telemedicine Association (ATA) and working with attorneys who are experienced in medical malpractice defense to develop policies and procedures for following those guidelines.

They should be vigilant about patient confidentiality, including written documentation, and ensure their software platforms have encryption, cybersecurity, and other safeguards that comply with federal and state privacy laws such as the Health Insurance Portability and Accountability Act and the Health Information Technology for Economic and Clinical Health Act, also known as HITECH.

Providers should educate patients on the proper protocols of virtual visits and describe the possible risks of seeking care remotely. They also need to be mindful that there will be an inherent lack of personal connection and continuity of care, which tend to reduce the risk of litigation in long-standing doctor-patient relationships.
What CMS data reveal about urology practice composition

More than a third of urologists work in a urology-dominant practice

Most of the demographic information about urologists in the United States today comes from the American Urological Association (AUA), an organization with 7415 active members. The self-reported information has been used to support concerns about urology manpower needs, the aging urology workforce, and other policy matters of interest to the specialty. The publicly available information cannot reliably describe other details of the contemporary urology practice: level of activity, who practices in a group setting, how large the group is, the number of specialties practicing in the same organization, etc. In this article, I will summarize data from another source of information that can begin to answer some of these questions and what it might mean for your practice.

AN ALTERNATIVE SOURCE OF INFORMATION
The Centers for Medicare & Medicaid Services (CMS) maintains several data sets of clinicians who participate in Medicare. Historically, it has been challenging to link providers to each other and to parent organizations in the National Provider Identifier (NPI) files where information has been inconsistently populated. CMS is now publishing a robust downloadable file associated with the Quality Payment Program (QPP). Updated every few weeks, this file is an alternative source of information about urology practice and may better reflect real-world practice circumstances because most of the included clinicians have participated in the QPP. CMS needs to identify relationships between organizations (essentially tax ID numbers) and clinicians (NPI numbers) to properly calculate scores and fee schedule adjustments. Those relationships can be derived from the downloadable file and inform us about urology practice. The data cannot tell us about supergroups (groups of groups), networks, or subgroups.

The CMS data include 9324 unique clinicians identified as urologists in 1921 unique organizations (1268 urologists are associated with more than 1 organization). A total 6672 of these clinicians in 1609 organizations received a final Merit-based Incentive Payment System score in 2019 (ie, were actively seeing Medicare patients). The file does not include age or birth year but does include the year of graduation from medical school—a rough proxy for age. Over two-thirds of the urologists in this Medicare data set graduated from medical school after 1990 (Table 1); 11% are women, and 89% are men. Fifty percent of urologists in this database practice in just 10 states (some urologists are associated with more than 1 state), and the average distribution of all urologists based on 2019 population estimates is 1 urologist per 34,323 people.

A total of 3285 urologists are associated with 408 organizations where urology is the dominant specialty (there are more urologists in the organization than any other single specialty). In 373 (91%) of these groups, urologists constitute at least 50% of the clinicians. The number of urologists in these 408 groups ranges from 1 to 118 (mean, 8.4; median, 4); only 43 groups have 20 or more urologists. The most common other specialties represented in the groups where urologists are the dominant specialty are physician assistants, nurse practitioners, radiation oncologists, and pathologists (Table 2). A total of 210 organizations have advanced practice partners (APPs; mean, 5 clinicians), 67 organizations have radiation oncologists (mean, 3.5), and 99 organizations have pathologists (mean, 1.7); 35 urology-dominant organizations have all 3 specialties. The size of these groups ranges from 2 to 281 clinicians (mean, 13; median, 5.5).

More than 3500 urologists are associated with organizations where urology is not the dominant specialty. These include very large organizations, such as health systems and universities, and much smaller organizations. The most common dominant specialties in these groups are primary care, APPs, and general surgery (Table 3). The size of these groups ranges from 43 to

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**TABLE 1.** Medicare Urology Clinicians by Decade of Medical School Graduation

<table>
<thead>
<tr>
<th>Graduation decade from medical school</th>
<th>Clinicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>1950s</td>
<td>9</td>
</tr>
<tr>
<td>1960s</td>
<td>225</td>
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<tr>
<td>1970s</td>
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<td>2000s</td>
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</tr>
<tr>
<td>2010s</td>
<td>1541</td>
</tr>
<tr>
<td>No date</td>
<td>15</td>
</tr>
</tbody>
</table>

Adapted from Centers for Medicare & Medicaid Services national downloadable file by Robert A. Dowling, MD.
7478 clinicians (mean, 486; median, 255); the urologists’ number ranges from 1 to 104 (mean, 6.5; median, 4).

Finally, the data include all unique practice locations for an individual clinician. The number of unique locations associated with 9234 unique urologists ranges from 1 to 55 (mean, 2.4; median, 1) than those urologists associated with urology-dominant groups have fewer unique locations per clinician (range, 1-12; mean, 2.0; median, 1) than those urologists associated with organizations where urology is not dominant (range, 1-55; mean, 2.3; median 1). Twenty-one percent of urologists in urology-dominant practices were associated with more than 3 addresses vs 29% of urologists in the other practices.

This analysis comes with caveats. First, the information may not be generalizable to the entire specialty, as some providers may not participate in Medicare. Second, many individual clinicians are associated with more than 1 organization—it isn’t possible to know which of the associations are primary in these cases. Similarly, it isn’t possible to know which of the associated practice addresses are active or inactive. It isn’t possible to reliably identify solo practices in these data—some urologists practicing by themselves may be part of a common billing organization. Finally, most of the information in this file is self-reported, such as year of graduation from medical school and name of medical school, and some clinicians have incomplete data. It is not possible to verify the accuracy of self-reported data.

MAKING SENSE OF THE DATA
What does this mean for your practice and your patients? The CMS downloadable file provides interesting food for thought. Physicians may be best positioned to control the clinical and business aspects of their practice if they are the dominant group in the parent organization. The Medicare data suggest that about 35% of urologists are in organizations they dominate (what might have once been called single-specialty groups). This compares favorably with general surgery (17%), cardiology (28%), and orthopedic surgery (31%). Many providers are probably familiar with factors that have caused specialists to consolidate, and these data help quantify that consolidation—at least among Medicare providers. Urology-dominated groups appear to have a foothold, which is good news for those who prefer this model of practice. Others might argue that a multispecialty model offers the potential for better care coordination and value-based care.

These data do not help answer that question but suggest that a majority of urologists practice in organizations where they are not the dominant specialist—at least among Medicare providers. One size does not fit all [urologists] today, but the demands of patients and payers are likely to shape the landscape of tomorrow.

### Table 2. Top Specialties in Organizations Where Urology is the Dominant Specialty

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Clinicians</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>All specialties</td>
<td>5129</td>
<td>408</td>
</tr>
<tr>
<td>Urology</td>
<td>3285</td>
<td>408</td>
</tr>
<tr>
<td>Physician assistant</td>
<td>557</td>
<td>153</td>
</tr>
<tr>
<td>Nurse practitioner</td>
<td>505</td>
<td>162</td>
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<tr>
<td>Radiation oncology</td>
<td>226</td>
<td>67</td>
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<tr>
<td>Pathology</td>
<td>116</td>
<td>99</td>
</tr>
<tr>
<td>General surgery</td>
<td>68</td>
<td>18</td>
</tr>
<tr>
<td>Certified registered nurse anesthetist</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>Diagnostic radiology</td>
<td>30</td>
<td>18</td>
</tr>
<tr>
<td>Obstetrics-gynecology</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>Otolaryngology</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>26</td>
<td>12</td>
</tr>
</tbody>
</table>

Adapted from Centers for Medicare & Medicaid Services national downloadable file by Robert A. Dowling, MD.

### Table 3. Top Specialties in Organizations Where Urology Is Not the Dominant Specialty

<table>
<thead>
<tr>
<th>Specialty</th>
<th>Clinicians</th>
<th>Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>All specialties</td>
<td>530,113</td>
<td>804</td>
</tr>
<tr>
<td>Urology</td>
<td>5522</td>
<td>804</td>
</tr>
<tr>
<td>Internal medicine</td>
<td>51,134</td>
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<tr>
<td>Nurse practitioner</td>
<td>60,151</td>
<td>791</td>
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<tr>
<td>Physician assistant</td>
<td>34,347</td>
<td>774</td>
</tr>
<tr>
<td>Family medicine</td>
<td>40,504</td>
<td>773</td>
</tr>
<tr>
<td>General surgery</td>
<td>12,398</td>
<td>771</td>
</tr>
<tr>
<td>Cardiovascular disease (cardiology)</td>
<td>12,356</td>
<td>731</td>
</tr>
<tr>
<td>Obstetrics-gynecology</td>
<td>15,800</td>
<td>727</td>
</tr>
<tr>
<td>Neurology</td>
<td>10,994</td>
<td>720</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>6701</td>
<td>701</td>
</tr>
<tr>
<td>Orthopedic surgery</td>
<td>9660</td>
<td>697</td>
</tr>
</tbody>
</table>

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### REFERENCES
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Long-term disability insurance: Worth the expense for physicians?

A policy can help protect your substantial earning potential

Q. I received a quote for supplemental long-term disability insurance, and the cost was higher than expected. Is long-term disability worth this added expense?

A. The simple answer is usually yes. Long-term disability insurance is often worth the added expense. A physician’s most valuable asset is their ability to practice and earn income in their specialty field for an extended period of time. Physicians can generate millions of dollars of income throughout their working lives, and it is important to protect this earning potential. Without the income generated from practicing medicine, a physician may need to forfeit many of their financial goals, such as purchasing a new home, paying for their children’s college education, or even retiring comfortably. Long-term disability insurance can ensure that many of these goals are reached, even in the event of a long-term sickness or disability.

You may be asking, “What are the chances of becoming sick or disabled and needing a long-term disability policy?” The answer is higher than you may think. A typical man, age 35, 5 ft 10 in, 170 lb, nonsmoker, with some outdoor physical activity, and who leads a healthy lifestyle has a 24% chance of becoming disabled for 3 months or longer during his working career. A typical woman, age 35, 5 ft 4 in, 125 lb, nonsmoker, with some outdoor physical activity, and who leads a healthy lifestyle has a 21% chance of becoming disabled for 3 months or longer during her working career. Long-term disability is a legitimate concern and one worth protecting against.

How does long-term disability insurance work? Typically, a disability insurance company is willing to insure up to 60% to 70% of a physician’s predisability income. In the event of a disability, the policy will pay out a monthly benefit amount. These funds can be used to pay for necessary expenses and save for financial goals, such as retirement. Pay attention to these key terms when considering purchasing a disability insurance policy:

**Elimination period.** This refers to the amount of time the insured must be sick or disabled and not working before the policy will start paying out a benefit. Common elimination periods are 90, 180, and 360 days.

**Benefit period.** This is the length of time the policy will pay out a benefit in the event a claim is made. A physician should always consider a policy that lasts until retirement age. The maximum benefit period typically offered is between ages 65 and 70. The thought is at these ages, a person becomes eligible for Social Security and Medicare.

**Definition of disability.** Physicians should consider True Own Occupation definitions to safeguard their specialty skill set. True Own Occupation ensures that if a physician is unable to work in their specialty field, the policy will still pay out the full benefit, even if they are able to work in another field. Compare this with just an Own Occupation or Any Occupation definition, which says if you can work in any capacity, the income earned from that job will either reduce or eliminate the benefit being paid out by the policy.

Typically, a disability insurance company is willing to insure up to 60% to 70% of a physician’s predisability income.

When should you consider getting disability insurance? As soon as possible. The younger you are, the lower the premiums will be. Additionally, the younger you are means there are likely to be fewer red flags in your medical history that could cause the disability insurance company to exclude certain disabilities or completely reject you for coverage.

If you are still in a residency or fellowship program, many companies will offer as high as a 20% discount if you get a policy while still in your training. When can you drop your disability coverage? Some physicians consider dropping disability coverage when they believe they have sufficient assets to produce the inflation-adjusted income they need for the rest of their lives, even if they are no longer able to work. This requires a careful assessment of their financial and health situations.

Insurance can sometimes be seen as an annoyance and something rarely used. However, disability insurance is important, as it protects your most valuable asset—your ability to practice medicine and earn income in your specialty field. It may be the difference between accomplishing all your goals or accomplishing none of them.

**REFERENCE**

How has the resurgence of the pandemic affected your practice?

Nina Davis, MD, FACS
Portland, Oregon

Pandemic 2 is far worse. The only good news is that we planned for this originally, so we have options for delivering care. Our intensive care unit [ICU] is 100% full, so we turned our recovery room into another ICU. Luckily, we haven’t had to go to the next level and set up a ward in the auditorium.

The [US] Air Force came to help with things that don’t require medical skill—like screening guests at the door.

Pandemic 2 really locked us up. It’s much worse than before. Individuals were coming back to the office; now they’re retreating home to do patient care.

A lot of us—oncologists particularly or ones, like me, who do female medicine—must examine patients. I can’t do much surgery because mine is mostly elective.

Patients started coming out with the vaccine but now they’re retreating. It’s difficult to get individuals to follow up.

Many elderly patients aren’t computer literate, so they can’t do virtual visits. I won’t do new patients on the phone. You can’t form a therapeutic relationship over the phone—I’m sorry. Face-to-face, there’s more opportunity to establish a connection.

During emergencies like this, the VA [Veterans Affairs] reaches out and takes civilian patients. The VA provides tertiary clinical care when the university can’t.

I treat patients with multiple sclerosis [MS]. During the first phase, we had no losses. The MS population did awesome. Now, however, we’re getting secondary cases; I’ve had people hospitalized. It makes me sad because they’re doing everything right. Now, they’re evidently quite susceptible to Delta [variant] and we’re almost 100% Delta in this state. It spread fast because we have so many unvaccinated.”

Yusef Salem, MD
Alexandria, Virginia

The resurgence hasn’t affected us too much here in Virginia. Because of precautions, we aren’t getting hit as hard.

One impact is the hospital’s seeing a staff shortage, especially nurses. Our hospital system went out of the country to hire nurses from different countries because they can’t get enough here.

It affects us because it’s hard to find staff for the right job. We have high turnover. It’s hard to find somebody with experience. We hire somebody, train them, and after a few months some of them are overwhelmed by the work and leave. Then we must do it again. Health care is hard because you have contact with patients. That increases your risk.

Urology is a bit different because patients come in for a specific need. They have symptoms that simply cannot wait—a staph infection, bleeding, or stones. Those patients really can’t delay.

Patients who need medication for ED or other medication refills don’t have to come in. Their needs are met without risking exposure in the office.

We are affected financially, however, because much of what urologists do are procedures, like cystectomies. Telehealth appointments aren’t as beneficial to the practice because often patients are charged based on time spent and the complexity of the visit. We lose a lot of revenue because we’re not doing a cystoscopy- or urodynamics—all of which make money, maybe 30% to 40% of practice revenue. We had to stop doing them, so practice income is affected.”

Yousef Salem, MD
Alexandria, Virginia

“Nashville is getting hit really hard. Fortunately, or unfortunately, we got hit hard the first time. We learned a lot, so we were able to quickly transition back to telemedicine where appropriate. We also canceled our more elective cases when it got bad.

Vanderbilt [University Medical Center] had to do strategic redeployment of providers of all specialties to help accommodate overflow intensive care units [ICUs], and critical care doctors who are caring for patients with COVID-19.

I’m more likely to get with patients who are following up for routine care over the phone or our online portal instead of them coming in.

Patients are more wary of undergoing surgery. I’ve had several who decided to hold off until COVID-19 is under better control.

ICUs are overwhelmed, between providers getting sick themselves or the number of patients they’re caring for. They’re asking other providers to assist in the ICU, just to have manpower.

We’re continuing with high-priority patients with cancer, important or life-threatening cases, but the truly, purely elective cases are being held off.

We look at it on a day-to-day basis. It’s not just a blanket shutdown. We look at the census; talk to the surgery board; look at how many and types of beds are available. The day before surgery, we coordinate with all the surgical specialties, shutting down a room, cancelling cases as necessary, if staffing’s unavailable.

Patients in the community may hesitate to go to Nashville because of the larger population and the way COVID-19 is. They prefer to stay in their smaller town or in the country.”

Jacob A. McCoy, MD
Nashville, Tennessee
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