

## Updated NCCN Guidelines Grant Tivozanib Category 1 Status for Pretreated RCC

CAROLINE SEYMOUR

**THE KIDNEY CANCER TREATMENT** guidelines, housed within the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology, have been revised, granting tivozanib (Fotivda) Category 1 status as a subsequent therapy for patients with renal cell carcinoma (RCC) who have received at least 2 prior lines of treatment, according to an announcement from AVEO Oncology.<sup>1,2</sup>

On March 10, 2021, the FDA approved tivozanib for the treatment of adult patients with relapsed/refractory advanced RCC following 2 or more prior systemic therapies.<sup>3</sup>

The approval was based largely on findings from the phase 3 TIVO-3 trial (NCT02627963). Tivozanib demonstrated a significant improvement in progression-free survival (PFS) compared with sorafenib (Nexavar), with similar overall survival (OS), in patients with highly relapsed/refractory metastatic RCC.<sup>4</sup>

The controlled, multicenter, open-label, phase 3 trial randomized 350 patients with highly refractory metastatic RCC who had failed 2 or more prior regimens, including VEGF-TKI treatment, 1:1 to receive oral tivozanib or sorafenib. Crossover between arms was not permitted.

Primary findings from the study demonstrated an increased independent review committee-assessed median PFS for tivozanib compared with sorafenib at 5.6 months vs 3.9 months, respectively (stratified HR, 0.73; 95% CI, 0.56-0.95;  $P = .016$ ). The final hazard ratio (HR) for OS was 0.97 (95% CI, 0.75-1.24;  $P = .78$ ).

Findings from an exploratory analysis from the study presented at the 2022 Genitourinary Cancers Symposium demonstrated that the investigator-assessed HR for PFS favored tivozanib compared with sorafenib (HR, 0.624; 95% CI, 0.49-0.79). That result was comparable to the primary IRC-assessed HR for PFS (unstratified HR, 0.672; 95% CI, 0.52-0.87).<sup>5</sup>

Additionally, landmark long-term PFS rates were significantly higher with tivozanib vs sorafenib, at 12.3% and 2.4%,

respectively, at 3 years, and 7.6% and 0%, respectively, at 4 years. Moreover, mature OS data also reflected a nonsignificant trend in continued favor of tivozanib (HR, 0.89; 95% CI, 0.70-1.14).

“Category 1 is the highest Category recommendation offered by NCCN, which is based on strong clinical evidence and perception of the product among the NCCN Panel Members. The NCCN guidelines are recognized and followed by both academic and community oncologists when selecting appropriate therapeutic options for their patients,” Michael Bailey, president and chief executive officer of AVEO, said in a press release. “This year we presented encouraging long-term, PFS and OS follow-up data from the phase 3 TIVO-3 study. These new data demonstrate the durability of FOTIVDA’s anti-tumor activity which has translated into an improving OS hazard ratio.” ■

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# FDA Accepts BLA for N-803 in BCG-Unresponsive Non–Muscle Invasive Bladder Cancer in Situ

CAROLINE SEYMOUR

**THE FDA HAS ACCEPTED** for review a biologics license application (BLA) for the IL-15 superagonist N-803 for the treatment of patients with Bacillus Calmette-Guérin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC) carcinoma in situ (CIS) with or without Ta or T1 disease.<sup>1</sup>

The BLA is based in part on findings from the ongoing phase 2/3 QUILT 3.032 trial (NCT03022825), in which 71% (95% CI, 60.1%-80.5%) of patients with BCG-unresponsive NMIBC who progressed on prior treatment achieved a complete response (CR). The 12-month CR rate with the regimen was 62% (95% CI, 48%-74%); at 24 months, this rate was 52% (95% CI, 37%-65%).

The regulatory agency is scheduled to decide on the BLA by May 23, 2023, under the Prescription Drug User Fee Act. If approved, N-803 plus BCG would represent the first immunotherapy combination for this indication in 23 years that can be delivered directly to the bladder to generate natural killer (NK) cells and T cells.

“This BLA acceptance brings us a very important step closer to being able to offer this promising combination therapeutic to more people living with NMIBC and, ultimately, reduce the incidence of cystectomies,” Patrick Soon-Shiong, MD, executive chairman and global chief scientific and medical officer at ImmunityBio, stated in a press release. “This is a compelling example of the power of inducing trained innate immune memory to potentially provide long-term, durable effects against serious, life-threatening diseases.”

N-803 is an antibody cytokine fusion protein that generates NK and T cells that, when combined with BCG, results in a synergistic immune response.

Previously, N-803 was granted a breakthrough therapy designation and fast track designation for use in combination with BCG in patients with BCG-unresponsive NMIBC CIS.

QUILT 3.032 is an open-label, multicohort, multicenter study that enrolled patients with histologically confirmed BCG-unresponsive disease with persistent or recurrent CIS, with or without recurrent Ta or T1 disease. Patients were enrolled within 1 year of receiving BCG. Those with CIS comprised cohort A, and those with papillary histology (n = 77) made up cohort B.

Patients received 50 mg of intravesical BCG in combination with 400 µg of N-803 weekly for 6 cycles followed by 6 cycles of maintenance treatment in those who experienced a CR for up to 2 years. Those who did not experience a CR

but responded to treatment were allowed to receive another 6 cycles of re-induction with the combination regimen.

The primary end point was CR at any time, and secondary end points included CR duration, cystectomy avoidance, and time to cystectomy. Serious toxicities and immune adverse effects (AEs) were also evaluated.

Additional findings presented during the 2022 Genitourinary Cancers Symposium demonstrated that with a median duration of follow-up of 23.9 months (range, 0.3-37.5), the median duration of response (DOR) was 24.1 months (95% CI, 9.9-not reached) in cohort A.<sup>2</sup> Sixty-two percent (95% CI, 48.0%-73.5%) of patients experienced a DOR of at least 12 months, 55% (95% CI, 40.1%-67.3%) experienced a DOR of at least 18 months, and 52% (95% CI, 37.0%-64.9%) had a DOR of at least 24 months.

Moreover, the cystectomy avoidance rate was 93%, and the median time to cystectomy was 5.1 months.

The 24-month rate of bladder cancer-specific progression-free survival was 91% (95% CI, 81.2%-95.4%), and the 24-month bladder cancer-specific overall survival rate was 100%.

In terms of safety, no patients in cohort A experienced treatment-related grade 4 and 5 AEs, treatment-related serious AEs, or immune-related AEs. The most common grade 1/2 AEs included dysuria (22%), pollakiuria (19%), and hematuria (18%). All grade 3 AEs occurred in less than 1% of patients, which included arthralgia, bacteremia, dysuria, encephalopathy, Escherichia bacteremia, hematuria, myalgia, pain in extremity, pollakiuria, sepsis, urinary tract infection, and urine flow decrease.

“We are pleased the FDA has begun its review, and ImmunityBio is prepared to move rapidly to manufacturing and marketing should the Agency approve our therapeutic for this indication,” Richard Adcock, president and chief executive officer of ImmunityBio, said. ■

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# Adjuvant Nivolumab/Ipilimumab Fails to Meet DFS End Point in Localized RCC

CHRIS RYAN

**THE COMBINATION OF** nivolumab (Opdivo) and ipilimumab (Yervoy) failed to elicit a statistically significant improvement in disease-free survival (DFS) compared with placebo as adjuvant treatment in patients with localized renal cell carcinoma (RCC) who had undergone a full or partial removal of the kidney and were at moderate or high risk of relapse, failing to meet the primary end point of part A of the phase 3 CheckMate-914 trial (NCT03138512).<sup>1</sup>

A full evaluation of the data will be published in the future.

“Even with notable progress in the treatment of metastatic RCC, there are still limited treatment options available for patients with localized disease,” said Dana Walker, MD, MSCE, the vice president and development program lead of Genitourinary Cancers at Bristol Myers Squibb, stated in a press release. “[Nivolumab] and [nivolumab]-based combinations have shown survival benefits in several earlier-stage and advanced cancers, including genitourinary tumors, and we are disappointed that the final analysis of CheckMate-914 part A did not show this same benefit for the post-surgical treatment of patients with localized RCC. Nonetheless, we are dedicated to continuing research and advancing cancer care for all patients with RCC.”

Nivolumab/ipilimumab has demonstrated benefit in other patient populations with RCC. In April 2018, the FDA approved the combination of nivolumab and ipilimumab as a frontline treatment for intermediate- and poor-risk patients with advanced RCC.<sup>2</sup> Additionally, in January 2021, the combination of cabozantinib (Cabometyx) and nivolumab earned FDA approval for the frontline treatment of patients with advanced RCC.<sup>3</sup> Furthermore, cabozantinib plus nivolumab/ipilimumab generated a significant improvement in progression-free survival (PFS) vs nivolumab/ipilimumab in patients with previously untreated advanced intermediate- or poor-risk RCC, meeting the primary end point of the phase 3 COSMIC-313 trial (NCT03937219).<sup>4</sup>

The randomized, double-blind, placebo-controlled CheckMate-914 trial evaluated the combination of nivolumab and ipilimumab vs placebo in part A, and nivolumab monotherapy vs nivolumab plus ipilimumab vs placebo in part B. Patients were required to be at least 18 years of age with localized RCC at a moderate or high risk of relapse who had their kidney tumor resected with negative surgical margins

obtained.<sup>5</sup> Randomization needed to occur between 4 and 12 weeks following nephrectomy.

Additional inclusion criteria included tumors with a predominantly clear cell histology, including patients with sarcomatoid features; no clinical or radiological evidence of macroscopic residual disease or distant metastases after nephrectomy; and an ECOG performance status of 0 or 1.

Exclusion criteria included active known or suspected autoimmune disease; a known history of a positive test for HIV or known AIDS; prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, or anti-CTLA-4 antibody, or any other agent targeting T-cell co-stimulation or checkpoint pathways; or any severe or serious acute or chronic medical or psychiatric condition.

DFS served as the primary end point in parts A and B. Secondary end points in both parts of the trial included overall survival and the incidence of adverse effects. DFS for nivolumab monotherapy vs the nivolumab/ipilimumab combination will also be accessed as a secondary end point in part B, which is ongoing.

Findings from part A of CheckMate-914 showed that the safety profile of nivolumab plus ipilimumab was consistent with previously reported studies of the combination in patients with solid tumors. ■

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## Penile Cancer Is Treatable, But the Armamentarium is Thin

JASON HARRIS

**AMONG MEN IN THE UNITED STATES**, incidence-based mortality (IBM) is growing for penile cancer even though incidence remained consistent from 2000 to 2018. Existing treatments are of limited efficacy, and there has been a lack of research that might identify better options.

Penile squamous cell carcinoma (PSCC), the most common form of the disease, is a rare cancer in high-income countries, with prevalence of less than 1%. In contrast, the disease accounts for up to 10% of cancers in men in some African, Asian, and South American regions.<sup>1</sup> The American Society of Clinical Oncology estimates that 2070 people will be diagnosed in the United States this year. In 2020, it was estimated that 36,068 worldwide were diagnosed with this disease.<sup>2</sup>

The disease can be fatal, but treatment is often successful—especially when diagnosed early. The 5-year overall survival (OS) rate in the United States for patients with this disease is 65%. For men with local disease, the 5-year OS rate is 80%, declining to 9% for those with distant metastases.<sup>2</sup>

“The simple reason I think we are seeing that, unfortunately, is that we have not developed, nor have we identified, very effective systemic therapies for patients with penile cancer. Oftentimes, we can cure early penile cancer, fortunately,”

— Philippe E. Spiess, MD, MS

However, the 5-year relative survival rate has declined slightly but steadily, dropping from 67.7% from 2000 to 2004 to 65.67% from 2010 to 2014.<sup>3</sup> Philippe E. Spiess, MD, MS, an assistant chief of surgical services and senior member in the Department of Genitourinary Oncology at Moffitt Cancer Center, as well as a professor of oncology and urology in the Department of Urology at University of South Florida Morsani College of Medicine, said

that medical science simply has not done enough for these patients.

“The simple reason I think we are seeing that, unfortunately, is that we have not developed, nor have we identified, very effective systemic therapies for patients with penile cancer. Oftentimes, we can cure early penile cancer, fortunately,” Spiess told *OncLive*<sup>®</sup>. “However, when patients have advanced disease, I think we are still very challenged in identifying good chemotherapies or immunotherapies or combination treatments that are going to be very effective for patients.”

The current standard of systemic care is 4 courses of the TIP chemotherapy regimen, which is comprised of neoadjuvant paclitaxel at 175 mg/m<sup>2</sup> on day 1 plus 1200 mg/m<sup>2</sup> of ifosfamide and 25 mg/m<sup>2</sup> of cisplatin on days 1 and 3 for patients with N2 and N3 disease. In a landmark phase 2 study (NCT00512096) published in 2010, 23 of 30 men completed all 4 courses of therapy. The overall response rate in the 30 patients with this approach was 50% (95% CI, 31%-69%), which included 3 complete responses and 12 partial responses (PRs).<sup>4</sup>

More recently, investigators in China evaluated 19 men with advanced PSCC who received TIP treatment from June 2009 to June 2016. Five men previously underwent partial amputation of the penis. The remaining 14 patients had local carcinoma and fixed inguinal lymph node metastasis.<sup>5</sup>

Twelve patients achieved PRs and proceeded to surgery. Five patients underwent bilateral inguinal lymphadenectomy (ILND) and pelvic lymph node dissection (PLND), and 6 had partial amputation of the penis plus ILND and PLND. One patient had penectomy plus ILND and PLND.

“Early-stage penile cancer is curable with surgery alone,” Hao G. Nguyen, MD, PhD, the Richard and Leilani Grinold Endowed Professor

in Urology and a professor in the department of urology at the University of California, San Francisco and chief urologic oncologist at the Zuckerberg San Francisco General Hospital and Trauma Center, told *OncLive*<sup>®</sup>. “We have been relying on the same chemotherapy for the past decade or so. We have not made headway in terms of treating metastatic disease. [That is why] you see a static, or even a slight decline in, survival rate for penile cancer.”

He added that awareness of the disease is poor, and there is no established strategy for prevention or early detection. Furthermore, there is no biomarker or pathway to identify PSCC and although the disease is associated with human papillomavirus (HPV) infection in 50% of the cases, investigators do not know whether the HPV vaccine prevents penile cancer.

Depending on the size and extent of the lesion, partial or total penectomy is considered to be the standard oncologic treatment. However, amputation is disfiguring and has a significant negative effect on quality of life (QoL). European Association of Urology guidelines recommend penile-sparing surgery whenever possible, and there is some evidence to suggest that less invasive surgery is equally as effective.

In a systemic review of 88 studies involving 9578 men, European investigators found a cumulative mean 5-year recurrence-free rate of 82.0% with penile-sparing surgery vs 83.9% with amputation. Studies reporting poor recurrence-free rates involved patients who underwent penile-sparing surgery for advanced disease. In contrast, those reporting higher recurrence-free rates involved cohorts who received amputation for less advanced disease.<sup>6</sup>

No matter the method chosen, surgery has a negative impact on QoL. Additionally, patients reported more concerns about appearance and life interference due to disfigurement following amputative surgery. Investigators cautioned that the quality of evidence was poor but the findings support the use of penile-sparing surgery, if possible.

### Gender and Sexuality Raise Unique Concerns

It has been documented that patients are very concerned about organ function posttreatment. Surgery “is usually associated with mutilation,” according to 1 report, and affects sexual and urinary functions and health-related QoL.

“Our goal is to have organ-sparing surgery without compromising an oncologic control in our surgery approach,” Nguyen explained. “I would say that depending on the location, if the lesion is at the tip of the gland, then most of the time, even in T2 disease, we should [be able to] spare a lot of the organ.”

Spiess said surgery has significant ramifications for cisgender, nonbinary, and transgender patients. Preserving sexual function is key for physical and emotional health.

“One thing with this type of cancer, which is underreported, is the implications it has on how patients identify themselves after they have had sometimes, unfortunately, fairly mutilating surgery of the penis and that area, and how it affects their sexual identity, and their relationships with their partners,” Spiess said. “What I do in my practice,

and several centers have started to also do this, is [leverage] psychosocial counselors and essential educators to work with the patients. We screen them for depression, for suicidal ideation. [Traditionally,] that is something that has not been done very frequently. We need to be very aware [of this,] and support our patients [to help them to understand] how this is going to affect them. And this is going to be for many, many years to come.”

Spiess and Nguyen agreed that shame can prevent patients from seeking treatment. Findings from 1 small study conducted at Sweden’s Örebro University Hospital showed that 65% of patients delayed treatment for more than 6 months.<sup>7</sup> Data show that a delay of just 3 months was associated with increased risks for adverse clinical characteristics, low penis-sparing rate, and poor sexual function restoration.<sup>8</sup>

Of the patients who delayed treatment, 23.2% stated that they were embarrassed to describe the problem to practitioners. Nearly 20% said they did not think their symptoms were serious.<sup>8</sup>

“To counter that, we have to build a way to screen for penile cancer into the healthcare system. We screen for prostate cancer; we screen for colorectal cancer,” Nguyen said. “Why not have every man get a penis exam on a yearly basis? Then, it takes away these feelings or emotions associated with the exam, and it is just makes everything more objective.” ■

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## Successful Treatment Options Expand to Earlier Lines in RCC and Urothelial Cancer

ASHLING WAHNER

**INCREASINGLY EFFECTIVE TREATMENTS** in renal cell carcinoma (RCC) and bladder cancer are shifting forward from later lines and broadening the frontline landscape, said Tian Zhang, MD, who also emphasized that a heightened focus on treatment sequencing can help optimize the utilization of the various options available for all disease stages.

“These landscapes are expanding, and we are seeing great growth, development, and life-prolonging treatments for both bladder cancer and kidney cancer,” Zhang said in an interview with *OncLive*<sup>®</sup> following a State of the Science Summit™ on RCC and bladder cancer, which she chaired.

In the interview, Zhang, an associate professor in the Department of Internal Medicine at the Harold C. Simmons Comprehensive Cancer Center at UT Southwestern Medical Center, highlighted key points from each presentation shared at the meeting, including the benefits of multidisciplinary collaboration, how to select the best agents for each patient, and how treatments such as radiation in RCC and bladder-sparing chemoradiation in urothelial cancer fit into the overall treatment paradigms for these diseases. She also noted the importance of referring eligible patients to clinical trials that could provide them with the most effective treatments, and shed light on several clinical trials that are currently accruing patients with RCC and urothelial cancer.

***OncLive*<sup>®</sup>: Since 2017, there have been 9 FDA approvals for frontline treatments for patients with metastatic RCC. What factors go into making treatment decisions with all these options?**

*Zhang*: The treatment landscape has expanded quite a bit, just in the past 5 years for first-line metastatic kidney cancer. When we approach patients in the clinic to make those first-line treatment decisions, we consider their degree of tumor burden, their International Metastatic RCC Database Consortium [IMDC] risk stratification, and whether [their tumor is] more inflamed or less inflamed and driven by angiogenic factors.

Treatments can range from single-agent cabozantinib [Cabometyx], for example, for patients who are not candidates for immunotherapy, all the way to pure immunotherapy combinations with ipilimumab [Yervoy] and nivolumab [Opdivo], or VEGF TKIs and immunotherapy combinations. We currently have a host of these combinations, the most common of which are axitinib [Inlyta] plus pembrolizumab

[Keytruda], cabozantinib plus nivolumab, and lenvatinib [Lenvima] plus pembrolizumab. All these [regimens] are great options.

[When making these decisions,] we think about patient characteristics. Now, we also use a lot of clinical characteristics. I am hopeful that we will start to use more molecular typing and gene signatures to tailor treatments for individual patients. For example, we currently have some data on sarcomatoid features. We know patients with sarcomatoid features respond well to immunotherapy-based combinations, so they should receive checkpoint inhibition. On the other hand, pancreas metastases seem to be more driven by angiogenic factors. Therefore, I favor more of a VEGF antiangiogenic agent in those cases.

**Could you highlight the rationales for the phase 3 PDIGREE (NCT03793166), PROBE (NCT04510597), COSMIC-313 (NCT03937219), and MK-6482-012 (NCT04736706) trials that are exploring different combinations of approved frontline agents in RCC?**

Several large first-line phase 3 trials are ongoing. Two are being done in the cooperative group setting, 1 of which I am fortunate to lead. The PDIGREE trial is an adaptive trial where all patients have IMDC intermediate- and poor-risk disease and start with a pure immunotherapy combination of ipilimumab and nivolumab. At 3 months, they are randomized to either nivolumab or nivolumab with cabozantinib and assessed for radiographic response. Our key end point is overall survival. Hopefully, studying this sequence of treatments and including the early addition of the doublet VEGF/immunotherapy combination will make a difference and help patients live longer.

The other cooperative group trial is the PROBE study. This trial is specifically addressing the role of cytoreductive nephrectomy with immunotherapy-based combinations. All patients are put on their immunotherapy combination of choice. At the 3-month mark, they are randomized to either consolidative nephrectomy to resect the primary tumor, or a continuation of the systemic treatment. Both trials are open and accruing across the cooperative group settings.

The COSMIC-313 trial is an industry-sponsored triplet trial that has closed to accrual. The triplet [under examination] is ipilimumab, nivolumab and cabozantinib. We anticipate some results of COSMIC-313 soon.

Finally, the last trial that is ongoing globally is

MK-6482-012, an industry-sponsored study investigating a triplet [comprised] of lenvatinib, pembrolizumab, and belzutifan [Welireg]. This trial is investigating whether adding the hypoxia inducible factor-2 alpha [HIF2 ] inhibitor belzutifan to lenvatinib plus pembrolizumab makes a difference. A third cohort in that trial is receiving lenvatinib with pembrolizumab and the novel CTLA-4 inhibitor quavonlimab [MK-1308].

All these trials are ongoing in the front line and are open at UT Southwestern, so we encourage our patients to participate when they are good candidates.

**Tivozanib (Fotivda) is now approved in the second-line setting for patients with RCC. What has been observed with this agent, and what is the rationale of ongoing trials that are investigating it in combination with nivolumab?**

[Tivozanib was approved in March 2021.] The registrational trial, [the phase 3 TIVO-3 trial (NCT02627963)], compared tivozanib with sorafenib [Nexavar] and showed an improvement in progression-free survival in patients who had been previously treated with VEGF inhibition. Tivozanib is a good option and is generally tolerable—even in the refractory setting, where patients who are frailer may be able to tolerate it.

Several ongoing trials are studying tivozanib in combination with nivolumab. For example, 1 trial that is about to open at UT Southwestern is the [phase 3] TiNivo-2 trial [NCT04987203]. It is already open in multiple [sites] across the world. Another ongoing trial in the refractory space that is investigating combinations with immune checkpoint inhibitors is the [phase 3] CONTACT-03 trial [NCT04338269], which is looking at cabozantinib with atezolizumab [Tecentriq]. That trial is fully accrued, and it [randomized patients to either] cabozantinib with atezolizumab or cabozantinib alone. We are looking forward to seeing the results.

Finally, as my colleague, [James Brugarolas, MD, PhD, of the UT Southwestern Harold C. Simmons Comprehensive Cancer Center] highlighted, HIF2 inhibitors have also made a splash in refractory disease, particularly for patients with von Hippel-Lindau syndrome. Multiple trials are now looking at belzutifan in the refractory space for clear cell kidney cancer, as well as belzutifan in combination with cabozantinib and other VEGF TKIs.

An ongoing phase 3 study, [MK-6482-005 (NCT04195750)], is comparing belzutifan with everolimus [Afinitor] and is enrolling across the country. Another trial, [the phase 3 MK-6482-011 trial (NCT04586231)], is studying belzutifan and lenvatinib compared with cabozantinib in the phase 3 setting. Those are 2 other trials to look out for that may inform the refractory landscape.

**In your presentation, you spoke about MET inhibitors in the second line and later. What contributing factors go into selecting those agents as treatment options in these patients?**

In the refractory setting, tivozanib is a good option, even after patients have received immunotherapy-based combinations with cabozantinib, for example. We also have mTOR inhibition in the refractory setting, so many patients will see either everolimus alone or everolimus with lenvatinib, [which is] an approved combination. Those are all good treatment options.

In terms of sequencing treatments, each of the trials [I have mentioned] have shown improvements in prolonging overall survival in population-based data. However, when we are able to treat a single patient with these life-prolonging therapies, that is when we see a difference in terms of getting individual patients to live longer with sequential treatments. We are in a time where we are lucky enough to have multiple agents in the first line, as well as in the refractory space, so we need to optimize sequencing all these agents to help our patients live longer.

**Raquibul Hannan, MD, PhD, of the UT Southwestern Harold C. Simmons Comprehensive Cancer Center, spoke about radiation in oligometastatic RCC. How does radiation fit into the treatment paradigm for these patients?**

Oligometastatic kidney cancer is a special disease state where there are only a few sites of metastasis. If those sites can be ablated, perhaps we can delay systemic treatments and toxicities. That was the premise of Dr Hannan's discussion. He was able to prospectively conduct a phase 2 trial [NCT02956798] at UT Southwestern, [which evaluated] oligometastatic radiation to the oligometastatic disease, [and showed] a delay in systemic treatment. He is currently in the process of developing a potential further noninferiority trial that will likely be [done] in the cooperative group setting.

**Yair Lotan, MD, of the UT Southwestern Harold C. Simmons Comprehensive Cancer Center, spoke about the multidisciplinary approach to localized urothelial cancer. How important is this approach for these patients?**

In non-muscle invasive bladder cancer and muscle-invasive bladder cancer [MIBC] in the localized settings, we have many multidisciplinary discussions about optimizing treatments. For MIBC, we often do neoadjuvant chemotherapy followed by surgery, or we think about chemotherapy, radiation, and bladder preservation. [We certainly employ] a multidisciplinary approach for disease management in these patients.

In addition, as our systemic treatments are active, and we are seeing improvements in the refractory settings, these treatments are also moving into the localized settings. Our urologists and radiation oncologists are [conducting] multiple trials [that are] adding systemic treatments that are effective in the refractory space to the localized setting.

Dr Lotan also talked about an interesting new way to deliver chemotherapy within the bladder. For a long time, we have had intravesical delivery of chemotherapy, but there is a novel tool called a pretzel, a little device that can be inserted into the bladder, where it dwells and slowly releases chemotherapy before it is retrieved. That is an interesting, and hopefully effective, way to treat intraluminal bladder cancer.

**Neil Desai, MD, of the UT Southwestern Harold C. Simmons Comprehensive Cancer Center, spoke about bladder sparing in localized urothelial cancer. What patients would be the ideal candidates for this treatment approach?**

We carefully select patients for chemoradiation and talk through the risks and benefits when we are considering this option. Often, when tumors are less than 5 centimeters, we think radiation will be a definitive approach. My role in chemoradiation is to give radiosensitizing chemotherapy, oftentimes with agents such as a regimen from the UK of 5-fluorouracil and mitomycin, or a regimen of weekly cisplatin or twice-weekly gemcitabine. These are all standard options for patients when they are getting chemoradiation. These approaches are basically layering the chemotherapy on top of the radiation to hopefully improve the effects of definitive radiation.

**Qian Qin, MD, and Waddah Arafat, MD, both of the UT Southwestern Harold C. Simmons Comprehensive Cancer Center, spoke about treatment options in the first, second, and later lines of metastatic urothelial cancer. What does the current treatment space look like in the metastatic setting, and how has it evolved in recent years?**

Dr Qin gave a tour de force discussion about first-line metastatic bladder cancer treatments. She took us all the way through definitive trials looking at chemotherapy; methotrexate, vinblastine sulfate, doxorubicin hydrochloride, and cisplatin [MVAC]; dose-dense MVAC; gemcitabine with cisplatin; and gemcitabine with carboplatin. Those are still our go-to chemotherapy regimens for patients in the first-line setting. We often add maintenance avelumab [Bavencio], an immune checkpoint inhibitor, to frontline chemotherapy in patients who have achieved stable disease or better.

Finally, in the refractory space, we now have several good options in terms of standard-of-care treatments for patients

who have *FGFR* alterations that are translocations, infusions, or mutations of *FGFR2* or, more commonly, *FGFR3*. We have *FGFR* inhibitors, the approved one being erdafitinib [Balversa]. We also have accelerated approvals for 2 antibody-drug conjugates, enfortumab vedotin-ejfv [Padcev] and sacituzumab govitecan-hziy [Trodelvy]. Both [agents] are highly effective for stabilizing and managing patients with refractory urothelial cancer.

Because these treatments are so effective, we are also seeing them move into the frontline setting. The trial to watch out for is the [phase 3] EV-302 trial [NCT04223856]. This trial is based on the premise of the phase 2 [EV-103] study [NCT03288545], where enfortumab vedotin was combined with pembrolizumab [and showed] an objective response rate of 73.3% and a disease control rate of 93.3%. Almost all patients experienced disease control or better with the combination.

EV-302 is randomizing patients in the first-line metastatic setting to either enfortumab vedotin with pembrolizumab or standard gemcitabine and cisplatin chemotherapy. This trial, if successful, could unseat chemotherapy in the frontline setting. Stay tuned because it is still ongoing and accruing across the country. We are participating at UT Southwestern. Hopefully, we will see some good results and make the first-line metastatic urothelial [treatment] landscape even broader.

**What studies is UT Southwestern currently involved in?**

We participate in multiple trials, both at the industry-sponsored level as well as at the investigator-initiated level. We participate in these studies with collaborating institutions like Memorial Sloan Kettering Cancer Center, Dana-Farber Cancer Institute, and Fox Chase Cancer Center. I would encourage any referring physicians who are thinking that their patients might be a candidate for a trial to reach out to our group to see whether there is a trial that meets their patients' needs.

**What main message encapsulates the topics discussed at the meeting and the broader updates in RCC and urothelial cancer?**

As these treatments develop, we are seeing great advances. We are also hopefully improving care and prolonging life-extending treatments for all our patients in the standard-of-care setting. [We should also be] thinking about clinical trials when our patients are good candidates. We have trials available in all lines and all spaces of both bladder and kidney cancer. We are seeing active systemic treatments move into earlier disease spaces and earlier disease settings, to hopefully help with disease control and to prevent metastatic disease. ■