New Data Complicate the Treatment of Hormone-Sensitive Prostate Cancer

Featuring Celestia S. Higano, MD

DNA Repair Defects Are Strong Targets for Therapeutic Development in PC
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Making the Right Choices

ONCOLOGIC DISCOVERY AND DRUG approvals can sometimes outpace understanding and the adoption of new agents in practice. Clinical trial results that challenge the standard of care also make it more difficult for physicians to decide how to treat patients.

In this issue of Urologists in Cancer Care, we feature 3 articles on treatment decision-making for patients with prostate cancer. The first is a presentation by Celestia S. Higano, MD, professor in the Medical Oncology Division at the University of Washington School of Medicine in Seattle, Washington. She discusses the complexity of whether to use docetaxel (Taxotere) or abiraterone acetate (Zytiga) in combination with androgen deprivation therapy (ADT).

The 2 agents demonstrated efficacy in the CHAARTED, LATITUDE, and STAMPEDE trials, but the question of which drug to use in the clinic remains unanswered. On one hand, abiraterone improved overall survival with ADT in STAMPEDE and LATITUDE; on the other, docetaxel was effective with ADT in CHAARTED. For physicians trying to determine the best treatment option for their patients, the data seem to offer few clues as to which strategy is best. Higano says that toxicity profiles of the drugs and comorbidity burden can help determine which of these agents to use, or whether to use ADT alone.

Other options are starting to emerge in research, although not yet approved in clinical practice. According to Maha Hussain, MD, the Genevieve E. Teuton Professor of Medicine and deputy director of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois, when patients with metastatic castration-resistant prostate cancer (mCRPC) have DNA repair defects, poly (ADP-ribose) polymerase (PARP) inhibitors can be useful because of their ability to prevent tumor cells from repairing themselves.

These drugs may be most beneficial if a patient with mCRPC does not seem to be responding to ADT or even chemotherapy. Mutations in the BRCA1/2, ATM, PALB2, and RAD51B/RAD51C genes can indicate whether PARP inhibition would be beneficial. Genomic screening, which is also rapidly gaining traction in clinical practice, can help to identify which patients would receive the most benefit from PARP inhibitors.

When patients have prostate cancer and bone metastases, which further complicates treatment decision making, radium-223 (Xofigo) is the standard approved treatment. According to Richard G. Stock, MD, professor and director of genitourinary oncology at the Icahn School of Medicine at Mount Sinai in New York, moving isotope therapy with radium-223 earlier in the treatment paradigm could improve the outlook for these patients. Bone metastases tend to pose an extra challenge for treatment, but Stock maintains that radium-223 is a viable option due to its mechanism of action and tolerability.

Deciding on the best course of treatment for a patient with prostate cancer is challenging, but there are ways to determine which therapy is best for each individual. More studies are being conducted, more data will emerge, and this can only lead to a better understanding of these options and when to use them.

Mike Hennessy, Sr
Chairman & CEO
A Call for Clinical Research

WHEN I GRADUATED FROM medical school in the 1980s and decided to pursue a career in urologic surgery, most of the residency programs in the United States took 6 years—2 years of general surgery followed by 4 years of urology. Part of those 4 years of urologic training included, for the most part, a year spent in the research lab. There were 5-year residency programs available, but the majority at the time were built around the 2/4 construct.

I had the good fortune to be accepted into the urology program at Vanderbilt University Medical Center, and my time in the lab coincided with my first year of urology training, 3 years after medical school. This offered me a welcome respite after 2 long years of being on call every other night in general surgery, as it did for friends in other disciplines who were undergoing the same regimen.

Fortunately for me, my residency chairman at the time was committed to basic science research, particularly renal physiology and electrolyte imbalance. I was very interested in how the diversion technique of continent urinary reservoirs and orthotopic bladder reconstruction—new at the time—could result in a better quality of life without a stoma bag once a cystectomy had been performed. Consequently, I initiated 2 projects during that period. First, using a rat model and inducing unilateral obstruction of varied times, I tried to isolate the humoral factor that resulted in renal compensatory hypertrophy of the kidney. Second, in a canine model, I configured tubularized and detubularized segments of intestine, then measured and characterized peristaltic activity in these types of reconstruction.

What started as a period I initially viewed as a time away from the clinic, less stress, and not being on call became one of my most valuable experiences, because it shaped much of my clinical thinking and approach to science. (The downside was that it subjected my immune system to a daily barrage of rat and canine dander, rendering me deathly allergic.) The academic rigor necessary to approach the hypothesis and devise the study also was invaluable early in my career. Additionally, during this experience I had the good fortune to be befriended by 2 people—with strikingly diverse backgrounds—whom I would never have met otherwise.

James Phillips was a gentleman and high school graduate who essentially took care of most of the animals in the lab and assisted with anesthesia, intravenous procedures, etc, especially with the larger species. As a young teenager in Nashville, Tennessee, before World War II, he had the opportunity to work with Vivien Thomas, who would leave the Vanderbilt University labs and join Alfred Blalock, MD, at Johns Hopkins Hospital in Baltimore, Maryland, to pioneer pediatric heart surgery and correction of tetralogy of Fallot. The stories of those early days in the lab were mesmerizing.

The second was a pipe-smoking scholar whose lab was on the way to our favorite watering hole. Although I stopped by on many occasions and asked him to join us for lunch, which was always politely declined, he would often take the time to try to understand what the surgeons were doing in the lab. This was the great Stanley Cohen, PhD, who earlier, in 1986, shared the Nobel Prize in Physiology or Medicine for his discovery of the epidermal growth factor family and its receptors. My intermittent discussions in his lab would change the way I viewed cancer biology.

Many do not realize that residents do not get such opportunities today. Save for a few, most programs have gone back to a 5-year training, the required minimum to achieve board certification in urology; the research year is not funded by Medicare, so hospitals do not receive direct graduate medical education funds from the government. Thus, an institution that still provides basic science research time has to support that resident with internal sources or grants. The focus of research for the residents today is less about science or drug development and more about health economics outcome research and real-world practice patterns with attempts to optimize care, which are all very much needed in today’s medical environment.

However, there is still a role for urologists, even those currently in practice, to be active participants in research and become clinical scientists. Many successful groups across the United States have launched clinical research divisions within the practice that have played an important role in the development and ultimate approval of many of the new therapies for advanced prostate cancer that we prescribe, as well as some of the biomolecular markers being used for diagnosis and management. I see this trend continuing into the future. Newer technologies and treatment paradigms are constantly being introduced into the marketplace and require validation and randomized trials. There is no reason we as specialists should not be involved in these trials, as rapid accrual is essential.

We talk about creating centers of excellence and physician champions to advance care. I truly believe that by doing the research, one gets a deeper and better understanding of the disease state, which will ultimately improve care and outcomes. We should all strive to support these collaborative efforts.
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FDA Approves Nivolumab/Ipilimumab for Frontline RCC

The FDA has approved the combination of nivolumab (Opdivo) and ipilimumab (Yervoy) as a frontline treatment for intermediate- and poor-risk patients with advanced renal cell carcinoma (RCC). The approval is based on the results of the phase III CheckMate-214 trial in which frontline treatment with the combination of nivolumab and ipilimumab reduced the risk of death by 32% compared with sunitinib (Sutent) for patients with metastatic RCC. The risk reduction was 37% in patients with intermediate- and poor-risk RCC, who constituted about 75% of the intent-to-treat (ITT) population.

In the randomized trial, the median overall survival (OS) was not reached with the combination versus 32.9 months with sunitinib (HR, 0.68; 99.8% CI, 0.49-0.95; \( P = .0003 \)). In those patients with intermediate- and poor-risk RCC, the median OS was not reached in the nivolumab/ipilimumab arm but was 26.0 months in the sunitinib arm (HR, 0.63; 99.8% CI, 0.44-0.89; \( P < .0001 \)). There was not a benefit for the combination versus sunitinib in those with favorable risk.

The most common sites of metastasis were the lungs (approximately 70%), lymph nodes (approximately 50%), liver (approximately 20%), and bone (approximately 20%). Coprimary endpoints were overall response rate per independent radiology review committee (iRRC), progression-free survival (PFS; per iRRC), and OS.

Across the full ITT population, the median PFS was not improved (12.4 vs 12.3 months; HR, 0.98; 99.1% CI, 0.79-1.23; \( P = .8498 \)). PFS in the intermediate- and poor-risk group was 11.6 months with the combination versus 8.4 months with sunitinib (HR, 0.82; 99.1% CI, 0.64-1.05; \( P = .0331 \)). A \( P \) value of .009 was required for significance.

Across the full study, the confirmed objective response rate was 39% and 32% (\( P = .0191 \)) in the nivolumab/ipilimumab and sunitinib groups, respectively. The confirmed overall response rate in the intermediate/poor-risk patients was 42% in the nivolumab/ipilimumab group compared with 27% in the sunitinib group (\( P < .0001 \)). Nine percent of patients in the nivolumab/ipilimumab group had a complete response (CR) and 32% had a partial response (PR), compared with 1% CR and 25% PR rates, respectively, in the sunitinib group. The median duration of response was significantly superior with the combination compared with sunitinib (not reached vs 18.2 months).

Favorable-risk patients, in contrast, had a significantly higher confirmed overall response rate with sunitinib versus the combination (52% vs 29%; \( P = .0002 \)), as well as a significantly longer PFS (25.1 vs 15.3 months; \( P < .0001 \)).

In those with PD-L1 expression \( \geq 1\% \), the median PFS was significantly longer with the immunotherapy combination than with sunitinib (22.9 vs 5.9 months; HR, 0.48; \( P = .0003 \)). Those with PD-L1 expression <1% did not benefit from the combination (HR, 1.00; \( P = .9670 \)).

FDA Warns Against Single-Agent Checkpoint Inhibition for PD-L1-Low Untreated Urothelial Carcinoma

The FDA has issued a drug safety notification warning against the use of frontline single-agent immune checkpoint inhibition for patients with PD-L1–low expressing platinum-eligible urothelial carcinoma, following a demonstration of lower overall survival with pembrolizumab (Keytruda) and atezolizumab (Tecentriq) compared with platinum-based chemotherapy.

The FDA warning was based on an assessment conducted by a data monitoring committee (DMC) for the phase III KEYNOTE-361 study and the phase III IMvigor130 study. The KEYNOTE-361 (NCT02853305) and the IMvigor 130 (NCT02807636) studies are exploring pembrolizumab and atezolizumab, respectively, with or without chemotherapy compared with chemotherapy or the immunotherapy alone.

The DMC identified that patients with PD-L1–low status had decreased overall survival in the single-agent immunotherapy arms compared with chemotherapy. Both trials have stopped enrolling patients with PD-L1–low status to the monotherapy arms. Other arms of the trials will remain open to patients with PD-L1–low tumors.

Each study used a different technique and cutoff points to define PD-L1 status. The KEYNOTE-361 trial used a combined positive score (CPS) for testing, which is the percentage of PD-L1–low tumors to the monotherapy arms. Other arms of the trials will remain open to patients with PD-L1–low tumors.

Across the full study, the confirmed objective response rate was 39% and 32% (\( P = .0191 \)) in the nivolumab/ipilimumab and sunitinib groups, respectively. The confirmed overall response rate in the intermediate/poor risk patients was 42% in the nivolumab/ipilimumab group compared with 27% in the sunitinib group (\( P < .0001 \)). Nine percent of patients in the nivolumab/ipilimumab group had a complete response (CR) and 32% had a partial response (PR), compared with 1% CR and 25% PR rates, respectively, in the sunitinib group. The median duration of response was significantly superior with the combination compared with sunitinib (not reached vs 18.2 months).

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New Data Complicate the Treatment of Hormone-Sensitive Prostate Cancer

By Ariela Katz

CLINICAL TRIAL RESULTS THAT challenge the standard of care sometimes make it more difficult for physicians to decide how to treat their patients. Such is the case with the CHAARTED, LATITUDE, and STAMPEDE trials1-3, which expanded information on the value of docetaxel (Taxotere) or abiraterone acetate (Zytiga) in combination with androgen deprivation therapy (ADT) in prostate cancer. Data from these trials demonstrate the heterogeneous nature of prostate cancer and its subtypes, highlighting the importance of a more cautious approach in choosing therapies for patients with metastatic hormone-sensitive prostate cancer (mHSPC). Disease characteristics, comorbidities, treatment-related toxicities, and patient preferences all deserve heightened consideration, according to Celestia S. Higano, MD.

“Historically, the standard of care for mHSPC was, and continues to be, ADT. But now this paradigm is a bit disturbed by the fact that we have the option of adding either docetaxel or abiraterone,” said Higano, professor in the Medical Oncology Division at the University of Washington School of Medicine in Seattle, during a presentation at New York GU™: 11th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies that Physician’s Education Resource® (PER®) hosted in March.

In the CHAARTED study, which looked at ADT with or without docetaxel, volume of disease had an inverse relationship with overall survival (OS). High-volume metastatic disease was defined as the presence of visceral disease and/or more than 4 bone metastases.4

“When we look at [patients with] high-volume disease in CHAARTED, we see this rather dramatic improvement in overall survival with the addition of docetaxel. But in the low-volume disease [group], we didn’t see that, and that was confirmed when they looked at the longer-term follow-up for these patients,” Higano said. Therefore, it looks like docetaxel does not benefit patients with low-volume disease, whereas patients with high-volume disease do benefit.

When considering disease volume and status, generally high-volume and de novo disease are the worst factors of outcome, Higano said. High-volume disease with a de novo
presentation has a median OS of about 3 years, whereas high-volume disease with recurrent or low-volume disease with de novo presentation has a median OS of close to 5.5 years. In low-volume, recurrent disease, the median OS is about 8 years.5

In arm G of the STAMPEDE trial, which studied ADT with or without abiraterone acetate, there was an OS benefit for all patients treated with abiraterone because the investigators did not stratify patients by disease volume, Higano said, and they looked at patients with N1M0 disease. However, she noted that there was excellent prostate-specific antigen (PSA) control over 3 to 5 years. In a meta-analysis of patients with low-volume disease in the CHAARTED and GETUG-AFU15 studies, there was no OS benefit for adding either docetaxel or abiraterone.6

Another factor that should be considered is the adverse event (AE) profiles of docetaxel and abiraterone. In CHAARTED and arm C of STAMPEDE, there were more cardiac-related toxicities noted with abiraterone versus placebo, along with higher rates of vascular events, mainly hypertension.1,3 For docetaxel, in terms of grade 3/4 toxicities, neutropenia was the most common (12.1%). Febrile neutropenia occurred in 6.1% of patients, while other common AEs included fatigue (4.1%) and sensory neuropathy (0.5%) (TABLE 1).2

It is also important to consider treatment duration and patient age. Docetaxel is given for 6 cycles in the 2 trials, translating to a regimen of ADT plus 4 months of chemotherapy. Although abiraterone is an oral agent, the median duration of treatment is 33 months, making it a continuous therapy until the patient develops castration-resistant prostate cancer, Higano said. She noted that in STAMPEDE arm G and the LATITUDE trial, which both looked at added abiraterone, when the patient populations were assessed for age, the magnitude of survival benefit seemed to be greater for patients younger than 70 versus those who were 70 or older (HR, 1.54; 95% CI, 1.14-2.08; \( P = .005 \)). This could be due to the fact that there tend to be more comorbidities with an older population; however, Higano cautioned that the proportion of patients younger than 70 years was fairly small in both trials.2,3

Patients’ responses to ADT alone should also be considered before adding docetaxel and/or abiraterone. In the SWOG 9346 trial, investigators assessed 1134 patients who were being treated with intermittent versus continuous ADT for 8 months. At the 7-month mark, they looked at the patients’ PSA levels and separated them into low, intermediate, and high risk.7 “Those with PSA less than or equal to 0.2 were the lowest-risk group and had a median survival of 75 months, which is dramatically different from those whose PSA [was up to a] 4, whose median survival was 44 months. The high risk category included those with a PSA over 4, with a median survival of 13 months,” Higano explained.

She added that ADT alone is still a viable option for some patients. “If you’re in a situation where you may be wondering if ADT alone may be reasonable for a patient, you may want to give them ADT alone and see where they fall at 6 or 7 months, because at that point it’s not too late to add abiraterone or docetaxel,” Higano recommended. “If they fall into the low-risk group, you might want to consider ADT alone or ADT plus abiraterone, and for intermediate- and high-risk, you...”

<table>
<thead>
<tr>
<th>Table 1. Clinically Significant Toxicities for Consideration in Treatment Decision Making for mHSPC</th>
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<tr>
<td><strong>Docetaxel</strong></td>
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<tr>
<td>Hematologic</td>
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<tr>
<td>Liver</td>
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<td>Diarrhea</td>
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<td>Nausea</td>
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<td>Pulmonary</td>
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<td>Atrial fibrillation</td>
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<td>Hypertension</td>
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<td>Peripheral neuropathy</td>
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<td>Alopecia</td>
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<tr>
<td>Skin rash</td>
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<tr>
<td>Fatigue/asthenia</td>
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<tr>
<td>Hypersensitivity</td>
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mHSPC indicates metastatic hormone-sensitive prostate cancer.

<table>
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<th>Table 2. Suggested Framework for Therapy Selection in mHSPC</th>
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<tr>
<td><strong>Favors ADT plus docetaxel</strong></td>
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<tr>
<td>Shorter treatment duration: 18 weeks vs continuous</td>
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<tr>
<td>Patient has difficulty swallowing medications or taking them on an empty stomach</td>
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<tr>
<td>Patient has poor diabetic control</td>
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<tr>
<td>Patient has contraindications for prednisone</td>
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<tr>
<td>Patient is at risk for heart failure or hypervolemia</td>
</tr>
<tr>
<td><strong>Favors ADT plus abiraterone acetate and prednisone</strong></td>
</tr>
<tr>
<td>Patient prefers oral to IV therapy or is unfit for chemotherapy</td>
</tr>
<tr>
<td>Patient has preexisting neuropathy</td>
</tr>
<tr>
<td>Patient has low-volume disease</td>
</tr>
<tr>
<td><strong>Favors ADT alone with or without bicalutamide</strong></td>
</tr>
<tr>
<td>Patient has excellent PSA decline, especially with low-volume metastases</td>
</tr>
<tr>
<td>Patient is unfit for docetaxel</td>
</tr>
<tr>
<td>Patient has a high degree of comorbidities (hepatic, cardiac dysfunction)</td>
</tr>
<tr>
<td>Less financial cost</td>
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ADT indicates androgen deprivation therapy; IV, intravenous; mHSPC, metastatic hormone-sensitive prostate cancer; PSA, prostate-specific antigen.
could consider ADT with either abiraterone or docetaxel." She stressed that this was not based on level 1 evidence, but it is how she operates as a clinician. Higano also detailed some other guiding factors for therapy selection in mHSPC (TABLE 2).

Looking to the future, no head-to-head trials are set to begin that explore whether docetaxel or abiraterone is a superior agent to add to ADT. However, Higano said, the real question at present is how the use of all of these agents earlier in mHSPC, or even in nonmetastatic castration-resistant disease, will impact subsequent therapies.

**References**


**THE USE OF POLY (ADP-RIBOSE) polymerase (PARP) inhibitors in patients with a variety of tumor types is backed by a growing body of research. According to Maha Hussain, MD, the Genevieve Teuton Professor of Medicine and deputy director of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago, Illinois, there is now strong justification for clinical trials of PARP inhibitors in patients with prostate cancer.**

“Metastatic prostate cancer is very complex, with a marked inter- and intra-patient heterogeneity and diversity. Therapy development, from my perspective, must focus on the totality of the biology if we want better care for our patients. DNA repair deficiencies have emerged as a promising therapeutic target in metastatic castration-resistant prostate cancer [mCRPC],” Hussain said during a presentation at New York GU*: 11th Annual Interdisciplinary Prostate Cancer Congress* and other Genitourinary Malignancies.

She noted that there are compelling data implicating PARP-1 in the mediation of DNA repair responses to alkylating agents, cellular survival in BRCA-deficient cells, and androgen receptor (AR)-mediated prostate cancer cellular proliferation. Further, PARP-1 interacts with the androgen signaling cascade, and castration-resistant tumor cells exhibit increased PARP-1 activity.

These data prompted a clinical trial looking at the combination of temozolomide (Temodar) and the PARP inhibitor veliparib (ABT-888) in patients with mCRPC, with the idea to replicate what was done preclinically. However, the overall results were not that promising, with a prostate-specific antigen (PSA) response rate of 8% based on 2 of 25 evaluable patients achieving a confirmed PSA decline of ≥30%. In the remaining 23 patients, 13 had stable PSA and 10 had PSA progression. None of the 16 patients with measurable disease for whom data were available achieved an objective response.¹

Hussain noted that the reason for this lack of significant response could be that adding PARP inhibition to castration therapy provides a better tumor effect, targeting AR-signaling and the PARP pathway simultaneously. Additionally, Hussain said, there have been no predictive biomarkers to select patients for response to this regimen, but some emerging data suggested that ERG fusions could be a predictor for sensitivity to AR and PARP targeting.

In an ongoing phase II trial, investigators, led by Hussain, tested the hypotheses that targeting AR and PARP would lead to better outcomes in patients with mCRPC and that ETS fusions would serve as a predictive biomarker for the

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**DNA Repair Defects Are Strong Targets for Therapeutic Development in PC**

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**REFERENCES**


response to treatment. Every patient underwent a metastatic disease biopsy. If eligible, they were stratified either as ETS fusion positive or negative and then randomized to receive the control arm of abiraterone acetate (Zytiga) and prednisone or the experimental arm of abiraterone acetate and prednisone plus veliparib. The primary endpoint was PSA response rate.

The study was negative overall, and although there was a trend in favor of the combination treatment, this was not statistically significant. ETS fusion positivity or negativity also did not predict for a better outcome. However, the investigators observed that in a cohort of 80 patients with adequate tissue for tumor sequencing, 20 had DNA damage repair defects, which were either homozygous or deleterious mutations. The most frequent were BRCA2 (65%), ATM (20%), BRCA1 (5%), PALB2 (5%), and RAD51B/RAD51C (5%).

“There was a fair amount of genomic alteration, but the 1 consistent factor was that the patients had DNA repair defects and had a response as reflected by PSA, and these responses were quite deep,” Hussain said.

PSA declines were statistically significant in patients with DNA repair defects compared with patients with wild-type disease (90% vs 56.4%, respectively; \( P = .007 \)), and the measurable disease response rate was also higher for patients with DNA repair defects (87.5% vs 37.5%; \( P = .0009 \)).

“Contrary to conventional wisdom up to now, where the belief was that patients with DNA repair defects did worse, in our trial, those patients did better,” Hussain said. “This is a previously unknown observation that the patients who were on the abiraterone-only arm still did better compared with patients who had wild-type disease.”

Hussain et al then performed a multivariate analysis of progression-free survival (PFS) by biomarker status that incorporated clinical factors and other molecular factors. They noted that when they controlled for these factors, DNA damage repair defect was the biomarker that predicted the best outcome to PARP inhibition therapy. The median PFS for patients with DNA damage repair defects was 14.5 months compared with 8.0 months for those with wild-type disease (\( P = .02 \)).

Other molecular alterations also had a significant association with benefit from PARP therapy. Patients with a TP53, PTEN, or PIK3CA mutation all had worse outcomes; however, DNA damage repair defects were the strongest predictor (TABLE 1).

“When we are designing clinical trials,” Hussain said, “it is very difficult for us to understand the genomic or molecular profile of the tumor because no tumor has such a unique feature that it’s going to predict 100% response to treatment.”

The main observation noted in these data was that patients with DNA damage repair defects responded to AR-targeted drugs with or without a PARP inhibitor. Another study’s findings recently demonstrated a similar observation based on germline data, affirming that these patients with mCRPC seem to respond better than expected to AR-targeted therapy.

In the single-arm phase II TOPARP-A trial, a group of heavily pretreated patients with mCRPC were given the PARP inhibitor olaparib (Lynparza) as an experimental treatment and underwent tumor sequencing. “Interestingly, there were 16 patients of a cohort of about 50 patients with [the] DNA repair defect, and 14 of the 16 responders were biomarker positive, and this translated into what I would consider meaningful clinical benefit in terms of delaying [progression] and in PFS,” she commented.

Hussain noted that the trial showed that about 90% of mCRPC tumors harbor potentially clinically actionable molecular alterations. Several of these molecular alterations appear to be novel, and there are clinical trials starting that address some of those. However, she said that an important finding of the TOPARP trial was that over 20% of patients with mCRPC harbor DNA damage repair pathway defects, specifically in BRCA1/2, ATM, and other genes.

Clinically, in other cancers, these are considered the “canonical” DNA damage repair defects. In prostate cancer, it seems there are other potential BRCA1ness alterations, but Hussain posed the question of whether patients with these mutations are responsive to PARP inhibition.

The phase II BRCAAway trial is currently recruiting patients with mCRPC and DNA repair defects (NCT03012321). Patients will be entered into the study if they either have enough tissue for a biopsy or known germline mutations in BRCA1/2 or ATM. They will then be randomized to abiraterone plus prednisone, olaparib alone, or the combination, with the potential to cross over after progression. Patients who have a “noncanonical” alteration will be entered into a single-arm cohort to see if there’s a signal from treatment with olaparib monotherapy.

Currently, there are 6 PARP inhibitors being evaluated.
in prostate cancer in clinical trials (Table 2). Hussain notes that further study is needed to fully understand DNA repair defects and how to target them most effectively.

Table 2. Select Clinical Trials of PARP Inhibitors in Prostate Cancer

<table>
<thead>
<tr>
<th>Agent (developer)</th>
<th>Trial Description</th>
<th>Phase</th>
<th>Primary Endpoint(s)</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olaparib (AstraZeneca)</td>
<td>Versus enzalutamide or abiraterone in patients with mCRPC who have failed prior treatment with a new hormonal agent and have homologous recombination repair gene mutations (PROfound)</td>
<td>III</td>
<td>rPFS</td>
<td>NCT02987543</td>
</tr>
<tr>
<td></td>
<td>Combined with abiraterone and prednisone/prednisolone vs placebo in patients with mCRPC</td>
<td>II</td>
<td>Safety and tolerability; rPFS</td>
<td>NCT01972217a</td>
</tr>
<tr>
<td></td>
<td>With or without abiraterone and prednisone versus abiraterone and prednisone alone in patients with mCRPC and DNA repair defects</td>
<td>II</td>
<td>PFS</td>
<td>NCT03012321</td>
</tr>
<tr>
<td></td>
<td>With radium-223 dichloride in patients with mCRPC and bone metastases</td>
<td>I/II</td>
<td>MTD; rPFS</td>
<td>NCT03317392b</td>
</tr>
<tr>
<td></td>
<td>With or without cediranib in patients with mCRPC</td>
<td>II</td>
<td>rPFS</td>
<td>NCT02989317</td>
</tr>
<tr>
<td></td>
<td>In patients with high-risk, nonmetastatic, biochemically recurrent prostate cancer following radical prostatectomy</td>
<td>II</td>
<td>PSA response</td>
<td>NCT03047135</td>
</tr>
<tr>
<td></td>
<td>Maintenance following treatment with cabazitaxel, caboblatin, and prednisone in patients with aggressive variant prostate cancer</td>
<td>II</td>
<td>PFS</td>
<td>NCT03263650</td>
</tr>
<tr>
<td>Rucaparib (Clovis Oncology)</td>
<td>In patients with mCRPC and evidence of a homologous recombination gene deficiency (TRITON2)</td>
<td>II</td>
<td>ORR; PSA response</td>
<td>NCT02952534</td>
</tr>
<tr>
<td></td>
<td>Versus physician’s choice of therapy in patients with mCRPC and evidence of a homologous recombination gene deficiency (TRITON3)</td>
<td>III</td>
<td>rPFS</td>
<td>NCT02975934</td>
</tr>
<tr>
<td></td>
<td>In patients with mHSPC harboring germline DNA repair defects (TRIUMPH)</td>
<td>II</td>
<td>PSA response</td>
<td>NCT03413995b</td>
</tr>
<tr>
<td></td>
<td>Nivolumab in combination with rucaparib, docetaxel, or enzalutamide in patients with mCRPC (CheckMate 9KD)</td>
<td>II</td>
<td>ORR; PSA response</td>
<td>NCT03338790</td>
</tr>
<tr>
<td>Niraparib (Tesaro)</td>
<td>In patients with mCRPC and DNA repair anomalies (Galahad)</td>
<td>II</td>
<td>ORR</td>
<td>NCT02854436</td>
</tr>
<tr>
<td></td>
<td>With apalutamide or abiraterone and prednisone in patients with mCRPC with or without DNA repair defects (BEDIVERE)</td>
<td>I</td>
<td>Recommended phase II dose; incidence and severity of AEs</td>
<td>NCT02924766</td>
</tr>
<tr>
<td>Talazoparib (Pfizer)</td>
<td>In patients with mCRPC who previously received taxane-based chemotherapy and progressed on at least 1 novel hormonal agent (enzalutamide and/or abiraterone acetate/prednisone)</td>
<td>II</td>
<td>ORR</td>
<td>NCT03148795</td>
</tr>
<tr>
<td></td>
<td>With physician’s choice of a novel hormonal therapy in patients with mCRPC and a DNA repair defect versus novel hormonal therapy alone (TALAPRO-2)</td>
<td>III</td>
<td>Dose confirmation for combinations; rPFS</td>
<td>NCT03395197</td>
</tr>
<tr>
<td>GGB-290 (BeiGene)</td>
<td>With temozolomide in patients with locally advanced or metastatic solid tumors</td>
<td>I/II</td>
<td>DLTs; incidence and severity of AEs</td>
<td>NCT03150810</td>
</tr>
<tr>
<td>Veliparib (AbbVie)</td>
<td>With or without abiraterone acetate and prednisone in patients with mCRPC</td>
<td>II</td>
<td>PSA response</td>
<td>NCT01576172b</td>
</tr>
<tr>
<td></td>
<td>In patients with solid tumors that did not respond to prior therapy</td>
<td>I</td>
<td>MTD, DLT, recommended phase II dose</td>
<td>NCT00892736b</td>
</tr>
</tbody>
</table>

AE indicates adverse event; DLT, dose-limiting toxicity; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; MTD, maximum tolerated dose; ORR, objective response rate; PARP, poly(ADP-ribose) polymerase; PFS, progression-free survival; PSA, prostate-specific antigen; rPFS, radiographic progression-free survival.

*Trial is active but not recruiting participants

**Trial is not yet recruiting participants

REFERENCES


Moving Radium-223 Forward in the Treatment Timeline for PC With Bone Metastases

By Ariela Katz

RADIUM-223 (XOFIGO) HAS EFFICACY in treating patients with prostate cancer and bone metastases, but is usually introduced into the patient’s treatment plan after they have symptomatic disease. These symptoms are often painful, and the metastases can be difficult to treat at this stage. Moving radium-223 up in the treatment paradigm for these patients could provide better outcomes and longer survival, according to Richard G. Stock, MD, professor and director of genitourinary oncology at the Icahn School of Medicine at Mount Sinai in New York.

“Clearly, what we know is, when bone metastases are present, patients have a decrease in overall survival. This is a problem that needs to be addressed, and skeletal tumor burden is an independent predictor of death in patients with advanced prostate cancer,” Stock said during a presentation at New York GU*: 11th Annual Interdisciplinary Prostate Cancer Congress® and Other Genitourinary Malignancies.

Bone metastases are quite common in prostate cancer, Stock said. About 14% of the patients who undergo surgical or chemical castration will develop castration-resistant prostate cancer (CRPC), and about 90% of those patients will develop metastases in the bone. The 5-year survival rate for patients with bone metastases is about 30%.1

Typically, prostate cancer progresses from nonmetastatic local disease (M0), with a possible rise in prostate-specific antigen levels and biochemical relapse, to CRPC when patients fail androgen-deprivation therapy. Patients with newly diagnosed metastatic CRPC (M1) are often chemotherapy naïve, and 4% of patients with prostate cancer present initially with M1, hormone-sensitive disease.

The treatment challenge is that prostate tumor cells may colonize the bone during this disease progression. In vitro data show that the colonization of bone tissue may be driven by chemotraction and preferential attachment.2,3 Prostate cancer metastases are also associated with osteoblastic activity, so the balance shifts from bone destruction to bone deposition, where the osteoblasts secrete more proteins to form excess bone beyond the body’s bone resorption capabilities. This leads to osteoblastic lesions in the mineralized bone tissue where tumor cells have gathered, and it correlates with higher levels of alkaline phosphatase and osteocalcin, which would signify liver or gallbladder toxicity.4,5

When bone metastases are present, overall survival (OS) is lower. Results from a population-based cohort study of patients with prostate cancer showed that fewer patients with bone metastases were alive at 5 years (3%; 95% CI, 2.2%-3.4%) than patients with no bone metastases (56%; 95% CI, 54.9%-56.7%). In the study, 23,087 patients had an initial diagnosis of prostate cancer; 22,404 of those patients had no bone metastases, and 569 presented with bone metastases at diagnosis.6

Investigators in the field of prostate cancer therapeutics have seen different isotopes being used to treat bone metastases in patients with prostate cancer, but most have fallen by the wayside due to bone marrow toxicities. Radium-223 has remained a standard radiotherapy since its approval by the FDA in 2013, due in part to its more favorable toxicity profile and its mechanism of action.

Radium-223 is an alpha-pharmaceutical that targets bone metastases by mimicking calcium, forming complexes with the bone mineral hydroxyapatite at areas of increased bone turnover, such as bone metastases. The short range of the alpha particles emitted (<10 cell diameters) limits damage to the surrounding normal tissue, leading to less bone marrow toxicity. The alpha particles predominantly cause double-strand DNA breaks in adjacent cells, resulting in the antitumor effect on bone metastases.7

Because radium-223 is absorbed primarily by the bone marrow, there is a small risk for bone marrow–related toxicities, such as myelosuppression. However, radium-223 can also lead to adverse events (AEs) outside of the bone. The agent can be absorbed by other organs, including the gastrointestinal system, leading to AEs that can include nausea, diarrhea, and vomiting.7

Stock recommended watching out for these and other AEs. “For those of us who do this in a clinical practice, we check the blood count, and it is very rare that patients have to discontinue treatment due to myelosuppression,” he said. It is important, he continued, to monitor patients with evidence of compromised bone marrow reserve closely and provide supportive care measures when clinically indicated. Radium-223 should be discontinued in patients who experience life-threatening complications despite supportive care for bone marrow failure.

Stock also said that a key reason why radium-223 is an effective drug for patients with prostate cancer is how it’s eliminated. After an intravenous injection, less than 1% of radium-223 dichloride remains in the blood after
Although we don’t really know why it leads to the increased fractures.11 “We now know not to use that combination treatment, with abiraterone (Zytiga), which led to greater risk of fractures,” Stock said. Ultimately, Stock said, radium-223 is generally used early in the management of castration-resistant disease if the patient exhibits symptomatic bone metastases with or without small-volume pelvic or retroperitoneal lymph node metastases, with no evidence of visceral metastases, and with good hematologic function.

Looking to the future, there are other clinical trials testing the efficacy and safety of radium-223 in patients with prostate cancer with bone metastases combined with other therapies (Table). However, Stock cautioned that in a phase III trial (NCT02043678), radium-223 was combined with abiraterone (Zytiga), which led to greater risk of fractures.11 “We now know not to use that combination treatment, although we don’t really know why it leads to the increased risk of fracture,” he said.

<table>
<thead>
<tr>
<th>Agent Combined With Radium-223</th>
<th>Phase</th>
<th>ClinicalTrials.gov Identifier</th>
<th>Description</th>
<th>Primary Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzalutamide (Xtandi)</td>
<td>III</td>
<td>NCT02194842</td>
<td>Combination versus enzalutamide monotherapy in patients with asymptomatic or mildly symptomatic CRPC and bone metastases</td>
<td>Radiological PFS</td>
</tr>
<tr>
<td>Pembrolizumab (Keytruda)</td>
<td>II</td>
<td>NCT03093428</td>
<td>Safety and tolerability of the combination as a treatment for CRPC and bone metastases</td>
<td>Extent of immune cell infiltration</td>
</tr>
<tr>
<td>Atezolizumab (Tecentriq)</td>
<td>I</td>
<td>NCT02814669</td>
<td>Safety and tolerability of the combination in patients with metastatic CRPC who have progressed after treatment with an androgen pathway inhibitor</td>
<td>ORR, DLT rate, percentage of patients with AEs</td>
</tr>
</tbody>
</table>

AE indicates adverse event; CRPC, castration-resistant prostate cancer; DLT, dose-limiting toxicity; PFS, progression-free survival; ORR, objective response rate.

REFERENCES


24 hours. Fecal excretion, the major route of elimination, removes 63% of the agent within 1 week; less than 5% is excreted through the urine.7

In the phase III ALSYMPCA study of radium-223 in patients with symptomatic CRPC with skeletal metastases (NCT00699751), results showed that radium-223 significantly improved OS versus a placebo (median OS, 14.9 vs 11.3 months; HR, 0.70; 95% CI, 0.55-0.88; P <.001). In a subgroup analysis of the study, radium-223 provided benefit to patients in all subgroups.8

In a phase II prospective study of radium-223 in patients with CRPC with bone metastases (NCT01516762), results showed that the agent was well tolerated with no new safety concerns observed. The study found that patients with more advanced disease were less likely to benefit from radium-223, and investigators recommended that clinicians consider baseline characteristics and therapy sequence for greatest clinical value.9

The phase II prospective study was part of an expanded access program that was approved in 2012, with the goal to monitor acute and long-term safety of radium-223 in patients with CRPC and symptomatic bone metastases. The drug was made available at qualified clinical sites to patients who could not participate in a controlled clinical trial.10 Ultimately, Stock said, radium-223 is generally used early in the management of castration-resistant disease if the patient exhibits symptomatic bone metastases with or without small-volume pelvic or retroperitoneal lymph node metastases, with no evidence of visceral metastases, and with good hematologic function.

Looking to the future, there are other clinical trials testing the efficacy and safety of radium-223 in patients with prostate cancer with bone metastases combined with other therapies (Table). However, Stock cautioned that in a phase III trial (NCT02043678), radium-223 was combined with abiraterone (Zytiga), which led to greater risk of fractures.11 “We now know not to use that combination treatment, although we don’t really know why it leads to the increased risk of fracture,” he said.
The current FDA announcement pertains only to the two
phase III studies, and it remains unclear whether the FDA will
mandate stricter testing for other early-stage clinical trials for
the checkpoint inhibitors in urothelial carcinoma, as studies are
beginning to explore these agents in patients with non-muscle
invasive bladder cancers.

Task Force Changes Stance
on Value of PSA Test
In a departure from earlier guidance, the US Preventive Services
Task Force (USPSTF) has concluded that there is a small mortal-
ity benefit associated with prostate-specific antigen (PSA)-based
prostate cancer screening for men aged 55 to 69 years, “justify-
ing the offer of PSA testing selectively to men in this age group
based on the judgment of the physician and the values of the
patient” (TABLE).

Table. USPSTF Updated Guidelines on PSA Testing

| ▶ Men aged 55 to 69 years should make an individual decision regarding whether to undergo periodic PSA-based screening for prostate cancer. |
| ▶ A discussion with a clinician should include the benefits of screening, as well as these potential harms: |
| ▶ False positive results that require additional testing and possibly prostate biopsy |
| ▶ Overdiagnosis and overtreatment |
| ▶ Complications such as incontinence and erectile dysfunction |
| ▶ PSA testing for prostate cancer is not recommended for men aged 70 years and older. |

PSA indicates prostate-specific antigen.

The USPSTF decision changes a 2012 recommendation that discouraged the use of routine PSA screening for men of all ages and concluded that there was “moderate certainty” that the benefits of asymptomatic screening did not outweigh the harms. That decision was based in part on high rates of negative prostate cancer biopsies and a tendency to overtreat low-grade prostate cancer.

Whereas previously the USPSTF was concerned about a lack of evidence from high-grade trials about the merits of PSA screening, the latest recommendation is based on what the task force considers more reliable information. “Adequate evidence from randomized clinical trials shows that PSA-based screening programs in men aged 55 to 69 years may prevent approximately 1.3 deaths from prostate cancer over approximately 13 years per 1000 men screened,” according to the recommendation published in JAMA. “The potential benefits and harms of screening for prostate cancer are closely balanced” in this age cohort, the authors stated. The task force gave the recommendation a C grade, meaning that there is moderate certainty that PSA screening produces a small net benefit in this patient population.

In 2008 the task force concluded there was insufficient evidence to make a recommendation on PSA screening for prostate cancer in men under the age of 70, it recommended against use of the test for men aged 75 and older. In the fresh guidance, the USPSTF recommends against routine testing for men aged 70 years or older.

In reassessing the guidelines, reviewers sought to determine, among other issues, whether clear evidence exists that PSA screening reduces short- or long-term prostate cancer morbidity and mortality. They also sought to determine the harms of screening for prostate cancer and diagnostic follow-up. Their search for evidence led to a review of 303 full-text articles, a total that was augmented by 17 new articles since 2011.

FDA Grants Enzalutamide Priority
Review for Nonmetastatic CRPC
The FDA has granted a priority review to a supplement-


Sonpavde Navigates the Evolving Bladder Cancer Treatment Landscape

THE ERA OF IMMUNOTHERAPY continues to progress in genitourinary malignancies, with 5 immunotherapies already approved by the FDA in advanced or metastatic urothelial carcinoma (UC). The role of chemotherapy in bladder cancer and UC is changing as a result.

Guru P. Sonpavde, MD, bladder cancer director, Dana-Farber Cancer Institute, Boston, Massachusetts, discussed the treatment landscape of UC during a presentation at the 2018 OncLive® State of the Science Summit™ on Genitourinary Cancers.

Roles of Chemotherapy

Cisplatin combined with other chemotherapy agents improves survival in the advanced disease setting, therefore it makes sense to give neoadjuvant chemotherapy before radical cystectomy in high-risk locally advanced or muscle-invasive bladder cancer, Sonpavde said.

In the phase III SWOG 8710 trial, investigators gave 3 cycles of neoadjuvant methotrexate, vinblastine, doxorubicin, and cisplatin over 12 weeks to patients with resectable muscle-invasive bladder cancer. Findings showed that the median overall survival (OS) with the combination was 77 months versus 46 months in the cystectomy-alone group.

“How good is adjuvant chemotherapy? Unfortunately, we do not have good adjuvant trials for bladder cancer post-radical cystectomy. These patients are frequently not in good condition to receive adjuvant chemotherapy,” said Sonpavde.

However, there is data to support the use of adjuvant chemotherapy. The POUT trial, a phase III randomized trial of perioperative chemotherapy versus surveillance in upper tract urothelial cancer, was stopped prematurely because the disease-free survival endpoint was met at the interim analysis with a hazard ratio of 0.49 (95% CI, 0.31-0.76; \( P = .001 \)).

Additionally, some patients are not fit for radical cystectomy or refuse it. Historically, these patients have been offered radiation therapy, Sonpavde explained. Radiation plus cisplatin has been offered to well-selected patients, usually without hydrenephrosis. Survival up to 5 years has been observed for those without hydrenephrosis.

Current chemoradiation for patients with locally advanced bladder cancer is 5-fluorouracil plus mitomycin-C, but not much data exist on recurrence after chemoradiation, Sonpavde said.

In the postplatinum setting, taxanes have been used to treat patients with UC in the United States, and vinflunine is often used outside of the United States. The median OS with vinflunine is suboptimal at 6.9 months, and the median survival of a patient taking a taxane is similar in the range of 7 to 9 months, Sonpavde said.

Some special second-line therapy situations that do not often get discussed include recurrence 1 year after perioperative platinum therapy. Ordinarily, if patients are more than 1 year out from perioperative neoadjuvant or adjuvant platinum therapy, platinum is repeated.

“Some retrospective data do suggest that if you repeat platinum-based therapy in patients who are more than 1 year out from perioperative cisplatin chemotherapy, you might get similar outcomes compared with patients who got first-line chemotherapy with cisplatin who had not had previous perioperative cisplatin,” Sonpavde said.

Patients less than 1 year out of preoperative platinum therapy receive a different second-line therapy.

“This is the era of immunotherapy,” Sonpavde said. “There is a lot of ‘push and pull’ in the immune system, and there are pathways that are inhibiting the immune system” from working in patients with bladder cancer. UC has a high somatic mutation burden; it has the fourth highest of all cancers behind melanoma,
squamous cell carcinoma of the lung, and lung adenocarcinoma, Sonpavde noted. Therefore, it is rational to expect immunotherapy to work well in this setting. Second-line therapy has been revolutionized by the approvals of 5 PD-1/PD-L1 inhibitors, he added.

CD8-Positive T Cells Are a Bellweather
In muscle-invasive bladder cancer, an increased infiltration of CD8-positive T cells can signify a good prognosis. In nonmuscle-invasive bladder cancer, PD-L1 expression is associated with poor outcomes when patients receive Bacillus Calmette-Guérin (BCG). PD-L1 expression also correlated with stage and grade—meaning that the higher the stage, the higher the expression.

Moreover, Sonpavde highlighted data from the phase III KEYNOTE-045 study, updated findings of which were presented at the 2018 Genitourinary Cancers Symposium. In the initial publication, there was an improvement in OS from 7.4 months with chemotherapy to 10.3 months with pembrolizumab (Keytruda), while progression-free survival did not improve. The hazard ratio improved from 0.73 to 0.70, which Sonpavde said is “a good sign.” Although PD-L1 expression is used as a predictor of response to immunotherapy, it is not the only marker for response to pembrolizumab.

“All subgroups seemed to benefit from pembrolizumab, regardless of PD-L1 expression,” Sonpavde said. “There is a dogma out there that immunotherapy yields very delayed responses, but that was not the case. The median time to response was the same with chemotherapy and pembrolizumab, at about 2.1 months.”

The duration of response with pembrolizumab was most impressive, added Sonpavde. While pembrolizumab is not the only approved PD-1 inhibitor in the post-platinum setting, it is the only one that has shown improvement in OS in the phase III setting.

Currently, durvalumab (Imfinzi), nivolumab (Opdivo)—both of which are approved in the second-line setting, in addition to avelumab (Bavencio)—and the combination of nivolumab and ipilimumab (Yervoy) are all being investigated in phase III trials for the first-line setting of advanced UC.

Notably, the FDA recently issued a drug safety notification warning against the use of frontline single-agent immune checkpoint inhibition for patients with PD-L1-low expressing platinum-eligible UC.

“Given the availability of first-line pembrolizumab and atezolizumab for cisplatin-ineligible patients, the selection of patients for PD-1/PD-L1 inhibitors versus carboplatin-based combination chemotherapy and optimal sequencing requires investigation,” Sonpavde concluded.

Standard of Care Continues to Shift in RCC

BY DANIELLE BUCCO

THE STANDARD OF CARE for patients with renal cell carcinoma (RCC) continues to change as novel therapies and combinations demonstrate efficacy and are adopted by clinicians, says Toni K. Choueiri, MD.

For example, the December 2017 FDA approval of cabozantinib (Cabometyx) was based on practice-changing data from the phase II CABOSUN trial, in which the multikinase inhibitor reduced the risk of progression or death by 52% compared with sunitinib (Sutent). Additionally, the median progression-free survival was 8.6 months with cabozantinib versus 5.3 months for sunitinib (HR, 0.48; 95% CI, 0.31-0.74; P = .0008).

After 30.8 months of follow-up, the median overall survival (OS) was 26.6 months (95% CI, 14.6-not evaluable) in the cabozantinib arm versus 21.2 months (95%CI, 16.3-27.4) in the sunitinib arm, representing a nonstatistically significant 20% reduction in the risk of death (HR, 0.80; 95% CI, 0.53-1.21; P = .29).1

Immunotherapy combinations also are extending survival, explains Choueiri. In the CheckMate-214 study, the combination of nivolumab (Opdivo) and ipilimumab (Yervoy) reduced the risk of death by 37% versus sunitinib in intermediate- and poor-risk RCC (HR, 0.63; P <.0001).2 The FDA approved this regimen for frontline treatment of this patient population in April 2018.

In an interview during the 2018 OncLive® State of the Science SummitTM on Genitourinary Cancers, Choueiri, director of the Lank Center for Genitourinary Oncology and the Kidney Cancer Center at Dana-Farber Cancer Institute, Boston, Massachusetts, discussed recent advancements and shared his insight on evolving treatments for patients with kidney cancer.

OncLive®: Please explain how the evolution of genitourinary cancer treatments was addressed at the meeting.

Choueiri: To start, there was a talk about robotic surgery in kidney and bladder cancer. It is very interesting how surgery has evolved from open, to laparoscopic, and now to robotic surgery.

Dr Lauren C. Harshman discussed the evolving role
of adjuvant therapy in high-risk patients with RCC in the era of tyrosine kinase inhibitors [TKIs]. There are still some ongoing trials that will read out in the next couple of years. She also spoke about integrating high-risk RCC treatments, both in the adjuvant as well as the neoadjuvant settings, followed by adjuvant therapy.

Dr Bradley A. McGregor tackled targeted therapy for patients with advanced RCC, and most recently combinations of immunotherapy. Immunotherapies are being looked at in combination with other immunotherapy regimens, such as nivolumab and ipilimumab, or with VEGF inhibitors. There is a lot to come in that advanced setting because many of the phase III trials against sunitinib have either finished accrual or are ongoing. The field may change again.

We had Dr Guru P. Sonpavde talk about integrating novel immunotherapy with chemotherapy in advanced bladder cancer in the early-stage setting.

Finally, Dr Xiao X. Wei discussed systemic therapy management with the focus on PD-1/PD-L1 inhibitors and the management of adverse events (AEs). Immunotherapy is a specific class of agents with a specific management for AEs.

**What did we learn from the CABOSUN trial?**

We are beyond single-agent VEGF receptors and TKIs. We still use other single agents, such as nivolumab or cabozantinib. In the frontline setting against sunitinib, cabozantinib showed superior response rates and an improved PFS. This randomized phase II trial was essentially for patients in the poor- and intermediate-risk subgroups. Cabozantinib was approved in December 2017 in the frontline setting.

**How will clinicians distinguish these emerging therapies from one another?**

Almost all of the large phase III trials are comparing combinations, such as immunotherapy plus VEGF inhibition, plus another immunotherapy regimen, or plus sunitinib. However, these studies are not head to head, so hopefully we will eventually have a head-to-head study. It is extremely important to compare combinations with the new standard of care. The combinations, especially with the high response rates that we are seeing, are going to be a significant part of the standard of care. However, the combination of nivolumab and ipilimumab has a higher response rate than sunitinib.

Also, with earlier studies, we are seeing TKIs such as axitinib [Inlyta] and lenvatinib [Lenvima]. Additionally, the combination of pembrolizumab [Keytruda] and [axitinib] was very well tolerated, resulting in response rates between 50% to 70% and higher. There are also studies with 2 antibodies, the PD-L1 inhibitor atezolizumab (Tecentriq) and bevacizumab (Avastin), which were presented at the 2018 Genitourinary Cancers Symposium. The PD-L1-positive population demonstrated a higher response rate with the combination when compared with sunitinib. However, it is still too early to determine the OS benefit.

**Is our understanding of biomarkers improving?**

We are still trying to come up with a biomarker for single-agent PD-1/PD-L1 inhibitors as well as VEGF TKIs. It is not easy, as we do not have anything to guide our clinical decision in practice. PD-L1 via immunohistochemistry was prognostic for nivolumab but when it was combined with ipilimumab in the CheckMate-214 study, it responded differently when looking at PD-L1 status. There was a much higher benefit for patients who were PD-L1 positive. This biomarker could tell us something. It has been integrated in most phase III trials but is still not ready for prime time.

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**Expert Underscores Importance of AE Management in GU Cancers**

**BY CAROLINE SEYMOUR**

**ALTHOUGH ADVERSE EVENTS (AEs) tend to be less common with use of immunotherapies, they still need careful management and a multidisciplinary approach, says Xiao X. Wei, MD, MAS. Although clinicians have gained a better understanding of how to manage immune-related AEs in genitourinary (GU) as well as other cancers, thanks to guidelines produced by the American Society of Clinical Oncology (ASCO), National Comprehensive Cancer Network (NCCN), and European Society for Medical Oncology (ESMO), more investigation and research are needed.**

“There are no prospective data per se or high-level evidence on how to best treat [adverse] effects, [and although] the ASCO, NCCN, and ESMO guidelines have given us more...
tools to work with…every patient is different, and we have to employ our clinical judgement,” Wei said.

In an interview during the 2018 OncLive® State of the Science Summit™ on Genitourinary Cancers, Wei, instructor of medicine, Harvard Medical School, Dana-Farber Cancer Institute, Boston, Massachusetts, discussed managing possible AEs of different systemic therapies in kidney and bladder cancer.

**OncLive®:** What are the safety profiles of some newly approved agents in GU cancers?

**Wei:** Some of the newer approved agents in kidney cancer include cabozantinib [Cabometyx] and the PD-1/PD-L1 agents, such as nivolumab [Opdivo]. In bladder cancer, there is also pembrolizumab [Keytruda] and atezolizumab [Tecentriq]. Cabozantinib has a relatively similar side effect profile compared with the other tyrosine kinase inhibitors, such as sunitinib [Sutent] and pazopanib [Votrient].

Data from the CABOSUN study compared cabozantinib with sunitinib, so physicians have an idea of how the 2 agents are side by side. Diarrhea is much more frequently seen with cabozantinib. It’s the most common reason why patients require dose reductions. When physicians use cabozantinib to treat patients with advanced kidney cancer, they should be ready to hold the agent and reduce the dose if necessary.

**What are some of the toxicities patients may experience with PD-1/PD-L1 inhibitors?**

The PD-1/PD-L1 inhibitors are generally very well tolerated, so the vast majority of patients don’t experience very many AEs. Nonetheless, we as clinicians need to be on the lookout for AEs because we can’t predict which patients will experience them. The faster we act, the better the outcome. Immune-related toxicities can affect any organ, but the organs that are commonly affected are the skin, gastrointestinal tract, liver, and the endocrine system. Some recent guidelines have changed our management approach.

**Is there anything in particular from those guidelines you would like to highlight?**

If you compare the guidelines, they’re fairly similar. There are subtle differences, and this highlights the fact that guidelines exist. We have to work in a multidisciplinary manner, and that includes working with a specialist depending on which organs are involved.

**Are there any ongoing studies focused on predicting response or tolerability to treatment?**

There is research being done on a genomics level to see if single-nucleotide polymorphisms are associated with immune-related toxicities. There is also interest in looking at how the microbiome might affect the development of toxicities.

**Is there a greater incidence of toxicities with combination regimens in GU cancers?**

We know that the efficacy is better when we add immunoncology drugs together. Although the combination of ipilimumab and nivolumab, for example, has a higher efficacy, it also has a higher toxicity associated with it. That is definitely a concern. There’s also a higher risk of severe toxicities that could lead to severe colitis, pneumonitis, myocarditis and neurological complication. These are things that patients and clinicians need to know.

**With combination therapy, is it difficult to discern which agent is responsible for reported toxicities?**

It’s not [a] clear-cut answer, but we do know that ipilimumab is associated with more diarrhea in and of itself. In general, when we encounter grade 2/3 diarrhea, we hold both drugs. Once the toxicity resolves to grade 1 or better, we need to determine whether to discontinue one or both agents. The decision should be based on what other treatment options the patient has and the severity of the patient’s toxicity course.

**Are patients hesitant to report their AEs because they believe it may lead to treatment discontinuation?**

It's important for oncologists to tell their patients that most of these side effects are reversible, especially if they are treated early with steroids and potentially other agents, if necessary. A lot of times we can resume therapy—that is assuming that the severity is not very high, or the heart and other vital organs are not affected.

“**We have to work in a multidisciplinary manner, and that includes working with a specialist depending on which organs are involved.**”

—Xiao X. Wei, MD, MAS
greater boston urology (GBU), the largest physician-owned urology practice in Massachusetts, strives to offer comprehensive urologic care that includes up-and-coming diagnostics and treatments, such as the prostate health index (PHI) blood test and high intensity-focused ultrasound (HIFU).

The practice also strives to improve outcomes from traditional medicine. It recognizes the necessity of prostate-specific antigen (PSA) testing to find out which patients are at risk of developing prostate cancer, but also that PSA testing is not fully reliable and may lead to unnecessary surgery and adverse events. GBU will not put a patient through a prostate biopsy or a diagnostic workup based on a single lab test because there other tests are now available to supplement the PSA and determine who is at risk. GBU utilizes the PHI test as a safer and more effective way to stratify prostate cancer risk than PSA alone.

According to Michael J. Curran, MD, practice chief executive officer, although results of national studies show prostate cancer is detected in 30% to 35% of biopsies, at GBU the use of supplemental tests has enabled physicians to achieve a positive biopsy rate of about 65%. The practice has halved the number of biopsies done on patients who may not have prostate cancer.

“There’s a tremendous benefit not only for those individual patients, but for the community, because that overall care process is going to lower the cost of delivery or urological care,” Curran said. “Because we mitigate problems with the most expensive part of the process, which is the biopsy, by reserving it for a more select group who are more likely to have prostate cancer, we can lower costs.”

GBU also uses genomic testing as part of the decision-making process to decide what treatment plan would be best for patients with prostate cancer. “We can identify the patient through genomic testing who may be at much lower risk for having cancer-causing morbidity or mortality in the future, and some patients with prostate cancer can go on to a surveillance program instead of active intervention,” Curran said.

The practice strives for minimally invasive outcomes for other genitourinary cancers. Most partial or radical nephrectomies are done laparoscopically or robotically.
At all GBU locations, advanced therapeutics for superficial bladder cancer treatment are offered in-office. For treatment of testicular cancer, patients are referred outside the practice for chemotherapy and radiation, although GBU coordinates with those cancer centers to manage care effectively and has in-house labs for diagnostic tests.

“There’s not much need for our patients to go outside our practice when they have complex oncology needs or if they have relatively common cancers, such as bladder and prostate,” Curran said. “We are comfortable managing those patients, and we try to cater to them; it’s very easy to get the patient to a doctor who’s going to be best for their needs. This way, the patients not only have a good outcome for their disease, but they also have a good experience.”

**HISTORICAL OF THE PRACTICE**

GBU formed in 2011 as a merger of independent urology practices primarily in southern Massachusetts and has since grown to a team of 14 urologists, 1 urologic oncologist, 1 pathologist, 4 physician assistants, and 79 other employees. They have 8 office locations in southeastern Massachusetts: Dedham, Falmouth, Framingham, Milton, North Easton/Brockton, Norwood, Plymouth, and Sandwich. The practice covers about 15% to 20% of total urology services in the state. All of the urologists practice general urology, with some concentrating on robotic surgery, advanced diagnostic techniques (primarily for prostate cancer), advanced therapeutics, or urologic gynecology.

The team can handle all aspects of urologic malignancies, managing patients with all stages of prostate cancer, and is currently the only group in New England offering HIFU for patients with prostate cancer. According to Curran, GBU was one of the first practices in the region to offer 3D MRI fusion biopsy of the prostate and is the only independent urology practice in New England where a patient can get the PHI blood test.

In addition to physicians, GBU has administrators and other background support to share the responsibility for successful management. This includes a chief operations officer, a vice president of operations, a legal firm and a political lobbyist on retainer, and a certified coder and medical billing expert in GBU’s centralized billing office.

**PHYSICIAN-OWNED BUSINESS MODEL**

GBU maintains its commitment to staying abreast of new technologies and techniques by keeping its physicians in control of the business. The practice reasons that the people who provide healthcare should be the same people who make the decisions about what technology or techniques to employ to deliver the best care.

At larger practices that are owned by hospitals or other entities that are not physician controlled, bureaucratic roadblocks may arise when physicians want to adopt new technology. The physicians first have to appeal to the institution or a board of directors to get the approval and funding, with the risk that their request could be turned down. GBU does not have this problem. “[Our independence] allows us a lot of freedom in adopting and incorporating new technology,” Curran said.

The practice’s philosophy is that physicians should also control how income is allocated. “The physician is the person who’s been put there to understand the medical needs of the patient and where their cash should be applied,” Curran said. Therefore, the physicians at GBU decided to maintain their control to provide the best care possible to their patients, as well as run the business as well as possible.

Although many practices are merging or partnering with larger nonurological entities, Curran believes that this trend does not necessarily equate with providing good healthcare. “Rather than turning to hospital networks, insurance networks, or venture capital, [practices] should be turning to their colleagues in the specialties or complementary specialties they’re in to align with people who have the same goals as they do,” he said.

When a new technique or technology is developed, the physicians who own GBU meet and discuss whether it is justified from a medical perspective to add it to their practice. When they agree to adopt it, they bring their case to the chief operations officer, who decides whether the addition makes sense financially or it would be better to partner with a facility that has the technique or technology already. For example, they have relationships with all of the major radiation centers in the area and are able to provide external beam radiotherapy for their patients with prostate cancer.

According to Curran, technology adoption can be done in a matter of hours or days instead of the weeks or months it would take for larger organizations, allowing GBU to consistently offer the latest and best care possible. This makes the practice stand out in the Boston metropolitan area, which has some of the largest and most distinguished medical centers in the country.

Another reason for offering the latest treatments is that patients tend to be well informed about them, mostly due to having the ability to research their disease online. They even ask for these treatments when they come into the office. “We view that as a really good thing. The more knowledge a patient has, the better that patient is going to be for themselves,” Curran said.

**REFERENCE**