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COVER PHOTO CREDIT: SCIEPRO@STOCK.ADOBE.COM
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EDITORIAL
Kristie L. Kahl, Vice President, Content
kkahl@mjhlifesciences.com
Jason M. Broderick, Associate Editorial Director
609-716-7777 | jbroderick@mjhlifesciences.com
Benjamin P. Saylor, Content Managing Editor
440-826-2870 | bsaylor@mjhlifesciences.com
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PUBLISHING AND SALES
Brian Haug, Executive Vice President
609-325-4780 | bhaug@mjhlifesciences.com
John Hydrusko, Vice President, Sales
jhydrusko@mjhlifesciences.com
Paul Barcikita, National Account Manager
718-354-6178 | pbarcikita@mjhlifesciences.com
Juliana Rice, National Account Associate
609-819-5617 | jrice@mjhlifesciences.com
Joanna Shipkiss, Account Manager, Recruitment
440-891-2615 | jshipkiss@mjhlifesciences.com
Eric Temple-Morris, Reprints, Permissions, Licensing
415-947-6231 | etemple-morris@mjhlifesciences.com

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Urologists in Cancer Care™ provides practicing urologists with practical, expert, multidisciplinary perspective on clinical advances and issues in genitourinary cancer. As a quarterly supplement to Urology Times™, Urologists in Cancer Care™ offers readers updates in prostate, bladder, kidney, and testicular cancer.

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At the end of this past year, it seemed as though much of the “buzz” in the urology world revolved around the gonadotropin-releasing hormone (GnRH) agonist relugolix (Orgovyx), which the FDA approved in December 2020 for the treatment of advanced prostate cancer. In this issue of Urologists in Cancer Care™, Elizabeth Pan, MD, and Rana R. McKay, MD, examine GnRH agonists and antagonists and discuss the many factors that play into the decision-making process when weighing these treatments. There are also adverse events (AEs) to consider when discussing these agents.

“Hormone therapy can significantly impact quality of life, and incorporating strategies to minimize AEs can be crucial,” Pan and McKay write.

In his From the Editor article, Urologists in Cancer Care™ Editor in Chief Raoul S. Concepcion, MD, FACS, makes mention of an exciting new addition to the publication. Beginning with this issue, Urologists in Cancer Care™ will include an article on genomics in genitourinary cancers in each issue. Be sure to read this issue’s unique and insightful piece from Justin Wright, MA, MBA, titled “A Primer on DNA Sequencing.” Wright opens with the premise: “Have you ever wondered what exactly happens to a patient sample when it disappears into a laboratory’s ether?... The answer is: a lot.” From there, Wright takes the reader through the history of genetic sequencing and polymerase chain reaction and also describes the clinical laboratory’s workflow. It is a fascinating read and a great way to kick off this new component of Urologists in Cancer Care™.

This issue of Urologists in Cancer Care™ also contains 2 case-based articles. The first article looks at updates in advanced imaging prostate cancer through discussion of a 62-year-old man with newly diagnosed cT1c prostate cancer.

The second is a recap from the monthly urologic live virtual event Around the Practice, which features case reviews from multidisciplinary experts, presented by Urology Times® in partnership with LUGPA. The discussion involves high-risk renal cell carcinoma in a 51-year-old man. You can catch up on past installments of Around the Practice at www.urologytimes.com/aroundthepractice.

As hard as it is to believe that we are nearly into summer, before we know it, it will be fall and with it “meeting season.” I am greatly anticipating the return of in-person scientific meetings, such as the American Urological Association annual meeting in September, as I’m sure many of you are. Take care, and thanks for reading.
Embracing change

RAOUL S. CONCEPCION, MD, FACS

For the most part, for progress to take place, change is inevitable. And change is often very difficult. As someone once told me, if you make a change in your golf swing and it is easy, more than likely you have not changed anything. The urology community has been very progressive over the decades, embracing changes in our clinical world that have led to optimizing patient care while maintaining control, if you will, of the disease states we are accustomed to treating. Although at times this has resulted in fewer operative procedures, which for many physicians is the reason we entered the field, the end result has been better patient outcomes.

Advances in technology generally are the driving force behind these changes, and fortunately, many forward-thinking urologists have been keen in applying them to our field. In the early 1920s, William T. Bovie, working alongside the acknowledged father of neurosurgery, Harvey Cushing, MD, was one of the first pioneers to demonstrate the advantages of electrocautery to stem bleeding in the surgical field. A decade later, a urologist in South Carolina, Theodore M. Davis, MD, was able to adapt this technology and incorporate both a cutting and cautery feature into the modern endoscope. Thus the birth of transurethral resection of the prostate, which continues to be the gold standard in which all newer therapies, including medical and minimally invasive, must show noninferiority.

For those of us who trained before 1990, prostate biopsy could be considered a form of medieval torture. Blind and either transrectal or transperineal, its complication rates of bleeding and sepsis were extraordinarily high, not to mention the suboptimal sampling due to the lack of imaging and inability to obtain quality samples. Fortunately, a number of our predecessors were prescient enough to adopt prostate ultrasound and template sextant biopsy, which have now led to MRI fusion techniques, again driven by our colleagues. Somewhat forgotten in this discussion is the perseverance of many during that time frame to have practicing urologists trained in prostate ultrasound, wrestling that away from our radiology colleagues. Had those efforts not been successful, it is unclear to me how our current practices might look today.

As alluded to earlier, many of us chose the field of urology for the surgical aspect of the specialty. From an oncologic perspective, mastering the art of nerve-sparing radical retropubic prostatectomy was key to developing a surgical practice. Identification of the neurovascular bundle obviously is a mandate, but controlling bleeding from the Santorini plexus early in the course of the procedure is truly what makes the procedure possible for adequate visualization in a relatively bloodless field. The principles remain the same, but open surgery has now given way to robotically assisted extirpation, which is what most patients opt for when they choose surgical intervention. But as our understanding of the biology of prostate cancer continues to evolve, we must also understand and accept that all prostate cancers do not necessarily need immediate treatment and that active surveillance is truly an option. It is somewhat against our surgical mentality, but it is the correct option for the appropriately identified patient.

In line with this theme, the late 2000s saw the emergence of new therapies for patients with advanced prostate cancer. Many urologists and practices were (and still are) slow to incorporate them into their model for a number of reasons. Probably the most commonly cited is the lack of expertise in prescribing such agents, which was not part of surgical training and belonged more to a “typical” medical oncologist. This paradigm continues to change with the realization that the urologist is perfectly suited to and capable of prescribing and managing these drugs. More importantly,
The FDA has approved the PSMA PET imaging agent 18F-DCFPyL (Pylarify) for identifying suspected metastasis or recurrence of prostate cancer. The approval is based on findings from the CONDOR and OSPREY studies.

The multicenter phase 3 CONDOR study enrolled men with rising prostate-specific antigen (PSA) after definitive therapy and negative or equivocal standard-of-care imaging. Patients were required to have a PSA level of 0.2 ng/mL or higher if they had undergone radical prostatectomy (RP) or a PSA level of 2.0 ng/mL or higher if they were treated with radiation therapy or cryotherapy.

The primary end point was correct localization rate (CLR), defined as percentage of patients with a 1:1 correspondence between at least 1 lesion identified by PyL-PET/CT and the composite standard of truth (pathology, correlative imaging, or PSA response). PyL scans were read by 3 blinded independent central readers.

Detection of disease as manifested by a positive 18F-DCFPyL-PET/CT scan was 65.9%, 59.6%, and 59.1% by the 3 readers. The CLRs were 85.6% (95% CI, 78.8%-92.3%), 87.0% (95% CI, 80.4%-93.6%), and 84.8% (95% CI, 77.8%-91.9%) by the 3 readers. Some 64% of the evaluable patients had a change in intended management because of the scan.

In the phase 2/3 OSPREY trial, PyL was assessed in 2 patient cohorts. Cohort A included men with high-risk, locally advanced prostate cancer, and the investigators assessed the capacity of PyL to detect prostate cancer in pelvic lymph nodes. Cohort B comprised patients with metastatic or recurrent disease, and the investigators examined the performance of PyL in detecting distant metastases.

In cohort A, results for PyL in detecting disease in pelvic lymph nodes showed a specificity of 96% to 99%, a sensitivity of 31% to 42%, and positive predictive value (PPV) of 78% to 91%. The sensitivity and PPV rates for detecting metastatic lesions in cohort B were 93% to 99% and 81% to 88%, respectively.

REFERENCES
GnRH agonists vs antagonists: How to choose

Many factors play into the decision-making process when weighing agents in prostate cancer

Elizabeth Pan, MD; Rana R. McKay, MD

In the 1940s, Huggins and Hodges’ Nobel Prize–winning work firmly established the therapeutic effect of testosterone deprivation in the treatment of prostate cancer. Since that time, hormonal treatments for prostate cancer have undergone continued advancement. In the modern era, the backbone of therapy is in the form of gonadotropin-releasing hormone (GnRH) agonists and antagonists, which decrease testosterone to the castrate range. This class of agents has distinct mechanisms of action and safety profiles that warrant attention because they optimize treatment for patients with prostate cancer. Herein, we describe the different mechanisms of action and safety profiles of GnRH agonists and antagonists and discuss their use in clinical practice.

GnRH is a peptide hormone synthesized and released by the hypothalamus to stimulate the synthesis and secretion of the gonadotropins luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland. GnRH is typically produced in a pulsatile fashion, and its synthesis is regulated by circulating levels of testosterone and estrogen. LH acts on Leydig cells in the testes to secrete the majority of the body’s testosterone, whereas FSH targets Sertoli cells in the seminiferous tubules of the testis to regulate spermatogenesis. Androgens then promote prostate cancer growth via activation of cytoplasmic androgen receptors.

GnRH agonists were introduced in 1984 and act via continuous GnRH receptor stimulation that differs from the normal physiologic pulsatile effects of GnRH. Continuous signaling initially causes a surge in testosterone and then leads to a drop-off in endogenous hypothalamic GnRH production and downregulation of pituitary GnRH receptors through overstimulation from the GnRH agonist, resulting in decreased LH and FSH levels and downstream castrate levels of testosterone.

The adverse events (AEs) of GnRH analogues are largely due to the impact of these agents on androgen levels. Androgen deprivation therapy (ADT) leads to hypoandrogenism in men, manifested as fatigue, vasomotor symptoms including hot flashes, decreased libido, erectile dysfunction, and gynecomastia. ADT can also impact cardiovascular, bone, and muscle health and cause cognitive/psychiatric changes. Effects on glucose and lipid metabolism have been noted, with data suggesting that low testosterone levels lead to insulin resistance, central obesity, hypercholesterolemia and hypertriglyceridemia, and other precursors of metabolic syndrome.

GnRH antagonists suppress LH and FSH more effectively than LHRH agonists and are associated with fewer cardiotoxicities. Several hypotheses have been proposed in attempts to explain how this mechanistic difference affects cardiac outcomes. Stimulation of FSH receptors on the endothelial surface of proliferating tissues could lead to decreased lipid metabolism and increased fat accumulation, leading to increased cardiovascular risk with GnRH agonists. Additionally, GnRH agonists, but not antagonists, bind to and stimulate GnRH receptors on T cells that could result in a hyperinflammatory state causing plaque destabilization.

One disadvantage of GnRH agonists is tumor flare from the initial testosterone surge, which can be seen in up to 63% of patients with advanced prostate cancer. Complications from tumor flare can lead to urethral obstruction, worsening pain, and cord compression in more severe cases. Antiandrogens are usually given pri-
or to GnRH agonist administration to mitigate this flare phenomenon. GnRH antagonists were evaluated in efforts to find alternative agents not associated with a testosterone surge. GnRH antagonists act via direct competitive inhibition of the GnRH receptor, thereby blocking its downstream signaling and leading to a rapid decrease in LH, FSH, and testosterone levels. Abarelix (Plenaxis) was the first direct GnRH antagonist approved by the FDA (in 2003) for advanced, symptomatic prostate cancer. The phase 3 clinical trials that led to its approval showed that when compared with leuprolide or leuproline plus an antiandrogen, abarelix monotherapy had a faster time to medical castration and a greater percentage decrease in prostate-specific antigen.10,11

Unfortunately, abarelix in clinical practice was associated with a higher rate of potentially life-threatening hypersensitivity reactions that eventually led to its withdrawal from the US market in 2005.12 It wasn’t until 2008 that the GnRH antagonist degarelix (Firmagon) was approved, and in December 2020, relugolix (Orgoyx), the first oral-formulated GnRH analogue, was added to the short list of GnRH antagonists.6

Pivotal clinical trials
ADT with GnRH agonists and antagonists has a role in the treatment of prostate cancer in the local or locally advanced, relapsed/recurrent, advanced/metastatic, and palliative settings.

A pivotal phase 3 clinical study (NCT00295750) compared the efficacy and safety profile of degarelix with leuprolide. The study population was men with prostate cancer of any stage determined to be candidates for ADT, including patients with metastatic disease or biochemical progression with less than 6 months of prior ADT given in the neoadjuvant or adjuvant setting with curative-intent local therapy.

Results showed that degarelix was not only noninferior to leuprolide in the primary end point of suppressing testosterone to 0.5 ng/mL or lower at all monthly measurements for 1 year, but also significantly faster in achieving castrate levels of testosterone in 3 days compared with 28 days for leuprolide. Additionally, degarelix lacked observed testosterone surge and maintained undetectable testosterone levels throughout the 1-year treatment period.6

Degarelix was the only approved LHRH antagonist in the US until relugolix was recently added to the treatment armamentarium for prostate cancer. In the phase 3 HERO trial (NCT03085095) that led to the FDA approval of relugolix, patients with advanced prostate cancer received either oral relugolix daily or leuprolide injections every 3 months for 48 weeks. The study population was comprised of patients with prostate cancer who were eligible for at least 1 year of continuous ADT in the setting of either biochemical or relapsed disease following local definitive therapy, newly diagnosed hormone-sensitive metastatic disease, or locally advanced disease unlikely to be cured with local definitive therapy.

The addition of an antiandrogen to leuprolide was left to the investigator’s discretion, and 23 of 201 (11%) patients in the leuprolide group received concomitant antiandrogen. Relugolix was found to be superior to leuprolide in its ability to maintain castration-level testosterone (96.7% vs 88.8%, respectively; \( P < .001 \) for superiority), as well as superior in the time to testosterone suppression (4 days vs 29 days) and proportion of patients with testosterone recovery to normal range within 90 days of treatment discontinuation (54% vs 3%).6 Testosterone recovery can be clinically relevant for patients receiving either intermittent or short-course ADT or for those suffering from significant ADT AEs or other disease-related complications. However, the HERO trial did not evaluate patients who received ADT with definitive local therapy, and therefore the role in this context is less defined.

GnRH agonist vs GnRH antagonist
The decision to use a GnRH agonist vs antagonist depends on several factors. Given the shorter time to testosterone suppression and lack of testosterone surge, GnRH antagonists may be more clinically beneficial for patients with more advanced disease and at higher risk of developing prostate cancer–related symptoms.13 Additionally, the absence of tumor flare with GnRH antagonists may seem especially appealing in patients with impending cord compression or urethral obstruction; however, GnRH agonists in conjunction with antiandrogen agents for flare prophylaxis have been shown to achieve similar effects.14

From a practical standpoint, degarelix is given on a monthly basis compared with the less frequent dosing options of GnRH agonists. With oral relugolix, issues of adherence and the likely need for continual testosterone monitoring are possible barriers that are not routinely of concern for patients receiving injection therapy.

AE profiles also play a large role in the selection of a GnRH agonist or antagonist. Both the phase 3 degarelix trial and the HERO trial...
showed that AEs were similar across all treatment groups, with flushing/hot flashes being the most common AE. Relugolix had increased reports of diarrhea compared with leuprolide. Leuprolide had higher rates of arthralgia and urinary tract infection compared with degarelix, whereas degarelix was associated with more injection-site reactions.

One of the notable findings from the HERO trial was the differential cardiovascular profile between the 2 agents. Although the trial included patients with a distant history of cardiovascular events, patients with major cardiovascular events 6 months prior to trial enrollment were excluded. Relugolix had a lower incidence of major cardiovascular events in the overall study population (2.9% vs 6.2%, respectively) and in patients with a prior history of a major cardiovascular event (3.6% and 17.8%). The latter findings are particularly notable given the association between hormone therapy and cardiovascular events and the aforementioned mechanistic differences between GnRH agonists and antagonists on FSH. Even prior to data from the HERO study, observational studies and meta-analyses demonstrated that patients with preexisting cardiovascular disease have a higher risk of cardiovascular morbidity and mortality with GnRH agonists compared with GnRH antagonists.

The link between cardiotoxicity and ADT prompted a phase 2 trial that prospectively assessed serum cardiac biomarkers in patients with prostate cancer with underlying cardiovascular disease who were treated with GnRH agonists or antagonists. Findings from that study showed that patients with baseline elevations in N-terminal pro-brain natriuretic peptide, dimerized plasmin fragment D, C-reactive protein, and high-sensitivity troponin had higher incidences of cardiovascular AEs when treated with LHRH agonists but not antagonists. It was suggested by the authors that patients with known cardiovascular disease who are candidates for ADT may benefit more from a GnRH antagonist.

There has yet to be a prospective study evaluating cardiovascular outcomes in ADT-treated patients with cardiovascular disease; however, ongoing trials such as the PRONOUNCE study (NCT02663908) may help further elucidate this. Differences with regard to other ADT-associated AEs are less defined. In a study comparing the GnRH antagonist degarelix with leuprolide, degarelix was associated with more-pronounced reductions in serum alkaline phosphatase; however, whether this translates to an impact on bone strength or fracture risk remains to be determined.

Final thoughts
Hormone therapy can significantly impact quality of life, and incorporating strategies to minimize AEs can be crucial. When the more common AEs of ADT arise—such as muscle loss, weight gain, decreased libido, and fatigue—a supervised exercise program or resistance training can limit or potentially reverse some of them. Additionally, ADT can accelerate bone resorption, which comprises bone integrity and increases the risk of osteoporotic fractures. Interventions to preserve bone health include calcium and vitamin D supplementation, fracture risk assessments, and use of antiresorptive therapy with denosumab or bisphosphonates. Regarding cardiotoxicity, optimizing preexisting cardiovascular conditions prior to ADT initiation is recommended.

Although not yet investigated, medications such as β-blockers, angiotensin-converting enzyme inhibitors, or low-dose rivaroxaban, as well as modified lifestyle interventions and increased cardiac monitoring, may have beneficial effects in patients receiving ADT. Intermittent androgen deprivation (IAD) has also been utilized in clinical practice and involves alternating on- and off-treatment periods. Several phase 2 and phase 3 randomized, controlled trials comparing IAD with continuous androgen deprivation (CAD) have shown that IAD can decrease AEs while maintaining or improving quality of life and preserving the overall survival and progression-free survival benefits of CAD. However, these findings must be interpreted with caution because a majority of these studies included only patients with nonmetastatic disease.

In general, many factors play into the decision-making process when choosing between a GnRH agonist and antagonist. Additional studies are needed to better understand the relationship between different ADT agents and their toxicity profiles so that treatment selection and management strategies can be optimized.

ABOUT THE AUTHOR

PAN
is a hematology/oncology fellow at the University of California San Diego, La Jolla.

McKAY
is an associate professor of medicine and urology at the Moores Cancer Center at the University of California San Diego, La Jolla.

For full reference list, visit

UCC0621_013-015_PCa Scientific Review GNRH agonists.indd 15
**INDICATION**

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

**IMPORTANT SAFETY INFORMATION**

**Warnings and Precautions**

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

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

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

**Adverse Reactions**

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

**ORGOVYX achieved sustained testosterone suppression**

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

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

![Graph showing sustained testosterone suppression rates for ORGOVYX and Leuprolide](image)

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

CI=confidence interval.

†Kaplan-Meier estimates within each group.

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

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

§Two patients in each arm did not receive the study treatment and were not included.
Introducing ORGOVYX, the only once-a-day* oral androgen deprivation therapy for advanced prostate cancer1,2

*One pill, once a day, after initial loading dose of 3 pills.

ORGOVYX offers a new option for testosterone control13

- **RAPID TESTOSTERONE SUPPRESSION WITHOUT A SURGE**: 56% of men treated with ORGOVYX achieved testosterone suppression to <50 ng/dL on Day 4 - 0% of men treated with leuprolide had testosterone levels <50 ng/dL on Day 4
- **PROFOUND TESTOSTERONE SUPPRESSION**: 95% of men treated with ORGOVYX achieved profound testosterone suppression to <20 ng/dL on Day 29 - 57% of men treated with leuprolide had testosterone levels <20 ng/dL on Day 29
- **90-DAY TESTOSTERONE RECOVERY**: in a substudy, 55% of the 137 men treated with ORGOVYX had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after treatment discontinuation1,2 - 3% of 47 men treated with leuprolide had their testosterone return to above the lower limit of the normal range (>280 ng/dL) or baseline values 90 days after discontinuation

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

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

**Drug Interactions**

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

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

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

**References:**


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BRIEF SUMMARY

ORGOVYX™ (relugolix) tablets, for oral use

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

1 INICATIONS AND USAGE

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

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 QT/QTc Interval Prolongation

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

5.2 Embryo-Fetal Toxicity

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

5.3 Laboratory Testing

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

6 ADVERSE REACTIONS

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

• QT/QTc Interval Prolongation.

6.1 Clinical Trials Experience

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

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

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

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

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

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

Table 1 summarizes the adverse reactions in HERO.

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

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

†Includes fatigue and asthenia.

‡Includes diarrhea and colitis.

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

Table 2 summarizes the laboratory abnormalities in HERO.

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

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

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on ORGOVYX

P-gp Inhibitors

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

If co-administration is unavoidable, take ORGOVYX first, separate dosing by at least 6 hours, and monitor patients more frequently for adverse reactions. Treatment with ORGOVYX may be interrupted for up to 2 weeks for a short course of treatment with certain P-gp inhibitors.

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

Combined P-gp and Strong CYP3A Inducers

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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

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

Data

Animal Data

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

8.2 Lactation

Risk Summary

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

Data

Animal Data

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

8.3 Females and Males of Reproductive Potential

Contraception

Males

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

Infertility

Males

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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

12.3 Pharmacokinetics

Specific Populations

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

Drug Interactions Studies

Clinical Studies

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

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

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

In Vitro Studies

Cytochrome P450 (CYP) Enzymes: Relugolix is a substrate of CYP3A and CYP2C8. Relugolix is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2D6, or CYP3A4. Relugolix is an inducer of CYP2B6 and CYP26B1, but not an inducer of CYP1A2.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

In human GnRH-receptor knock-in mice, oral administration of relugolix decreased prostate and seminal vesicle weights at doses ≥ 3 mg/kg twice daily for 28 days. The effects of relugolix were reversible, except for testis weight, which did not fully recover within 28 days after drug withdrawal. In a 59-week repeat-dose toxicity study in monkeys, there were no significant effects on male reproductive organs at oral relugolix doses up to 50 mg/kg/day (approximately 53 times the human exposure at the recommended dose of 120 mg daily based on AUC).

13.2 Animal Toxicology and/or Pharmacology

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

17 PATIENT COUNSELING INFORMATION

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

GT/GtC Interval Prolongation

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

Androgen Deprivation

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

Embryo-Fetal Toxicity

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

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

Infertility

- Inform patients that ORGOVYX may cause infertility.

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

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

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Update on advanced imaging in prostate cancer

Advances allow for more accurate detection of metastatic disease

Jacob E. Tallman, MD; Christopher J.D. Wallis, MD, PhD, FRCSC; and Kristen R. Scarpato, MD, MPH

THE CASE
To contextualize the rapidly evolving landscape of evaluation of patients with prostate cancer, consider a case example: A 62-year-old White man presents for consultation because of an elevated prostate-specific antigen (PSA) level of 8.2 ng/dL that was confirmed on repeat testing. He has no prior values available for comparison. Symptomatically, he has an American Urological Association symptom score of 11 without other complaints. His medical history is unremarkable with only hypertension, for which he takes amlodipine 5 mg daily and a baby aspirin. He’s undergone a laparoscopic cholecystectomy. He has no known drug allergies and is married with 2 healthy adult male children. Notably, his family history includes prostate cancer in his father (diagnosis at age 58 years and alive) and breast cancer in his paternal grandmother (diagnosis at age 50 years and now deceased from the disease).

On physical examination, the prostate is estimated at 50 g, symmetric, and without nodules or induration. The patient undergoes a prebiopsy multiparametric MRI scan, which demonstrates a prostate volume of 65.3 cc and a Prostate Imaging Reporting and Data System 4 lesion at the right peripheral zone (base, 1.2 cm). He then undergoes a fusion biopsy; the pathologic results show:

- Target lesion: 2 of 3 cores (+), grade group (GG) 4, approximately 65% involved
- Systematic Bx: 6 of 12 cores (+)
- R base: 2 of 2 cores (+), GG 4, approximately 70% involved
- R mid: 1 of 2 cores (+), GG 4, < 50% involved
- R apex: 1 of 2 cores (+), GG 3, < 50% involved
- L base: 2 of 2 cores (+) GG 3, approximately 60% involved

Staging
This patient has newly diagnosed cT1c prostate cancer, which is very high risk—according to the National Comprehensive Cancer Network (NCCN) criteria—because of the presence of more than 4 cores of GG 4 disease.

As we evaluate this patient, our goal is to accurately determine his current and future risk of disease spread to inform treatment, prognosis, and counseling. Current guidelines recommend staging with conventional imaging (CT or MRI, and bone scan) as well as genetic testing. However, advances in staging imaging are allowing more accurate detection of metastatic disease and play an increasingly large role in other parts of the world, with adoption in the US expected to follow.

Guideline-concordant conventional imaging in patients with high- and very high-risk disease includes abdominopelvic cross-sectional imaging, often a CT scan, and a technetium-99m methylene diphosphonate bone scintigraphy scan. Multiparametric MRI (mpMRI) has emerged in the past 5 to 10 years as a common staging imaging modality, and NCCN guidelines endorse the superiority of mpMRI compared with abdominopelvic CT for staging.1

For this patient, we would follow a current guideline-based approach and complete his staging with a nuclear medicine bone scan to complement his mpMRI. If the bone scan is negative for evidence of metastasis, he falls into a group of men with apparently localized disease who are at high risk for recurrence despite appropriate primary therapy, likely because of the inability of conventional imaging to identify small metastases at low PSA levels. Closing this gap in diagnostic accuracy is an area of active research.

Newly published data suggest that advanced imaging techniques using PET-CT may complement or supplant conventional imaging in the near future. The use of PET-CT in prostate cancer in the US has been led, to date, by the approval of 3 radiotracers in the management of recurrent or metastatic pros-
tate cancer: choline C 11, sodium fluoride F 18, and fluciclovine F 18 (Axumin). Newer prostate-specific membrane antigen (PSMA)–based tracers including gallium 68 (68Ga) and DCFPyL F 18 are increasingly being used, first in Australia and Europe and now in the US. These PSMA-based tracers are the subject of several recent clinical trials that support the diagnostic superiority of PSMA PET-CT over conventional and previously approved advanced imaging modalities.

PSMA is a cell surface glycoprotein that is highly overexpressed in most prostate cancer cells. Multiple recent studies have added to the growing body of evidence supporting the use of PSMA PET-CT across the prostate cancer disease spectrum. The proPSMA study was a multicenter clinical trial of patients with high-risk prostate cancer who were randomized to receive conventional imaging vs 68Ga PSMA PET-CT for the purposes of pretreatment staging. The investigators found that 68Ga PSMA PET-CT had a 27% greater area under the curve for diagnostic accuracy when compared with conventional imaging, driven by its improved sensitivity (85% vs 38%) and specificity (98% vs 91%). Use of PSMA PET-CT was more likely to effect a significant change in management vs conventional imaging (28% vs 15%, respectively). For this patient, PSMA PET-CT may be more likely to identify small regional or distant metastatic disease that, if found, may influence our treatment decision.

Although proPSMA compared 68Ga PSMA PET-CT with conventional imaging, Calais et al compared fluciclovine F 18 PET-CT with 68Ga PSMA PET-CT in the biochemical recurrence setting among men with PSA level lower than 2 ng/mL. The indication for imaging in this study was different from proPSMA. Here, imaging was used to detect recurrent disease, whereas proPSMA examined the pretreatment staging setting. The investigators demonstrated that PSMA PET-CT had higher detection rates at low PSA level compared with fluciclovine F 18, adding to the evidence of the superior sensitivity of PSMA-based PET-CT over fluciclovine F 18 PET-CT. 

A pair of recently published trials, OSPREY and CONDOR, led to the recent FDA approval of 18F-DCFPyL (Pylarify), another novel radiotracer used for PSMA-targeted PET-CT, for both initial staging and biochemically recurrent disease.

The multicenter phase 2/3 OSPREY study enrolled 2 cohorts to evaluate the diagnostic performance of DCFPyL F 18 PET-CT: Cohort A—most relevant to our patient—enrolled men with high-risk prostate cancer undergoing radical prostatectomy with pelvic lymphadenectomy to assess its accuracy detecting prostate cancer in the pelvic lymph nodes; cohort B enrolled patients with suspected recurrent or metastatic disease on conventional imaging who then underwent tissue biopsy. In cohort A, DCFPyL F 18 PET-CT had a median specificity of 98%, sensitivity of 40%, positive predictive value (PPV) of 87%, and negative predictive value (NPV) of 83% for detecting pelvic nodal involvement. The performance of DCFPyL F 18 PET-CT was superior compared with conventional imaging with CT/MRI by most measures (3-fold higher PPV: 87% vs 28%, respectively), higher specificity (98% vs 65%), slightly higher NPV (83% vs 78%), and similar sensitivity (40% vs 43%).

The multicenter phase 3 CONDOR study enrolled men with biochemical recurrence after definitive therapy with negative or equivocal conventional imaging and again found that DCFPyL F 18 PET-CT had PPV of 80% to 90% and that 64% of participants experienced a change in intended management after undergoing DCFPyL F 18 PET-CT.

There are some advantages and disadvantages to the different radiotracers from a technical perspective that may guide their real-world adoption. First, as highlighted in the data from Calais and colleagues, 68Ga PSMA PET-CT outperforms fluciclovine F 18 PET-CT. Further, 68Ga was the first well-described PSMA-based radiotracer and has, therefore, garnered significant research interest. However, 68Ga requires specialized generators with batch production of 2 to 4 patient doses per generator elution and has a physical half-life of approximately 1 hour, which requires studies to be performed locally because central production with delivery to remote centers would be challenging. On the other hand, F 18–labeled PSMA tracers such as DCFPyL F 18 offer some advantages over 68Ga, namely large-scale radiosynthesis, allowing for a larger number of patient studies; a longer half-life of nearly 2 hours, which could enable centralized production with delivery to more remote centers; and increased maximum spatial resolution due to its lower positron energy than 68Ga.

On December 1, 2020, the FDA approved 68Ga PSMA PET-CT for staging in men with prostate cancer with suspected metastasis before initial definitive therapy and in men with biochemical recurrence, although the approval is, at this time,
limited to the University of California (UC), Los Angeles, and UC, San Francisco. 18F-DCFPyL (Pylarify) received FDA approval on May 27, 2021. Although current NCCN guidelines would not recommend the use of these advanced imaging techniques until after conventional imaging is performed and found to be negative, this may be rapidly changing. The dissemination and availability of DCFPyL F 18, expected to reach routine clinical use toward the end of 2021 dependent on identification of regional radiopharmacies to provide radiotracer, is expected to rapidly bring PSMA imaging from sparse research and clinical trial settings to routine clinical use, although this will, as always in US health care, depend on insurer reimbursement decisions.

Genetic testing

In addition to staging investigations, another important consideration for this patient is the use of genetic testing. For patients with high- or very high-risk disease, NCCN guidelines recommend germline genetic testing, and contemporary testing may offer actionable information for physicians and patients. BRCA1/2 mutations, if found, may hold prognostic information; studies have demonstrated that patients with prostate cancer and BRCA mutations have higher Gleason scores, nodal involvement, metastatic disease, and worse survival. In patients with metastatic disease, genetic testing for mutations in homologous recombination repair genes is required to determine suitability for treatment with PARP inhibitors, such as olaparib (Lupanara) and rucaparib (Rubraca). In addition, pembrolizumab (Keytruda) is approved for use in tumors with microsatellite instability or mismatch repair-deficiency, so approximately 5% of metastatic castration-resistant prostate cancer cases could qualify.

Genetic testing is also important for family counseling. Relatives of a patient with a known BRCA1/2 mutation may be at increased risk for breast, ovarian, pancreatic, colon, and prostate cancer. Data from the IMPACT study suggest that patients with BRCA1/2 mutations may benefit from annual PSA screening earlier than noncarriers or using a lower PSA cutoff value.

In this case, the patient’s high-risk disease and positive family history of prostate cancer in his father, diagnosed at a relatively young age, may also point toward a genetic predisposition and support the utility of the recommended germline testing. Although access to genetic counseling remains challenging at many centers and has limited broader adoption, its use is guideline recommended and should be a priority for these patients.

The diagnostic and treatment landscape across the spectrum of disease states in prostate cancer continues to rapidly evolve, as highlighted by this case. In the near future, we will, hopefully, better understand when and how to use these advanced tests as well as the implications for patient outcomes and survival.

REFERENCES

ABOUT THE AUTHOR
TALLMAN is a urology resident at the Vanderbilt University Medical Center in Nashville, Tennessee.

WALLIS is a urologic oncology fellow at the Vanderbilt University Medical Center in Nashville, Tennessee.

XXNAMEXX is an assistant professor of urology at the Vanderbilt University Medical Center in Nashville, Tennessee.
A primer on DNA sequencing

Embracing and understanding new and emerging molecular techniques will improve patient outcomes

Justin Wright, MA, MBA

Have you ever wondered what exactly happens to a patient sample when it disappears into a laboratory’s ether? Suddenly, a report filled with results magically shows up in your patient’s file, but what happens during that unknown period? The answer is: a lot. That sample goes through a complex molecular journey.

This article will walk you through the history of genetic sequencing and polymerase chain reaction (PCR), where they are today, touch on microarrays, explain some standard terminology and the questions those terms are asking, plus describe the clinical laboratory’s workflow.

DNA and Sanger sequencing

In today’s molecular testing world, there are 2 very common applications: sequencing and quantitative polymerase chain reaction (qPCR). The first method of sequencing, known as Sanger sequencing, was founded by Frederick Sanger, PhD, 1 of 2 people to win a Nobel Prize twice in the same category. He is considered a pioneer of sequencing DNA for his work with Walter Gilbert, PhD. Prior to his work, most research was done on RNA, which is single-stranded and was easily manipulated with RNase enzymes that cut at very specific nucleotide sequences.

With their discovery of DNA, Watson and Crick noted that nucleotides form the building blocks and that adenine binds with thymine and cytosine binds with guanine to form a base pair (bp). These nucleotides are called deoxynucleotides, meaning they are missing a hydroxyl group. In sequencing, in order to interrogate and “read” the genes and DNA of interest, the base pairs are read and identified. Sanger sequencing decided to throw a wrench into a small portion of those nucleotides and make them dideoxynucleotides, removing another hydroxyl group. When those dideoxynucleotides get added, sequencing immediately stops. Imagine you’re building a Lego tower out of regular-sized 2 by 4 pieces but mixed in about 10% of irregular, flat pieces where there aren’t bumps on top to add any more pieces. That’s how dideoxynucleotides work. They stop your Lego tower from growing.

Sanger sequencing was so revolutionary and important at the time, and for the next 20 years, it was used in the Human Genome Project. By overlapping the sequences, the human genome was built about 500 to 600 bp at a time, with Sanger sequencing being a critical aspect of the entire project. The method is still used to this day for very fast and inexpensive sequencing results and difficult-to-sequence portions of the genome.

Next-generation sequencing

As with any technology, companies are looking to improve the speed, accuracy, and cost of an assay. There have been a few iterations of the next step beyond Sanger, but the one that has become dominant is called next-generation sequencing (NGS), formerly known as massively parallel sequencing. Nowadays, there are 2 versions of sequencing: short reads (Illumina) and long reads (Pacific Biosciences and Oxford Nanopore). Short reads go up to 600 bp together in 1 run, whereas long reads can go beyond 10,000 bp at once, with some reads in the millions of bp. To put this in perspective, the BRCA2 protein is approximately 3000 amino acids in length. By definition, an amino acid is coded for by 3 base pairs, and each base has 2 nucleotides. Thus, there are over 9000 bp (18,000 nucleotides) in the BRCA2 gene.
Short-read NGS uses a flow cell to hybridize short pieces of DNA to it, replicate that DNA, and then copy it over and over, sometimes hundreds of times. Each nucleotide is fluorescent and will activate upon reading, allowing that nucleotide to be added to the sequence. Remember Lite-Brites when you were a kid? You’d put little pieces on a black board with holes, and the pieces would subsequently glow. Imagine having 1 Lite-Brite as a template, and trying to copy the same image hundreds of times, and each time you add a piece, it glows a specific color assigned to that light, or in this case, nucleotide. Along the way, you consistently make an error in the exact same spot. Because of the consistency of that light being incorrect, that’s not just a mistake. Instead, that becomes an interesting diagnostic possibility because that patient sample has a mutation.

There are 2 common ways to use short-read NGS: whole-genome sequencing (WGS) and targeted sequencing, also known as amplicon sequencing or panel sequencing. WGS refers to just that: sequence the whole genome at a certain level of coverage, which is how often you read a base pair compared with the reference genome. Most of the time, 30 times coverage, meaning each base pair on average was read 30 times, is sufficient for nondisease applications. Gene panel sequencing looks at a specific subset of known disease genes, at a much greater coverage, up to 1000 times but mostly 500 to 600 times. For example, a provider may want to run a gene panel on a patient with a history of colorectal cancer to determine whether there is a hereditary component. Genes included in this panel would include MSH1, PMS2, MLH2, MSH6, EpCAM, all of which are associated with Lynch syndrome, as well as APC and MUTYH, which are associated with other syndromic patterns where colorectal cancers are common. Prostate cancer–specific panels will often include BRCA1, BRCA2, ATM, CHEK2, PALB2, HOXB13, and others.

Long reads act a little differently from short reads. Instead of creating many short copies on a chip, long reads use a very large circular sequence of DNA and continuously run it through a mechanism, such as a protein pore, to consistently read the same DNA over and over. Comparatively, this is like copying a Lego tower repeatedly using the same colors in the same order vs riding a Ferris wheel and having the operator check each car every time it passes the bottom. Long reads will catch the same errors as short reads, but also provide some structural variant support and help getting through more difficult areas to read. This allows for some deeper understanding of possible disease states and their proximity to other possible issues.

**Quantitative PCR**

Kary Mullis, PhD, was a chemist at Cetus Corporation. One night while driving around Mendocino County with his girlfriend, also a chemist at Cetus, he recognized that DNA base pairs were constant in their pairing, and had a random thought to match/hybridize short pieces of DNA that were complementary to long pieces of DNA plus DNA polymerase. This matching added nucleotides to a piece of DNA. This allowed a short piece of DNA to be amplified repeatedly using different temperatures, creating billions of copies over many cycles, which would then be studied on an agarose gel (Figure 1). Hence, PCR was invented. Mullis was awarded the Nobel Prize in 1993 for this groundbreaking invention, which led to so many discoveries in science. Around the same time, Higuchi et al discovered that increasing amounts of DNA could be directly studied using a fluorescent marker without the need for agarose gel. And voilà! qPCR was invented.

**FIGURE 1.** Polymerase chain reaction in action. DNA is double-stranded. Heating up the DNA (denaturation) separates the strands. Annealing allows the complementary primers to bind each individual strand. Extension allows the DNA polymerase to bind the primers and DNA and add individual nucleotides to create a new, shorter DNA piece. Repeating this many times will create billions of copies of a very small piece of DNA of interest. (Enzoklop/Wikimedia Commons/CC-BY-SA-4.0)
In order to use qPCR in diagnostics, the clinic has to know which specific gene is of interest, as the primers have to flank the target sequence to be amplified. The high specificity of this type of assay is both a blessing and a hindrance. It's a blessing because the clinic can answer a diagnostic question with high confidence but a hindrance because it may miss other possible disease states that are outside the targeted region. Most of the time, a sample will be split up to run multiple different assays at the same time to cover a wider array of diseases. qPCR is also very commonly used to get to the heart of urinary tract infections (UTIs) and their persistent nature. Many companies are offering qPCR diagnostics for UTIs, prostatitis, and more. Most of the time, those companies will also offer an NGS panel in addition to cover all diagnostic bases.

Microarrays

Microarrays are small chips with imprinted specific DNA targets of interest (Figure 2). The test is run with a reference sample, often labeled with a green fluorescent dye, and the targeted DNA sample, labeled with a red fluorescent dye. Both are then hybridized to the chip, and a comparative analysis is done. If the targeted DNA is expressed at a higher rate, that small area will glow red. If the control DNA is expressed higher (or decreased expression in the target DNA), it will glow green. Finally, if expressed in equal amounts, essentially no mutation, the square will glow yellow. The sensitivity is generally low, but the ability to study many targets at once is a highlight. Microarrays are a common technique of many companies that offer testing for determining cultural heritage. Those companies will study up to 700,000 targets at 1 time. However, microarrays are slowly declining because of the greater adoption of NGS assays. These direct-to-consumer companies are really fun and interesting for those who are seeking information about their ancestry but should not be used for cancer risk assessment.

What happens to a sample in the clinical lab?

When a patient has a sample sent for molecular testing, whether it's tissue, urine, blood, or saliva, that specimen is immediately tagged with a number specific to that patient. The sample is transported to the lab with the appropriate storage. The lab receives the sample and inputs it into their system, also called accessioning. Then, the molecular journey is as follows:

1. Nucleic acid isolation: convert RNA to DNA if needed
2. Library preparation
   a. Sonication or enzyme digestion to create uniform DNA segments
   b. Enrich the target DNA if needed, as target enrichment and amplicon generation workflows used in gene panels
   c. Barcode ligation: also known as multiplexing, which is adding unique markers per patient sample so they can be mixed together, then parsed upon software analysis
   d. Adapter ligation: allows the DNA to bind to the flow cell
3. Sequence the DNA: 0.5 days to several days, depending on sequencing type and instrument used
4. Bioinformatics: Results are parsed and analyzed.
5. Report generated: Details around the disease state are provided, and sometimes potential treatment scenarios depending on the software's FDA approvals.
What does a clinical laboratory look for in their tests?

Although you’ve learned about generic methods and workflows, labs look for specific issues using molecular methods that cause various disease states. In this section, I’ll lay out a few of the more common terms in the lexicon of genomic testing.

**Single-nucleotide polymorphism (SNP).** As the name implies and by definition, this occurs when a single nucleotide change is identified in a particular gene and present in 1% of the population. This SNP results in a gene mutation but may or may not cause an alteration of downstream protein function, depending on whether the change affects the specific amino acid in which it is coding. There is significant interest in looking at a panel of SNPs to determine risk assessment for breast and prostate cancer.

**Copy number variation.** This is a duplication or deletion of a sequence of nucleotides, not just a single nucleotide like an SNP. Most genes in the human genome have 2 alleles, 1 each inherited from your mother and father. In rare instances, short sequences can be replicated many times. For example, the HTT gene codes for the protein huntingtin. In this case, the trinucleotide CAG can be repeated 36 times or more. The result is abnormal protein production, which can then lead to Huntington disease.7

In other cases, entire genes can be repeated or deleted, causing overexpression or underexpression, as in the case of α-amylase 1 and its overexpression because of dietary differences.8 The largest example of this is the trisomy issues that cause Down syndrome.

**Gene fusions.** Fusions occur when 2 genes fuse during replication, causing a pseudogene that creates expression issues. One of the earliest discovered examples of this is a reciprocal translocation where the ABL1 gene of chromosome 9 is translocated and fuses to the BCR gene on chromosome 22, causing a BCR-ABL1 gene (the Philadelphia chromosome), which induces chronic myeloid leukemia.9 This is difficult to detect using molecular testing because there are various fusion loci on each gene, but it can be done with proper techniques, such as digital PCR and NGS.

This partial list of 3 common issues is just a sample of what a molecular lab can discover. Some tests are more involved than others from a workflow and difficulty perspective, whereas others are fairly straightforward. The most challenging part for a lab is to discern the ability of a specific assay type to get the proper answer because some answers are much more difficult to come by.

**Conclusions**

The world of clinical diagnostics is changing. The development of targeted therapies is increasingly more specific to various molecular changes that are therapeutic resistance drivers. The development of companion diagnostics so patients can receive these new agents is mandatory. In addition, the ability to detect and potentially mitigate disease at a much earlier stage before systemic/metastatic disease has clear upside potential. Therefore, embracing and understanding these new and emerging molecular techniques will improve your patient outcomes and enhance your practice.

**REFERENCES**


**ABOUT THE AUTHOR**

WRIGHT has been involved in biotech and clinical sales and marketing for nearly 20 years. He has a Master’s in molecular biology from Washington University in St. Louis and an MBA in strategy and operations from Boston University. He has worked for companies such as Thermo Fisher and Illumina and has started multiple companies outside of the biotech world.
Adjuvant immune checkpoint blockade: A new era?

Recent trial demonstrates an improvement in outcomes with an adjuvant immune checkpoint inhibitor in urothelial cancer

Matthew D. Galsky, MD

Patients with muscle-invasive urothelial cancer of the bladder and invasive urothelial cancer of the upper urinary tract are at generally at high risk for metastatic recurrence despite curative intent surgery. A series of clinical trials investigating systemic therapies applied in the adjuvant setting have been performed over the past few decades in an attempt to mitigate this risk.1 Compared with the development of therapeutic approaches in the metastatic setting, the development of therapeutic approaches in the adjuvant setting is potentially more impactful but more complicated. That is, in the metastatic setting, we mainly face the question “Who benefits from treatment?” Whereas in the adjuvant setting, we face both the question “Who needs treatment?” and “Who benefits from treatment?” A large proportion of patients with muscle-invasive urothelial cancer will achieve cure with surgical resection alone. On the other hand, for those patients who harbor micrometastatic disease after surgery, just as in the metastatic setting, not all such cancers will be sensitive to the systemic therapy being applied.

Historically, we have addressed the “Who needs treatment?” question in the adjuvant setting by using pathologic features of the primary tumor and regional lymph nodes to help refine estimates regarding recurrence risk. Such features, in turn, have formed the eligibility criteria for clinical trials. The majority of adjuvant trials in urothelial cancer have enrolled patients with bladder-only primary tumors and have limited enrollment to patients who had not received prior neoadjuvant chemotherapy and had pathologic T3 or higher urothelial cancer or pathologic evidence of regional lymph node involvement. Randomized trials exploring adjuvant cisplatin-based chemotherapy in this context suffered from methodologic flaws and/or closed early due to poor accrual, leaving some doubt regarding the efficacy of this approach despite meta-analyses suggesting a benefit.2

Although trials of adjuvant cisplatin-based chemotherapy in high-risk urothelial cancer continued, for a number of reasons, neoadjuvant cisplatin-based chemotherapy became the standard preferred treatment standard supported by level I evidence.3,4 Therefore, regardless of one’s interpretation of the studies evaluating adjuvant cisplatin-based chemotherapy, additional unmet need populations at high risk for recurrence after surgery arose not addressed by the prior generation of studies: (1) patients with pT3 or higher and/or pN-positive disease who are considered cisplatin ineligible5 and (2) patients with residual ypT3 or higher and/or ypN-positive disease despite having received prior cisplatin-based neoadjuvant chemotherapy. These 2 distinct populations have formed the basis for large phase 3 trials exploring PD-1 and PD-L1 immune checkpoint inhibitors in the adjuvant setting triggered by the safety and efficacy of these therapies in metastatic urothelial cancer.

Three somewhat similarly designed adjuvant trials, with some nuances, have been conducted to test adjuvant PD-1 or PD-L1 blockade. IMvigor010 (NCT02450331) randomized patients with urothelial cancer of the upper tract or bladder at high risk for recurrence (as defined above) after definitive surgery to atezolizumab (Tecentriq) administered for 1 year vs observation.6 This was the first in the series of immune checkpoint blockade adjuvant trials...
to report and it was presented at the 2020 American Society of Clinical Oncology Annual Meeting, though it has not been published. The trial did not meet the primary end point of improvement in disease-free survival with atezolizumab in the intent-to-treat population, nor was there in an improvement in the subset of patients with tumors harboring increased PD-L1 protein expression.

The Checkmate 274 trial (NCT02632409) employed similar eligibility criteria but randomized patients to 1 year of adjuvant nivolumab (Opdivo) vs placebo (rather than observation). This trial, presented at the 2021 Genitourinary Cancers Symposium, met coprimary end points of an improvement in disease-free survival in the intent-to-treat population and in the subset of patients with tumors harboring increased PD-L1 protein expression.

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Informed censoring based on the proportion of patients randomized to observation that withdrew early from the study. Checkmate 274 represents the first trial demonstrating an improvement in outcomes with an adjuvant immune checkpoint inhibitor in urothelial cancer, addresses a patient population without previously available systemic therapies to mitigate risk of recurrence, and represents the first big step in a new era of immune checkpoint inhibitor for muscle-invasive urothelial cancer.

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ABOUT THE AUTHOR
GALSKY
is acting chief, Division of Hematology and Medical Oncology, and professor of medicine at Tisch Cancer Institute at the Icahn School of Medicine at Mount Sinai in New York City, New York.
KIDNEY CANCER

Case review: High-risk renal cell carcinoma

IN ASSOCIATION WITH

AROUND THE PRACTICE

A round the Practice is a monthly urologic virtual live event featuring case reviews from multidisciplinary experts, presented by Urology Times® in partnership with LUGPA. On April 21, 2021, a panel convened to discuss cases involving high-risk renal cell carcinoma (RCC) and metastatic castrate-resistant prostate cancer. What follows is an edited portion of the panel’s conversation regarding the RCC case. The panelists for this case included moderator Raoul S. Concepcion, MD, FACS; Vahan Kassabian, MD; Paul J. Kim, MD; and Abhishek Tripathi, MD.

CONCEPCION: This patient is a 51-year-old man who presents with left flank pain and gross hematuria. His medical history is significant for type 2 diabetes, hypertension, elevated cholesterol, hypogonadism, and depression. He’s had a right inguinal herniorrhaphy. He has allergies to aspirin, iodine contrast, walnuts, and cats. He’s taking a number of medications, including glyburide, statins, and lisinopril. His review of systems is noncontributory. He is married, has significant occupational exposure, and has a significant family history of esophageal cancer in his father. On exam, he has no abdominal masses and doesn’t exhibit any cutaneous lesions. For lab evaluations, his complete blood count, basic metabolic panel, and liver function test are all normal. His alkaline phosphatase is slightly elevated. On CT scan imaging, he has a large enhancing left renal mass of about 11 cm, no lymphadenopathy, and no evidence of metastatic disease. There is no evidence of metastases on his chest x-ray or bone scan.

After shared decision-making, the patient opted for a left robotically assisted radical nephrectomy. The final pathology showed mixed clear and granular cell type. The tumor itself was 10 by 7 cm. It was Fuhrman [nuclear] grade 3, with invasion into the renal vein, but negative margin at the renal vein resection site. He also had extension of the tumor into the perirenal fat and renal sinus adipose tissue, but Gerota fascia was not involved and it is intact. He has a pathologic T3N0M0 lesion.

TRIPATHI: High-risk RCC has been an area of active research for the past decade, if not longer, with several trials aimed at investigating different adjuvant therapies. These trials resulted in the approval of sunitinib [Sutent] in the adjuvant setting for high-risk RCC, which this patient meets the criteria for. However, this happens to be one of those situations where even though there is an FDA approval, there is not widespread consensus on whether we should be offering or strongly recommending these therapies for patients with high-risk disease.

The reason for that is the discordance between the results of the AS-SURE [NCT00326898] and S-TRAC [NCT00375674] trials, and the lack of an overall survival benefit to date and high rate of grade 3 adverse events.

Considering these factors, our practice is to try to enroll patients in a clinical trial if possible, and if a clinical trial is not available, then we have a balanced discussion with the patient regarding the available literature. A majority of the time, patients end up declining adjuvant sunitinib after understanding the limitations of current evidence. Interestingly, even though sunitinib is approved in the US, its approval raised quite a debate. The European Medical Agency did not approve the use of sunitinib...
KIDNEY CANCER

considering all elements of the data together. Consistent with these, the National Comprehensive Cancer Network has a category 2B recommendation on using sunitinib.

So this is one of those rare circumstances where there is a positive trial, but it did not necessarily change the practice for the majority of patients. Taking those things into account, I usually discuss the data and the adverse event profile and I don’t strongly recommend it, but it is an option for patients in the adjuvant setting.

CONCEPCION: Interesting. So we have an agent that’s FDA approved but NCCN gives it a 2B recommendation. Dr Kassabian, is that what’s happening with patients in your region also? Are you talking to them about the role of adjuvant therapy? Are you recommending that they see the medical oncology [department]? What’s been your practice pattern?

KASSABIAN: I have found that every single patient I sent to medical oncology colleagues for discussion and therapy with sunitinib have all declined for the reasons already explained. It was a category 2B recommendation, it had a lot of grade 3 toxicity, and it was for at least 9 months and there were a lot of dose interruptions and dose reductions. Basically, the consensus was that every patient I referred declined to have therapy.

I don’t do robotics, but I think this patient would have been a great candidate for open surgery given the size of the mass. The other point I want to make is that, at least in the metastatic setting of RCC, unimodality therapy is being replaced by multimodality therapy, especially immunotherapy. So I see in the future that perhaps single-agent therapy would not be efficacious in the high-risk patient following nephrectomy such as this, but I think multimodality therapy may be more efficacious and probably widely accepted.

CONCEPCION: Dr Kim, is there any role for radiation? Are there any data for radiation in a high-risk patient in the adjuvant setting?

KIM: There are not many good-quality data in terms of randomized trials. I think one of the few [trials whose results were] ever published was from a couple of decades ago...a study from Copenhagen with a low number of patients.1 They gave about 50 Gy for what they perceived to be high-risk pathologic features that would increase the risk of local recurrence, and they just didn’t find much of a benefit in terms of overall survival.

One of the challenges is that once you remove the kidney, it gets filled up with bowel. The bowel is one of the most sensitive organs to radiation and to try to deliver a therapeutic dose is difficult. I think that has contributed to some of what we’re seeing in the data where there’s not much of a clinical benefit.

CONCEPCION: At 6 months, the patient undergoes CT of the abdomen and pelvis, which shows subcentimeter nodules in the lower lung fields. Dedicated CT shows 6 nodules in the right lung and 4 nodules in the left lung, with the largest nodule being 7 mm. There is no change at follow-up at 12, 24, and 36 months. At 48 months, however, a chest CT shows a bilateral noncalcified pulmonary nodule, which has increased in size from 10 mm to 16 mm.

PET-CT was done, which showed no significant uptake in pulmonary nodules bilaterally. However, there is a mild uptake noted at the left lung base, which measured 2.6 on early and 2.6 on delayed. Dr Kassabian, what do you think about the increase in this nodule from 10 to 16 mm?

KASSABIAN: I think it’s significant. We’re always concerned that these are metastatic sites even though they’re small. They are clearly growing. Given his pathology, and the fact that he had this huge mass at such a young age, he has a high chance of recurrence and obviously now he has something that’s visible. I would think that starting off with a biopsy or resection to prove or disprove that he has metastatic disease before initiating therapy is perfectly reasonable.

CONCEPCION: This patient was referred to the interventional radiology [department] and had a CT-guided core biopsy of the left upper lobe nodule, which was negative. He also had a left thoracoscopic wedge resection, left lower lobe wedge resection, and bronchoscopy. Pathology on both lesions shows metastatic RCC, mixed clear cell and granular type. Pleura and margins are negative. So now we have a patient with documented pulmonary metastatic disease that has been resected. Dr Tripathi, what are your thoughts at this point?

TRIPATHI: At the time of diagnosis, this patient had high-risk, locally advanced disease. But after the resection, he had a relatively indolent course for about 4 years, after which he started developing growth in the pulmonary nodule. So based on the IMDC [International Metastatic RCC Database Consortium] criteria, I think he belongs in the favorable-risk category with oligometastatic disease and was treated appropriately with metastasis-directed therapy.
We can think about it in a couple of ways. This is a patient with favorable-risk disease who has shown indolent biology over the past 4 years with only recent change in growth dynamics. He has been rendered NED [no evidence of disease] after metastasis-directed surgery. I think one option would be to follow the patient closely. We have had longitudinal data on the subset of patients who have low-volume disease and undergo metastasectomy. A significant proportion of these patients can be followed post surgery and delay the need for and adverse events associated with systemic therapy. The postmetastasectomy pazopanib [Votrient] data presented in 2019 that showed us that postmetastasectomy pazopanib patients who were rendered potentially NED didn’t improve disease-free survival, and there was a trend toward worse overall survival in patients assigned to the experimental arm.2

Secondly, we have a lot of retrospective and corroborative data published recently indicating that a significant subset of favorable-risk patients with low-volume metastatic disease can delay the need for systemic therapy. As our therapies are getting more and more effective, patients are on these therapies for a much longer duration, and the cumulative toxicity, both financial and physical, could [be difficult for them to bear]. So we have to be mindful about the decision to start systemic therapy in these patients. That being said, I think if there was a patient in whom there was still residual measurable disease and the patient was strongly interested in starting systemic therapy, I would start that patient off on the combination regimen of a VEGF TKI and immunotherapy, which have shown improved overall survival compared with single-agent TKI therapy.

The regimen of choice is probably dependent upon the comfort of the treating physician in terms of management of adverse events. They all have an overall survival benefit over sunitinib. This includes axitinib [Inlyta] and pembrolizumab [Keytruda], lenvatinib [Lenvima] and pembrolizumab, and cabozantinib [Cabometyx] and nivolumab [Opdivo].

CONCEPCION: Is there a role for monotherapy immunotherapy in this particular patient?

TRIPATHI: We have data on that. The KEYNOTE-427 trial [NCT02853344] investigated pembrolizumab monotherapy in patients with favorable-, intermediate-, and poor-risk disease and had a response rate of around 35%. Although some patients had a durable response, that’s not the approved indication at this point, but it is a very rational question to understand which patients need intensification with both agents and who could get by with just monotherapy. I think biomarkers would play a role potentially. There are some data that suggest that favorable-risk patients are driven by VEGF signaling in tumors. And these tumors are sensitive to and more likely to respond to a TKI. Although a subset of patients with favorable-risk disease do respond to immunotherapy, I would not consider monotherapy with a PD-1 inhibitor to be standard of care. I would consider it only as part of a clinical trial in this situation, considering the available randomized data and the FDA label.

CONCEPCION: Let’s just say the patient also had a concomitant positive bone scan. As we know, bone metastases are not all that common in RCC, but it does obviously occur. Dr Kim, what about bone metastases in the setting of RCC? How do those patients generally respond to radiotherapy?

KIM: RCC as a histology is considered to be one of the more radioresistant types. You would need a pretty high biological effective dose to deliver an ablative therapy. Fortunately, the technology has matured where we are able to do that, and now it’s supported by data from studies such as the SABR-COMET trial [NCT01446744], which shows that in patients with limited oligometastases you can improve clinical outcomes by delivering ablative therapy in a case like this, up to 5 metastases. So, that is being done more and more these days ever since these data were published.