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Brian M. Shuch, MD

Dr. Shuch, MD, describes his career path through 20 years, working with several leading urologists as mentors during his training. *p.10*

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ASCO22 Focal Therapy for Prostate Cancer: Should it Become a Standard of Care? *p.26*

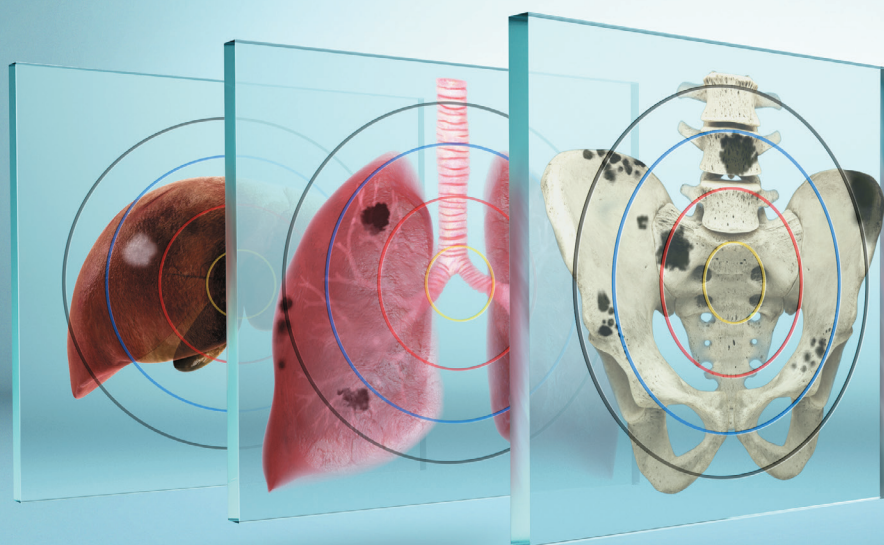
Treatment of Men with Metastatic Hormone-Sensitive Prostate Cancer: Triplet Versus Doublet Therapy *p.18*



NOW APPROVED



Target PSMA+ mCRPC wherever it goes—bone, nodal, or visceral metastases¹



Not an actual patient.

Indication

PLUVICTO™ (lutetium Lu 177 vipivotide tetraxetan) is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

IMPORTANT SAFETY INFORMATION

Risk From Radiation Exposure

PLUVICTO contributes to a patient's long-term cumulative radiation exposure, which is associated with an increased risk for cancer.

Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with PLUVICTO consistent with institutional practices, patient treatment procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection.

Ensure patients increase oral fluid intake and advise them to void as often as possible to reduce bladder radiation.

To minimize radiation exposure to others, advise patients to limit close contact (less than 3 feet) with household contacts for 2 days or with children and pregnant women for 7 days, to refrain from sexual activity for 7 days, and to sleep in a

separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

Myelosuppression

PLUVICTO can cause severe and life-threatening myelosuppression. In the VISION study, grade 3 or 4 decreased hemoglobin (15%), decreased platelets (9%), decreased leukocytes (7%), and decreased neutrophils (4.5%) occurred in patients treated with PLUVICTO. Grade ≥ 3 pancytopenia occurred in 1.1% of patients (including 2 fatal events). Two deaths (0.4%) due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia were observed. One death due to sepsis and concurrent neutropenia was observed.

Perform complete blood counts before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO and clinically treat patients based on severity of myelosuppression.

Renal Toxicity

PLUVICTO can cause severe renal toxicity. In the VISION study, grade 3 or 4 acute kidney injury (3%) and increased creatinine (0.9%) occurred in patients treated with PLUVICTO.

Advise patients to remain well hydrated and to urinate frequently before and after administration of PLUVICTO. Perform kidney function laboratory tests, including serum creatinine and calculated creatinine clearance (CrCl), before

In the pivotal phase 3 VISION trial, PLUVICTO + BSOC vs BSOC alone¹⁻⁴:

Alternate Primary End Points

Significantly improved median OS^{1,2}

15.3 vs 11.3
months, respectively

HR=0.62
(95% CI, 0.52-0.74)
P<0.001
(N=551 vs 280)

Significantly improved rPFS³

8.7 vs 3.4
months, respectively

HR=0.40
(95% CI, 0.31-0.52)
P<0.001
(N=385 vs 196)

Key Secondary End Point

Significantly improved ORR^{1,4a}

30% vs 2%
of patients, respectively

CR: 6% vs 0%
PR: 24% vs 2%
P<0.001^b
(N=319 vs 120)^c
(ORR=CR+PR)

Interpretation of the magnitude of the rPFS effect was limited due to a high degree of censoring from early dropout in the control arm

^a ORR is reported as a measure of response in soft tissue disease, lymph node, or visceral lesions. ^b Stratified Wald's Chi-square test 2-sided *P* value. ^c Patients with evaluable disease at baseline.

VISION trial design^{1,2}

VISION was an international, prospective, open-label, multicenter, randomized phase 3 clinical trial evaluating PLUVICTO in 831 adult patients with PSMA-positive mCRPC previously treated with at least 1 AR pathway inhibitor and 1 or 2 taxane regimens. Participants were randomized in a 2:1 ratio to receive PLUVICTO (7.4 GBq every 6 weeks for up to 6 cycles) + protocol-permitted BSOC or BSOC alone.

and during treatment. Withhold, reduce dose, or permanently discontinue PLUVICTO based on severity of renal toxicity.

Embryo-Fetal Toxicity

The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose.

Infertility

The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation-absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility.

Adverse Reactions

The most common adverse reactions (≥20%) occurring at a higher incidence in patients who received PLUVICTO plus best standard of care (BSOC) were fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation. Clinically relevant adverse reactions in <5% of patients included dry eye, vertigo, and pancytopenia (including bicytopenia).

Laboratory Abnormalities

The most common laboratory abnormalities that worsened from baseline in ≥30% of patients who received PLUVICTO plus BSOC were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium.

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

AR, androgen receptor; ARPI, androgen receptor pathway inhibitors; BSOC, best standard of care; CR, complete response; mCRPC, metastatic castration-resistant prostate cancer; ORR, overall response rate; OS, overall survival; PR, partial response; PSMA, prostate-specific membrane antigen; PSMA+, PSMA positive; rPFS, radiographic progression-free survival.

Learn more at [PluvictoHCP.com](https://www.pluvictohcp.com)

References:

1. Pluvicto [prescribing information]. Millburn, NJ: Advanced Accelerator Applications USA, Inc; 2022. 2. Sartor O et al; VISION Investigators. *N Engl J Med*. 2021;385(12):1091-1103. doi:10.1056/NEJMoa2107322. 3. Data on file. VISION [PSMA-617-01] study. Novartis Pharmaceuticals Corp; 2021. 4. Sartor O et al; VISION Investigators. *N Engl J Med*. 2021;385(12)(suppl):1091-1103. doi:10.1056/NEJMoa2107322.



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167200 3/22

PLUVICTO™ (lutetium Lu 177 vipivotide tetraxetan) injection, for intravenous use
Initial U.S. Approval: 2022

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

PLUVICTO is indicated for the treatment of adult patients with prostate-specific membrane antigen (PSMA)-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen receptor (AR) pathway inhibition and taxane-based chemotherapy.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Risk From Radiation Exposure

PLUVICTO contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

Minimize radiation exposure to patients, medical personnel, and household contacts during and after treatment with PLUVICTO consistent with institutional good radiation safety practices, patient treatment procedures, Nuclear Regulatory Commission patient-release guidance, and instructions to the patient for follow-up radiation protection at home.

Ensure patients increase oral fluid intake and advise patients to void as often as possible to reduce bladder radiation.

Before the patient is released, the healthcare provider should explain the necessary radioprotection precautions that the patient should follow to minimize radiation exposure to others [see *Patient Counseling Information* (17) in the full prescribing information]. Following administration of PLUVICTO, advise patients to limit close contact (less than 3 feet) with household contacts for 2 days or with children and pregnant women for 7 days. Following administration of PLUVICTO, advise patients to refrain from sexual activity for 7 days. Following administration of PLUVICTO, advise patients to sleep in a separate bedroom from household contacts for 3 days, from children for 7 days, or from pregnant women for 15 days.

5.2 Myelosuppression

PLUVICTO can cause severe and life-threatening myelosuppression, including anemia, thrombocytopenia, leukopenia, and neutropenia. In the VISION study, Grade 3 or 4 decreased hemoglobin (15%), decreased platelets (9%), decreased leukocytes (7%), and decreased neutrophils (4.5%) occurred in patients treated with PLUVICTO. Grade ≥ 3 pancytopenia occurred in 1.1% (which includes two fatal events) in patients treated with PLUVICTO. Two deaths (0.4%) due to intracranial hemorrhage and subdural hematoma in association with thrombocytopenia were observed in patients who received PLUVICTO. One death due to sepsis and concurrent neutropenia was observed in patients who received PLUVICTO.

Perform complete blood counts before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO and clinically treat patients based on the severity of myelosuppression [see *Dosage and Administration* (2.4) in the full prescribing information].

5.3 Renal Toxicity

PLUVICTO can cause severe renal toxicity. In the VISION study, Grade 3 or 4 acute kidney injury (3%) and increased creatinine (0.9%) occurred in patients treated with PLUVICTO.

Advise patients to remain well hydrated and to urinate frequently before and after administration of PLUVICTO. Perform kidney function laboratory tests, including serum creatinine and calculated CL_{cr}, before and during treatment with PLUVICTO. Withhold, reduce dose, or permanently discontinue PLUVICTO based on the severity of renal toxicity [see *Dosage and Administration* (2.4) in the full prescribing information].

5.4 Embryo-Fetal Toxicity

The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm [see *Clinical Pharmacology* (12.1) in the full prescribing information]. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose [see *Use in Specific Populations* (8.1, 8.3)].

5.5 Infertility

PLUVICTO may cause infertility in males. The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility [see *Use in Specific Populations* (8.3)].

6 ADVERSE REACTIONS

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

- Myelosuppression [see *Warnings and Precautions* (5.2)]
- Renal Toxicity [see *Warnings and Precautions* (5.3)]

6.1 Clinical Trials Experience

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

The safety of PLUVICTO was evaluated in the VISION study in patients with progressive, PSMA-positive mCRPC [see *Clinical Studies* (14) in the full prescribing information]. Of the 831 patients randomized, 734 patients received at least one dose of randomized treatment. Patients received at least one dose of either PLUVICTO 7.4 GBq (200 mCi) administered every 6 to 10 weeks plus BSoC (N = 529) or BSoC alone (N = 205). The median duration of exposure to randomized treatment was 7.8 months (range, 0.3 to 24.9) for patients who received PLUVICTO plus BSoC. Among patients who received PLUVICTO plus BSoC, the median number of doses of PLUVICTO received was 5 (range, 1 to 6). The median cumulative dose of PLUVICTO was 37.5 GBq (range, 7.0 to 48.3). The median duration of follow-up was 14.8 months for patients receiving PLUVICTO plus BSoC.

Serious adverse reactions occurred in 36% of patients who received PLUVICTO plus BSoC. Serious adverse reactions in $> 1\%$ of patients who received PLUVICTO plus BSoC included hemorrhage (4%), musculoskeletal pain (3.8%), sepsis (3.2%), anemia (2.8%), urinary tract infection (2.6%), acute kidney injury (1.7%), pneumonia (1.7%), pancytopenia (1.3%), pyrexia (1.3%), spinal cord compression (1.1%), and pulmonary embolism (1.1%).

Fatal adverse reactions occurred in 2.8% of patients who received PLUVICTO plus BSoC, including sepsis (0.9%), pancytopenia (0.6%), hepatic failure (0.4%), intracranial hemorrhage (0.2%), subdural hematoma (0.2%), ischemic stroke (0.2%), COVID-19 (0.2%), and aspiration pneumonia (0.2%).

PLUVICTO was permanently discontinued due to adverse reactions in 12% of patients. Adverse reactions leading to permanent discontinuation of PLUVICTO in $\geq 1\%$ of patients who received PLUVICTO plus BSoC were anemia (2.8%), thrombocytopenia (2.8%), and leukopenia (including neutropenia) (1.7%).

Adverse reactions leading to a dose interruption of PLUVICTO occurred in 16% of patients. The most frequent ($\geq 3\%$) adverse reactions leading to a dose interruption of PLUVICTO in patients who received PLUVICTO plus BSoC were anemia (5%) and thrombocytopenia (3.6%).

Adverse reactions leading to a dose reduction of PLUVICTO occurred in 6% of patients. The most frequent ($\geq 1\%$) adverse reactions leading to a dose reduction of PLUVICTO in patients who received PLUVICTO plus BSoC were thrombocytopenia (1.9%) and anemia (1.3%).

The most common adverse reactions ($\geq 20\%$) occurring at a higher incidence in patients who received PLUVICTO plus BSoC were fatigue, dry mouth, nausea, anemia, decreased appetite, and constipation.

The most common laboratory abnormalities that worsened from baseline in $\geq 30\%$ of patients who received PLUVICTO plus BSoC were decreased lymphocytes, decreased hemoglobin, decreased leukocytes, decreased platelets, decreased calcium, and decreased sodium.

Table 3 and Table 4 summarize the incidence of adverse reactions and laboratory abnormalities, respectively.

Table 3: Adverse Reactions ($\geq 5\%$) in Patients with PSMA-positive mCRPC Who Received PLUVICTO Plus BSoC in VISION

Adverse Reactions	PLUVICTO Plus BSoC (N = 529)		BSoC (N = 205)	
	All Grades (%)	Grades 3 to 4 (%)	All Grades (%)	Grades 3 to 4 (%)
General disorders				
Fatigue	43	6	23	1.5
Decreased appetite	21	1.9	15	0.5
Weight decreased	11	0.4	9	0
Peripheral edema ^a	10	0.4	7	0.5
Pyrexia	7	0.4	3.4	0
Gastrointestinal disorders				
Dry mouth ^b	39	0	0.5	0
Nausea	35	1.3	17	0.5
Constipation	20	1.1	11	0.5
Vomiting ^c	19	0.9	6	0.5
Diarrhea	19	0.8	2.9	0.5
Abdominal pain ^d	11	1.1	6	0.5

(continued)

Table 3: Adverse Reactions (≥ 5%) in Patients with PSMA-positive mCRPC Who Received PLUVICTO Plus BSoC in VISION

Adverse Reactions	PLUVICTO Plus BSoC (N = 529)		BSoC (N = 205)	
	All Grades (%)	Grades 3 to 4 (%)	All Grades (%)	Grades 3 to 4 (%)
Blood and lymphatic system disorders				
Anemia	32	13	13	4.9
Thrombocytopenia	17	8	4.4	1
Renal and urinary disorders				
Urinary tract infection ^e	12	3.8	1	0.5
Acute kidney injury ^f	9	3.2	6	2.9
Nervous system disorders				
Dizziness	8	0.9	4.4	0
Headache	7	0.8	2	0
Dysgeusia ^g	7	0	1.5	0

Abbreviation: BSoC, best standard of care.

^aPeripheral edema includes peripheral edema, fluid retention, and fluid overload.

^bDry mouth includes dry mouth, apyalsism, and dry throat.

^cVomiting includes vomiting and retching.

^dAbdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.

^eUrinary tract infection includes urinary tract infection, cystitis, and cystitis bacterial.

^fAcute kidney injury includes blood creatinine increased, acute kidney injury, renal failure, and blood urea increased.

^gDysgeusia includes dysgeusia and taste disorder.

Clinically relevant adverse reactions in < 5% of patients who received PLUVICTO plus BSoC included dry eye, vertigo, and pancytopenia (including bicytopenia).

Table 4: Select Laboratory Abnormalities (≥ 10%) That Worsened from Baseline in Patients With PSMA-positive mCRPC Who Received PLUVICTO Plus BSoC (Between Arm Difference of ≥ 5% All Grades) in VISION

Laboratory Abnormalities	PLUVICTO Plus BSoC ^a		BSoC ^b	
	All Grades (%)	Grades 3 to 4 (%)	All Grades (%)	Grades 3 to 4 (%)
Chemistry				
Decreased calcium	39	2.5	28	3
Decreased sodium	33	0.6 ^c	23	1
Increased aspartate aminotransferase	28	1.1	18	1 ^c
Increased creatinine	24	0.9 ^c	14	0.5 ^c
Increased potassium	24	0.6	18	0.5 ^c
Increased sodium	11	0 ^c	5	0 ^c
Hematology				
Decreased lymphocytes	85	47	51	18
Decreased hemoglobin	63	15 ^c	34	7 ^c
Decreased leukocytes	56	7	22	2
Decreased platelets	45	9	20	2.5
Decreased neutrophils	28	4.5	9	0.5

Abbreviation: BSoC, best standard of care.

^aThe denominator used to calculate the rate for each laboratory parameter varied from 506 to 529 based on the number of patients with a baseline value and at least one post-treatment value.

^bThe denominator used to calculate the rate for each laboratory parameter varied from 194 to 198 based on the number of patients with a baseline value and at least one post-treatment value.

^cNo Grade 4 laboratory abnormalities worsening from baseline were reported.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

The safety and efficacy of PLUVICTO have not been established in females. Based on its mechanism of action, PLUVICTO can cause fetal harm [see *Clinical Pharmacology (12.1) in the full prescribing information*]. There are no available data on PLUVICTO use in pregnant females. No animal studies using lutetium Lu 177 vipivotide tetraxetan have been conducted to evaluate its effect on female reproduction and embryo-fetal development; however, all radiopharmaceuticals, including PLUVICTO, have the potential to cause fetal harm.

8.2 Lactation

Risk Summary

The safety and efficacy of PLUVICTO have not been established in females. There are no data on the presence of lutetium Lu 177 vipivotide tetraxetan in human milk or its effects on the breastfed child or on milk production.

8.3 Females and Males of Reproductive Potential

Contraception

Males

Based on its mechanism of action, advise male patients with female partners of reproductive potential to use effective contraception during treatment with PLUVICTO and for 14 weeks after the last dose [see *Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) in the full prescribing information*].

Infertility

The recommended cumulative dose of 44.4 GBq of PLUVICTO results in a radiation absorbed dose to the testes within the range where PLUVICTO may cause temporary or permanent infertility.

8.4 Pediatric Use

The safety and effectiveness of PLUVICTO in pediatric patients have not been established.

8.5 Geriatric Use

Of the 529 patients who received at least one dose of PLUVICTO plus BSoC in the VISION study, 387 patients (73%) were 65 years or older and 143 patients (27%) were 75 years or older. No overall differences in effectiveness were observed between patients ≥ 75 years of age and younger patients. Serious adverse reactions occurred in 11% of patients ≥ 75 years of age and in 11% of younger patients. Grade ≥ 3 adverse reactions occurred in 40% of patients ≥ 75 years of age and in 31% of younger patients.

8.6 Renal Impairment

Exposure of lutetium Lu 177 vipivotide tetraxetan is expected to increase with the degree of renal impairment [see *Clinical Pharmacology (12.3) in the full prescribing information*]. No dose adjustment is recommended for patients with mild (baseline CLcr 60 to 89 mL/min by Cockcroft-Gault) to moderate (CLcr 30 to 59 mL/min) renal impairment; however, patients with mild or moderate renal impairment may be at greater risk of toxicity. Frequently monitor renal function and adverse reactions in patients with mild to moderate renal impairment [see *Dosage and Administration (2.4) in the full prescribing information*]. The pharmacokinetics and safety of PLUVICTO have not been studied in patients with severe (CLcr 15 to 29 mL/min) renal impairment or end-stage renal disease.

10 OVERDOSAGE

In the event of administration of a radiation overdosage with PLUVICTO, reduce the radiation absorbed dose to the patient by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding. Estimate the effective radiation dose that was applied and treat with additional supportive care measures as clinically indicated.

Distributed by:

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Millburn, NJ 07041

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U.S. Patents 10398791; 10406240

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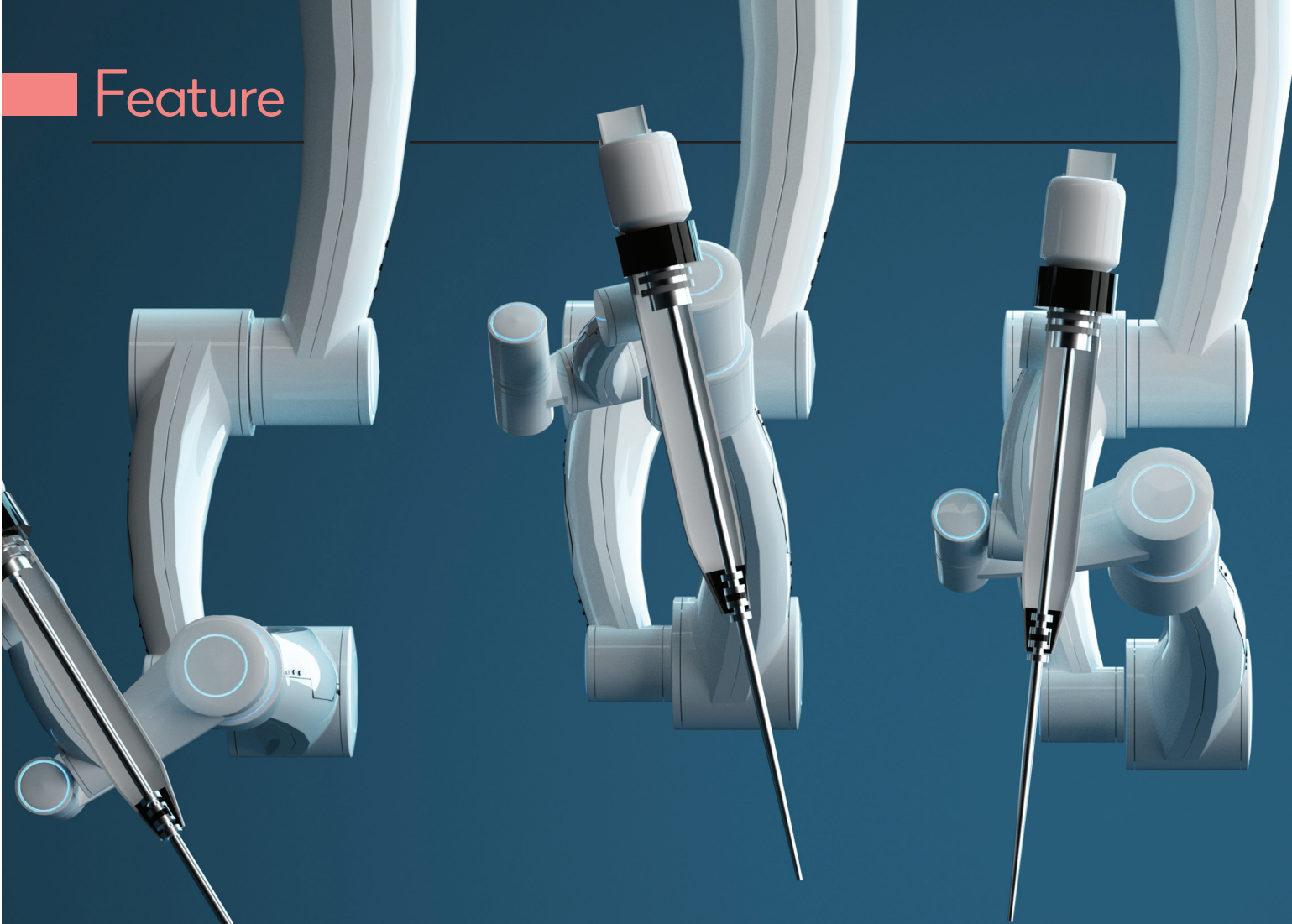
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Review of the Article on the Effect of Robot-assisted Radical Cystectomy Among Patients with Bladder Cancer

David Ambinder MD

THERE HAS BEEN SIGNIFICANT controversy over the adoption of robotic surgery for cystectomy with intracorporeal diversion over the traditional open radical approach. In a recent report published in *JAMA* by researchers in England—“Effect of robot-assisted radical cystectomy with intracorporeal urinary diversion

vs open radical cystectomy on 90-day morbidity and mortality among patients with bladder cancer: a randomized clinical trial”—Catto and colleagues aimed to demonstrate that robotic surgery yields superior morbidity and mortality outcomes for patients in the first few months after surgery.¹

The researchers began by noting that the standard of care for nonmetastatic aggressive bladder cancer is radical cystectomy with pelvic lymphadenectomy.² Many variables are prognostic for survival after surgery, including cancer characteristics, optimal therapy, and preoperative patient health. Radical cystectomy is associated with postoperative complications, and 20% to 30% of patients will be readmitted to hospital for a complication that occurs after discharge.³ Multiple factors have been, or are currently being investigated to reduce perioperative and postoperative complications. Among these are improvements in surgical technique and early recovery after surgery (ERAS) protocols.⁴

Radical cystectomy is associated with postoperative complications, and 20% to 30% of patients will be readmitted to hospital for a complication that occurs after discharge.

The pivotal RAZOR trial has thus far reported similar oncologic outcomes at 2 years after surgery with fewer perioperative setbacks (including lower blood loss, less transfusions, and shorter postoperative hospitalizations), although the procedures took more time.⁵ The limitation of the RAZOR trial, however, was that patients who had robotic-assisted radical cystectomy underwent extracorporeal urinary diversion via an open incision. Thus, the aim of the present study was to compare a total intracorporeal robot-assisted radical cystectomy with open radical cystectomy.

The study was a phase 3, multicenter, unblinded, randomized trial that recruited patients between March 2017 and March 2020. The hypothesis was that a total intracorporeal robotic-assisted radical cystectomy would be associated with a faster recovery time and fewer days in the hospital when compared to open radical cystectomy. Among the inclusion criteria were age over 18 years, classification as a good surgical candidate for both robotic and open approaches, a diagnosis of nonmetastatic bladder cancer, and an Eastern Cooperative Oncology Group (ECOG) status score of 1-3. Among the exclusion criteria were a history of previous abdominal or pelvic surgery, or radiation therapy. Surgeons involved in the study were using ERAS protocols, including thromboprophylaxis, early postoperative mobilization, avoiding bowel preparation, and preoperative caloric drinks. Surgeons had to have completed at least 30 previous radical cystectomies

independently. Other standard requirements included urethral preservation, when appropriate for neobladder reconstruction, and minimal necessary lymphadenectomy.

Primary outcomes were days alive and out of hospital within 90 days of surgery, postoperative duration of hospital stay, readmission rate, and deaths within 90 days. Among the secondary outcomes explored were rates of complications and adverse events up to 90 days, overall survival, oncologic outcomes (including recurrence-free survival, cancer-free survival, and metastasis-free survival), and health-related quality of life outcomes (assessed via patient questionnaires and with use of a wristband pedometer to evaluate patient activity). These outcomes were rigorously monitored at set intervals throughout the follow-up period. The authors noted that several secondary outcomes were not investigated in this study—including rates of admission to intensive care, conversion to an open approach, need to convert to extracorporeal urinary diversion, and surgeon fatigue. The study was powered to detect a difference of at least 2 days of postoperative hospital stay.

After screening, 338 patients were randomized to the 2 arms. After randomization, some patients did not undergo a cystectomy or underwent the approach of the other arm. In all, 157 patients underwent robotic-assisted radical cystectomy and 149 patients underwent open radical cystectomy. Participants were balanced with respect to demographic and disease factors. Nearly 80% of patients were male (mean age, 69 years) and most had a history of smoking (71%). A total of 34% of patients in each arm underwent neoadjuvant chemotherapy before surgery; 44% of patients had confirmed muscle-invasive bladder cancer, 30% had high-grade non-muscle-invasive bladder cancer, and 14% had no residual disease. At the time of surgery, nearly 90% of patients underwent ileal conduit reconstruction.

A total of 29 surgeons were involved in the study. Mean operative time was 4.9 hours for the robotic arm versus 4.5 hours for the open arm. Intraoperative blood loss was approximately 200 mL for patients in the robotic cohort versus 550 mL for the open cohort. Intraoperative transfusion rates were 2.6% for the robotic cohort versus 6.5% for the open cohort. Intraoperative visceral injuries were rare in both groups.

The median number of days out of hospital and alive was 82 days for the robotic cohort versus 80 days for the open cohort. Median length of postoperative hospitalization was 7 days in the robotic cohort versus 9 days for the open cohort. Readmission rates were 21.8% in the robotic cohort versus 32.2% in the open cohort. Results for length of time when readmitted were similar between the groups. Death occurred in 2 patients in the robotic cohort (attributed to cardiorespiratory failure and cancer progression) and 4 patients in the open cohort (2 attributed to intra-

abdominal sepsis/laparotomy/organ failure, 1 attributed to pulmonary embolus, and 1 due to cancer progression).

Findings for the secondary outcome of complications were reported as follows: 63.4% of patients experienced a complication in the robotic arm versus 67.9% in the open arm; 67% of complications were Clavien-Dindo grade 2 or less, and severity was similar between the 2 arms. Of note, compared with the open radical cystectomy arm, patients who underwent robotic surgery had fewer wound-related complications (5.6% vs 17.3%), thromboembolic complications (1.9% vs 8.3%), and a lower rate of blood transfusion (7% vs 12%). At 5 weeks, patients who had undergone open surgery reported worse health-related quality of life, but by 12 weeks, scores for the groups were similar. Disability scores, measured via patient-reported questionnaire, were worse in the open surgery group at week 5 (2.2-fold vs 2.9-fold) and were significantly different at that time and at week 12; however, at week 26, there was no significant difference. There also was no significant difference in physical activity, as measured by pedometer, between the 2 study arms. Strength and stamina, as measured by physical activity at interval follow-ups, initially were statistically significant and superior in the robotic arm at weeks 5 and 12. However, at week 26, there was no significant difference between the cohorts.

Some of the study limitations mentioned by the authors included lack of inpatient follow-up, owing to restrictions related to the COVID-19 pandemic.

The authors also reported on oncological and survival outcomes. At the median follow-up time of 18.4 months, the rate of cancer recurrence was 18% in the robotic arm versus 16% in the open arm. Death rates within 90 days of surgery were 1.2% in the robotic arm versus 2.6% in the open arm. No port site recurrences were reported. All-cause mortality was not statistically significant (14.3% for the robotic arm vs 14.7% for the open arm).

In their discussion, the authors noted that although the results indicate that robotic-assisted intracorporeal diversion led to statistically significant improvement in 90-day mortality for patients with nonmetastatic bladder cancer, the clinical importance of these findings remains uncertain.

Several previous studies have shown that robotic surgery offers benefits over open surgery for both the surgeon and patient, but this report highlights advantages

that occur after surgery in the immediate postoperative period. Intracorporeal reconstruction has potential to advance the minimally invasive approach by reducing incision, and theoretically reduce operative time, but with the cost of technical challenge and a possibly higher learning curve. However, these outcomes support the benefits of shorter hospitalization times and lower readmission rates, while potentially improving immediate surgical recovery through less disability, greater stamina, and lower rates of thromboembolism.

Some of the study limitations mentioned by the authors included lack of inpatient follow-up, owing to restrictions related to the COVID-19 pandemic. The study sites included high-volume centers, which may limit generalizability to community settings. The unblinded nature of the trial also may have introduced bias.

In summary, this study of great interest to the urologic community, showed that use of a robotic-assisted intracorporeal approach to treatment of patients with nonmetastatic bladder cancer resulted in a statistically significant increase in 90-day postoperative mortality when compared with the standard open radical approach. A longer follow-up study will be required to assess oncologic outcomes.

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Platinum (In)eligibility Among Patients with Metastatic Urothelial Carcinoma

Linda Brookes, MSc

ALTHOUGH CISPLATIN-BASED combination chemotherapy is still considered first-line standard of care in metastatic urothelial carcinoma (mUC), many patients are deemed ineligible for treatment with cisplatin. The first ineligibility criteria for cisplatin were set out by Galsky et al in 2011 as Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2; creatinine clearance (CrCl), (calculated or measured) <60 mL/min; grade r2 hearing loss; grade r2 neuropathy, and/or New York Heart Association (NYHA) Class 3 heart failure.¹ However, no consensus has been reached on cisplatin ineligibility or eligibility criteria for patients with mUC, and current treatment guidelines vary in their definitions, where they are specified.²⁻⁴ As a result, it is widely believed that cisplatin is being underused and that using a cutoff of CrCl <60 mL/min excludes many patients who might benefit from neoadjuvant cisplatin-based therapy but who are offered alternative, inferior regimens. Accordingly, there have been calls for a standardized definition of the cisplatin ineligibility in this patient population.^{5,6}

Shilpa Gupta, MD, Director of the Genitourinary Medical Oncology at Taussig Cancer Institute and Co-leader of the Genitourinary Oncology Program at Cleveland Clinic, Ohio, has been prominent in working toward a standardized definition of cisplatin ineligibility and co-authored a new algorithm for determining cisplatin eligibility for neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer (MIBC).⁶ In a recent discussion with **Thomas Powles, MBBS, MD** (Barts Cancer Centre, London, UK) and **Brian Rini, MD** (Vanderbilt University, Nashville, TN), Dr Gupta explained her approach to platinum ineligibility in her own practice.

In the real world, Dr Gupta maintained, physicians are very comfortable using cisplatin in patients with CrCl 50-60 mL/min, with split-dose cisplatin often used. “I think from a more practical point of view, CrCl <50 mL/min is a better accepted definition, and this is being increasingly used in clinical trials nowadays,” she noted. “For the most part, the population of platinum-ineligible patients is not very high in my practice,” she added.

Dr Gupta recalled that the need to define cisplatin ineligibility was highlighted in 2018 when the Food and Drug Administration (FDA) restricted the use of pembrolizumab and atezolizumab in cisplatin-ineligible patients with locally advanced or metastatic UC to those with high PD-L1-expressing tumors or those ineligible for any platinum therapy, regardless of PD-L1 status.⁷ The FDA’s decision was based on clinical trial data showing that patients with PD-L1 low status on monotherapy with either of these drugs have decreased survival compared with patients on cisplatin- or carboplatin-based chemotherapy. However, the FDA provided no definitions of cisplatin or platinum ineligibility, which were left to the clinician’s discretion.

Following the FDA’s decision, Dr Gupta and colleagues conducted a survey of US medical oncologists to determine what criteria they would use to define platinum (cisplatin and carboplatin) ineligible mUC.⁸ Based on the views of the respondents, Dr Gupta’s group recommended a definition based on one of five parameters: ECOG PS >3; CrCl <30 mL/min; peripheral neuropathy grade >3; NYHA Class >3 heart failure; or ECOG PS2 and CrCl <30 mL/min.

Among the survey respondents, there was little support for age as a criterion for cisplatin ineligibility, but about 50% support for hearing loss. Dr Powles was concerned that many older patients with hearing aids would face further loss with cisplatin. Dr Gupta believes that a patient with metastatic disease and a hearing aid, who is willing to take the risk, should be deemed eligible for cisplatin-based therapy. “I caution the patient that hearing loss can worsen, but that cisplatin is a curative treatment in the neoadjuvant setting, and most patients are willing to take that risk and be monitored closely, stopping if it worsens,” she said. “For the metastatic disease, I am OK with giving carboplatin to these patients,” she added, “but I tend to discuss with patients the nature of cisplatin and how it’s preferable over carboplatin in the neoadjuvant setting.”

Dr Rini stated that he is unwilling to give cisplatin to a patient with a hearing aid and risk further hearing loss, and Dr Powles cautioned that “in the neoadjuvant setting, many patients don’t need chemotherapy at all. Although it’s curative, the benefits are relatively modest, and one

is in danger of putting patients into a lifetime of hearing damage.” Dr Gupta agreed, but stressed that if patients have no other comorbidities deeming them ineligible for cisplatin, then they can be monitored closely for hearing loss “But if a patient has ECOG PS 2, CrCl 50 mL/min, and hearing loss, then they absolutely don’t qualify for any chemotherapy,” she noted.

Dr Powles recalled that the FDA has described the cisplatin-ineligible population as an area of unmet need. “Because of that, it was possible to get accelerated approvals and that resulted in looking at that population almost exclusively in our trials,” he noted. “The DANUBE,⁹ KEYNOTE-361¹⁰ and IMvigor30¹¹ trials showed the outcomes for cisplatin and the carboplatin patients are almost identical,” he said. “I would say that both populations are unmet needs and there are more similarities than differences in their outcomes.”

Dr Gupta pointed out that 2 years ago, the results of the JAVELIN Bladder 100¹² showed that gemcitabine plus carboplatin was ‘back in the game,’ followed by avelumab maintenance in patients who do not progress. “Even without the maintenance arm, those patients did better initially than with single agent immunotherapy,” she noted. “So we are back to the era of using carboplatin in these patients, followed by switch maintenance approaches. I think we have gone too much into cisplatin eligibility and defining anybody as platinum-ineligible to get non carboplatin-based treatments,” she said.

Dr Powles pointed out that this discussion might be less relevant in a few years’ time, after release of the results of the: EV-302 (NCT04223856) phase 3 study of enfortumab vedotin plus pembrolizumab versus chemotherapy in previously untreated advanced UC. “There is a good chance that enfortumab vedotin plus pembrolizumab will supersede platinum-based chemotherapy in the not-too-distant future,” he predicted. “If that is the case, where are we left with these definitions of platinum-eligible and cisplatin-eligible?” he asked. Dr Gupta agreed. “I think if EV-302 is a positive trial, platinum ineligibility will be a moot point, because everybody can get enfortumab vedotin plus pembrolizumab,” she said. “The question will then

be what long-term toxicities we’ll see with that regimen and how that compares with gemcitabine plus carboplatin followed by avelumab.”

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Brian Rini,
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Focus on Kidney Cancer

Brian M. Shuch, MD, describes his career path through 20 years, working with several leading urologists as mentors during his training.

Linda Brookes, MSc

WHEN DR BRIAN SHUCH began his career, kidney cancer was a small field and less of a mainstream interest than other cancers, as there were fewer available therapies at that time, he recalls. Nowadays, in a much larger community, his work combines surgery (open/laparoscopic/robotic surgery and percutaneous ablations) and clinical/translational research. “I’m ‘all things kidney,’” he declares. “If it has to do with kidney cancer, I’m very excited and motivated to be involved in it!”

As Director of the University of California, Los Angeles (UCLA) Kidney Cancer Program, Dr Shuch is responsible for coordinating clinical care and research studies for kidney cancer in a multidisciplinary setting. The Program offers patients a wide range of treatment options, including standard open and minimally invasive/robotic surgery and medical therapy, as well as a broad portfolio of clinical trials. Recognized as an expert in the genetics of kidney cancer, Dr Shuch also heads a translational research program at UCLA. He has been cited as “one of the few clinicians to bring their bench science to the bedside,” with an ongoing metastatic kidney cancer trial.

“Our overall goal is to match treatment intensity to the deep biology, and we know there’s it’s not ‘one size fits all.’ We would like to better individualize care for early and advanced stage kidney cancer,” he says.

Dr Shuch’s decision to study oncology was based on early family experience. “I come from a family of teachers who valued education and pushed me to find something that I was passionate about. That eventually was cancer biology, after a family member died from a glioblastoma,” he recalls. He first studied for a bachelor’s degree (BS) at the University of Michigan, where he became very excited about cancer, although his studies were not confined to oncology. “My senior thesis was on prehistoric salmon migration,” he reminisces.

After the University of Michigan, Dr Shuch attended New York University’s Grossman School of Medicine, graduating in 2004. He was already very excited about kidney cancer, having witnessed a partial nephrectomy. His mentor at NYU was Samir S. Taneja, MD, currently the James M. Neissa and Janet Riha Neissa Professor of Urologic Oncology in the Department of Urology, and Director of Urologic Oncology at NYU Langone Health, New York. “I wanted to be mentored by his mentor, which is why I came to UCLA. They had one of the strongest programs in kidney cancer,” Dr Shuch explains. “Basically, I’ve sought to be mentored by my mentors’ mentors each step in my journey,” he says. “It makes sense that if you’ve found someone and strive to be like them, you should understand how they got there by walking in their shoes.”

So Dr Shuch sought out Dr Taneja’s mentor at UCLA, Arie S. Beldegrun, MD, currently Director of the UCLA Institute of Urologic Oncology. “He’s probably been the most impactful urologist in the world with involvement in multiple FDA approved drugs,” Dr Shuch says. Besides his academic career, Dr Beldegrun is well known for his successes in the pharmaceutical industry, having co-founded numerous biotechnology companies, including Allogene Therapeutics (South San Francisco, CA), a clinical-stage biotechnology company focused on the development of allogeneic chimeric antigen receptor (CAR) T-cell products for cancer. “We are currently working with Allogene Therapeutics on CAR T-cell therapy for kidney cancer,” Dr Shuch notes.

So in 2004, Dr Shuch went to work with Dr Beldegrun on kidney cancer at the UCLA David Geffen School of Medicine/UCLA Medical Center, where he played a key role in the Kidney Cancer Program, completing residency in 2010. Then, following a similar path to the one that led him to UCLA, he again sought to work with his mentor’s mentor. Dr Beldegrun was mentored at the National Cancer Institute

(NCI) by W. Marston Linehan, MD, whom Dr Shuch calls “the godfather of kidney cancer genetics.” Dr Linehan is currently Chief of Urologic Surgery at the Urologic Oncology Branch, Center for Cancer Research at the NCI, Bethesda, MD. He and his team have identified numerous genes associated with hereditary kidney cancer and provided the basis for the development of new therapeutic strategies.

Following his plan, Dr Shuch started a Urologic Oncology Fellowship at the NCI, where he spent 3 years, training and “being mentored by a medical oncologist, Dr. Ramaprasad Srinivasan, to get more comfortable with clinical trials and systemic therapy.”

Dr Shuch was then appointed as an Assistant Professor of Urology and Diagnostic Radiology, and Director of the Genitourinary Cancer Genetics and Prevention Program at Yale University School of Medicine, New Haven, CT. There, he focused on building a strong kidney cancer program following the launch of the new urology department in 2012. He also established a collaborative genetics program for the evaluation and management of patients with complex genetic disorders. As Director of the Genitourinary Biospecimen Repository, he also helped establish standardized collection and workflow for accessing patient cancer material, such as plasma, urine, blood, “with wide distribution to Yale cancer researchers and beyond.”

“It was a very productive time, establishing research collaborations with amazing translational scientists, including Ranjit S. Bindra, MD, PhD,” Dr Shuch recalls. A chance meeting led to a fruitful collaboration and recent *Nature* and *Nature Genetics* papers. Dr Bindra is currently Harvey and Kate Cushing Professor of Therapeutic Radiology and Professor of Pathology and Scientific Director, Chênevert Family Brain Tumor Center at Smilow Cancer Hospital and Yale Cancer Center.

Having re-joined UCLA Health in 2018, Dr Shuch calculates that nowadays, he spends about one-quarter of his time in clinic seeing patients including those on trial, primarily in Westwood, the main UCLA campus—one-quarter doing kidney surgical procedures/surgery, and the remainder of his time on translational research activities.

In the era of improving targeted biologic and immune therapies for metastatic and high-risk kidney cancer, Dr Shuch confirms that he and his colleagues are performing less surgery nowadays. “We are doing a lot more surveillance, or a lot more needle-guided interventions or tumor ablation, and we are doing much less upfront surgery for patients with metastatic disease. We are doing more systemic therapy these days, where a lot of these patients will be going to medical oncology. However, I am keeping involved in this space to administer adjuvant therapy as a urologist can learn how to give these agents,” he stresses.

Dr Shuch’s work on genetics is split into two areas, he says. “We’re using information on genetics to guide individual

patient management, to the drivers of their localized kidney; and we are also working on trying to understand genetic predisposition for patients who have unusual disease biology or family history. The former is really acquired genetic changes, called somatic mutations, and the latter would be the inherited or germline mutations.” His team has started a clinical trial to sequence renal masses to determine whether the acquired genetic mutations could help risk-stratify patients prior to treatment selection.

In light of a national shortage of genetic counselors and the need to keep up with expanding criteria for genetic testing, UCLA launched an integrated telehealth cancer genetics program for patients with kidney and other genitourinary cancers. “We believe that this is a very scalable model across different practice types,” Dr Shuch says. “We aim to have next-day access and to do so, we partnered with a third party.”



Brian Shuch, wife Maria, and daughter Taylor at his Endowed Chair Ceremony.

Dr Shuch also finds time to serve as co-chair the SWOG Renal sub-committee and the NCI’s Renal Task Force, a subcommittee of the Cancer Therapy Evaluation Program (CTEP). “We’re trying to foster concepts that will improve the standard of care for kidney cancer,” he says.

Dr Shuch considers that for the past 20 years, his career has progressed, as he hoped to perform transformative work in this field. “Kidney cancer is a great field with many great colleagues,” he enthuses. “The incidence is rising, and the complexity of management is also increasing. So we need to train the next generation of motivated clinicians to understand the complex interdisciplinary management and identify and fill new knowledge gaps, so we can continue to advance the field with better treatment options,” he urges.

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Plenary Highlights for PSMA Diagnostics and Theranostics

Akhil Saji, MD

AT THE AMERICAN UROLOGICAL ASSOCIATION

(AUA) 2022 meeting in New Orleans, the Friday plenary session consisted of several high-yield discussions. One important topic covered by William Aronson, MD, professor of urology at University of California, Los Angeles (UCLA), was the “latest and greatest” in the realm of prostate-specific membrane antigen (PSMA) diagnostics and theranostics.

Dr Aronson began his presentation by providing an overview of the history of PSMA, citing preclinical studies conducted at Johns Hopkins and Weill Cornell Medical Center in the early 1990s.¹ He explained, however, that it was not until 2 decades later that clinical use of PSMA began to make a footprint, when a group in Heidelberg, Germany, reported the first patient with prostate cancer to be imaged with gallium-68 (⁶⁸Ga)-PSMA.¹ Since then, the prostate cancer community has become increasingly interested in PSMA, owing to its ability to serve as a reliable diagnostic and therapeutic target.

For example, one study, the proPSMA trial, demonstrated greater accuracy (92% vs 65%) and sensitivity (85% vs 38%) with PSMA, compared with conventional imaging, in identifying nodal metastatic prostate cancer in the diagnostic setting.² Dr Aronson went on to explain that the US Food and Drug Administration (FDA) approved ⁶⁸Ga-PSMA positron emission tomography/computed tomography (PET/CT; ⁶⁸Ga-PSMA-11) based on clinical trials reported from UCLA and UCSF (University of California San Francisco); it approved use of fluorine-18 (¹⁸F)-PSMA PET/CT (¹⁸F-DCFPyL) based on results from the CONDOR³ and OSPREY⁴ clinical trials.

Next, Dr Aronson spoke about the biology of PSMA. He explained that PSMA is found to have 100 to 1000 times greater overexpression in prostate cancer cells compared to benign prostatic tissue.⁵ He explained that the PSMA peptide is primarily expressed along the extracellular surface of the prostate cancer cell, allowing for small molecule binding. This binding site is used by the ⁶⁸Ga- and ¹⁸F-based radiotracers. He reminded the audience that the true biological function of PSMA is still unknown. Comparing the 2 radiotracers, he explained that they

have similar performance characteristics and that the process for reporting these imaging studies involves various grading algorithms that are subject to radiologist interpretation. Dr Aronson further highlighted that the combination of low PSMA expression in benign prostatic tissue, as well as in bone and lymph nodes, allows for a high signal-to-background ratio that facilitates targeted visualization of prostate cancer cells.

The prostate cancer community has become increasingly interested in PSMA, owing to its ability to serve as a reliable diagnostic and therapeutic target.

Switching gears to discuss patients with biochemical recurrence, Dr Aronson explained that both ⁶⁸Ga- and ¹⁸F-PSMA PET/CT scans are superior to conventional imaging for diagnosing patients with biochemical recurrence (BCR) after primary treatment. For example, he cited the CONDOR trial³ in which patients with BCR after primary radiotherapy or radical prostatectomy were enrolled and received ¹⁸F-PSMA PET/CT after negative findings with conventional imaging. Of these patients, 63.9% experienced a change in management based on the results of the ¹⁸F-PSMA PET/CT scan.³ In the BCR setting, Dr Aronson explained that both PSMA-based modalities have similar rates of detection, especially as PSA levels rise. However, despite better detection rates compared with conventional imaging, the question of improved outcomes remains. In a prelude to ongoing clinical trials that are yet to be fully reported, Dr Aronson cited a study by Phillips et al⁶ of the ORIOLE phase 2 trial, in which patients with oligometastatic prostate cancer after primary therapy were randomized to

stereotactic body radiation therapy (SBRT) or no SBRT to all PSMA avid lesions. The authors demonstrated that patients receiving therapy to all PSMA avid lesions had significant improvements in progression-free survival (hazard ratio, 0.26).⁶

Next, Dr Aronson discussed the utility of PSMA PET/CT in pre-primary treatment staging of prostate cancer. He cited data presented in reports of the OSPREY trial,⁴ specifically mentioning the cohort A population of patients with high-risk prostate cancer (Gleason grade group >4, PSA >20 ng/mL, clinical stage rT3a). He explained that the results of the trial demonstrated that PSMA PET/CT was superior to conventional cross-sectional imaging, although the findings were limited by low sensitivity levels (40%), owing to the inability to detect small pelvic lymph nodes. He noted that the take-home point from OSPREY was to not exclude performing a pelvic lymph node dissection during radical prostatectomy despite a negative PSMA PET/CT result.⁴ To emphasize the utility of PSMA PET/CT, he presented an example patient case where a 77-year-old man with Gleason grade 4+5 prostate cancer had a negative finding with conventional imaging, whereas PSMA PET/CT revealed 2 PSMA avid pelvic lymph nodes and 1 site of metastatic disease in the sacrum.

Moving from diagnosis to therapeutics, Dr Aronson spoke about the emerging field of PSMA “theranostics” (diagnostics plus therapy). He explained that earlier this year, the FDA approved Lu-177-PSMA-617 (¹⁷⁷Lu) for use in patients with metastatic castration-resistant prostate cancer (mCRPC) in whom hormonal therapy plus docetaxel has failed. This approval was based on the results of the VISION trial, presented in 2021, which demonstrated that 6 cycles of ¹⁷⁷Lu plus standard of care (SOC) versus SOC alone prolonged overall survival (15.3 vs 11.3 months) and extended radiographic progression-free survival (8.7 vs 3.4 months).⁷ Dr Aronson remarked that ¹⁷⁷Lu functions by emitting β -particles within a 2-mm radius of PSMA avid lesions, causing single-stranded DNA breaks. To highlight this promising new therapy, he demonstrated a case report in which a septuagenarian man with treatment-refractory mCRPC underwent 4 cycles of ¹⁷⁷Lu, which resulted in a substantial decrease in disease burden appreciable on imaging.⁸ As of early May 2022, Novartis was experiencing production issues with ¹⁷⁷Lu, but Dr Aronson said he expects resolution of these issues within 6 weeks.

At the end of his presentation, Dr Aronson spoke about the future utility of PSMA PET/CT for patients with elevated PSA levels, as well as the future direction for use of PSMA PET/CT overall. He presented the case of septuagenarian man with an elevated PSA level, negative prostate MRI results, and systematic biopsies utilizing

PSMA PET/CT that demonstrated focal grade group 3 lesion on targeted biopsy. He explained that combining PSMA PET/CT with prostate MRI may improve the diagnostic accuracy of prostate MRI. Looking toward the future, he remarked on several exciting developments within the PSMA sphere, including nascent clinical trials exploring PSMA theranostics in patients with early-stage prostate cancer and intraoperative detection of PSMA avid prostate cancer lesions. Dr Aronson remarked that it is too soon to determine if earlier detection of prostate cancer with PSMA PET/CT will improve patient outcomes or if doing so will run the risk of overtreating patients.

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Power You Can Get Comfortable With

The First and Only TKI Proven in rrRCC After 2 or More Systemic Therapies—Including CPIs

Achieved superior PFS (N=350)^{1,2}

**28% FOTIVDA vs
11% sorafenib**
Progression Free at 1 Year

**18% FOTIVDA vs
5% sorafenib**
Progression Free at 2 Years

**5.6 months mPFS FOTIVDA
vs 3.9 months sorafenib**
(HR=0.73 [95% CI: 0.56, 0.95]) P=0.02

Tolerability and Safety¹

- **Most common ARs (≥20%):** fatigue, hypertension, diarrhea, decreased appetite, nausea, dysphonia, hypothyroidism, cough, and stomatitis
- **Serious ARs (>2%):** bleeding, venous thromboembolism, arterial thromboembolism, acute kidney injury, and hepatobiliary disorders

AR=adverse reaction; CPI=checkpoint inhibitor; CI=confidence interval; HR=hazard ratio; PFS=progression-free survival; rrRCC=relapsed/refractory renal cell carcinoma; TKI=tyrosine kinase inhibitor.

INDICATIONS

FOTIVDA is indicated for the treatment of adult patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypertension and Hypertensive Crisis: Hypertension was reported in 45% of FOTIVDA-treated patients with 22% of the events ≥Grade 3. Hypertensive crises were reported in 0.8% of patients. Do not initiate FOTIVDA in patients with uncontrolled hypertension. Monitor for hypertension and treat as needed. Reduce the FOTIVDA dose for persistent hypertension not controlled by anti-hypertensive medications. Discontinue FOTIVDA for severe hypertension that cannot be controlled with anti-hypertensive therapy or for hypertensive crisis.

Cardiac Failure: Cardiac failures were reported in 1.6% of FOTIVDA-treated patients, with 1% of events reported as ≥Grade 3; 0.6% of events were fatal. Monitor for signs or symptoms of cardiac failure throughout treatment with FOTIVDA. Manage with dose interruption, dose reduction, or discontinuation.

Cardiac Ischemia and Arterial Thromboembolic Events: Cardiac ischemia in FOTIVDA-treated patients were reported in 3.2%; 0.4% of events were fatal. Arterial thromboembolic events were reported in 2.0% of FOTIVDA-treated patients, including death due to ischemic stroke (0.1%). Closely monitor patients who are at risk for, or who have a history of these events. Discontinue FOTIVDA in patients who develop severe arterial thromboembolic events, such as myocardial infarction and stroke.

Venous Thrombotic Events: Venous thromboembolic events were reported in 2.4% of FOTIVDA-treated patients, including 0.3% fatal events. Closely monitor patients who are at increased risk for these events. Discontinue FOTIVDA in patients who develop serious venous thromboembolic events.

Hemorrhagic Events: Hemorrhagic events were reported in 11% of FOTIVDA-treated patients; 0.2% of events were fatal. FOTIVDA should be used with caution in patients who are at risk for or who have a history of bleeding.

Proteinuria: Proteinuria was reported in 8% of FOTIVDA-treated patients, with 2% Grade 3. Monitor throughout treatment with FOTIVDA. For moderate to severe proteinuria, reduce the dose or interrupt treatment with FOTIVDA. Discontinue FOTIVDA in patients who develop nephrotic syndrome.

Thyroid Dysfunction: Thyroid dysfunction events were reported in 11% of FOTIVDA-treated patients, with 0.3% of events reported as ≥Grade 3. Monitor thyroid function before initiation and throughout treatment with FOTIVDA.

Wound Healing Complications: Withhold FOTIVDA for at least 24 days prior to elective surgery. Do not administer FOTIVDA for at least 2 weeks after major surgery and until adequate wound healing is observed. The safety of resumption of FOTIVDA after resolution of wound healing complications has not been established.



Learn More at **FOTIVDAhcp.com**

Reversible Posterior Leukoencephalopathy Syndrome (RPLS): RPLS, a syndrome of subcortical vasogenic edema diagnosed by MRI, can occur with FOTIVDA. Evaluate for RPLS in patients presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue FOTIVDA if signs or symptoms of RPLS occur.

Embryo-fetal Toxicity: FOTIVDA can cause fetal harm. Advise patients of the potential risk to a fetus, to avoid becoming pregnant and to use contraception during treatment and for one month after the last dose of FOTIVDA. Advise males with female partners of reproductive potential to use effective contraception during treatment and for one month after the last dose of FOTIVDA.

Allergic Reaction to Tartrazine: FOTIVDA 0.89 mg capsule contains FD&C Yellow No. 5 (tartrazine) as an imprint ink which may cause allergic-type reactions (including bronchial asthma) in certain susceptible patients.

ADVERSE REACTIONS

The most commonly reported ($\geq 20\%$) adverse reactions were: fatigue/asthenia, hypertension, diarrhea, decreased appetite, nausea, dysphonia, hypothyroidism, cough, and stomatitis. Serious adverse reactions reported in $>2\%$ of patients included bleeding (3.5%), venous thromboembolism (3.5%), arterial thromboembolism (2.9%), acute kidney injury (2.3%), and hepatobiliary disorders (2.3%).

DRUG INTERACTIONS

Strong CYP3A4 Inducers: Avoid coadministration of FOTIVDA with strong CYP3A4 inducers.

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed during FOTIVDA treatment and for at least 1 month after the last dose.

Renal Impairment: The recommended dosage for patients with end-stage renal disease has not been established.

Hepatic Impairment: Reduce the FOTIVDA dose for patients with moderate hepatic impairment. The recommended dosage in patients with severe hepatic impairment has not been established.

To report SUSPECTED ADVERSE REACTIONS, contact AVEO Pharmaceuticals, Inc. at 1-833-FOTIVDA (1-833-368-4832) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Please see the brief summary of the Prescribing Information for FOTIVDA® (tivozanib) on the following pages.

References: 1. FOTIVDA (tivozanib) [package insert]. Boston, MA: AVEO Pharmaceuticals, Inc, March 2021. 2. Rini BI, Pal SK, Escudier BJ, et al. Tivozanib versus sorafenib in patients with advanced renal cell carcinoma (TIVO-3): a phase 3, multicentre, randomised, controlled, open-label study. *Lancet Oncol.* 2020;21(1):95-104.

FOTIVDA® (tivozanib) capsules

BRIEF SUMMARY OF PRESCRIBING INFORMATION
PLEASE SEE THE FOTIVDA PACKAGE INSERT FOR
FULL PRESCRIBING INFORMATION.

INITIAL U.S. APPROVAL: 2021

1 INDICATIONS AND USAGE

FOTIVDA is indicated for the treatment of patients with relapsed or refractory advanced renal cell carcinoma (RCC) following two or more prior systemic therapies.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypertension and Hypertensive Crisis

Hypertension occurred in 45% of patients treated with FOTIVDA, with 22% of the events ≥Grade 3. Hypertensive crises occurred in 0.8% of patients.

Blood pressure should be well-controlled prior to initiating FOTIVDA. Patients should be monitored for hypertension and treated as needed with standard anti-hypertensive therapy. In the case of persistent hypertension despite use of anti-hypertensive medications, reduce the FOTIVDA dose. Discontinue FOTIVDA if hypertension is severe and persistent despite anti-hypertensive therapy and dose reduction of FOTIVDA, and discontinuation should be considered if there is evidence of hypertensive crisis. If FOTIVDA is interrupted, patients receiving antihypertensive medications should be monitored for hypotension.

5.2 Cardiac Failure

FOTIVDA can cause serious, sometimes fatal, cardiac failure. Cardiac failure in FOTIVDA-treated patients occurred in 1.6%, with 1% of events ≥Grade 3, and 0.6% of events were fatal. FOTIVDA has not been studied in patients with symptomatic cardiac failure within the preceding 6 months before FOTIVDA treatment initiation. Periodically monitor patients for symptoms of cardiac failure throughout treatment with FOTIVDA. Management of cardiac failure events may require interruption, dose reduction, or permanent discontinuation of FOTIVDA therapy.

5.3 Cardiac Ischemia and Arterial Thromboembolic Events

FOTIVDA can cause serious, sometimes fatal, cardiac ischemia and arterial thromboembolic events. Cardiac ischemia in FOTIVDA-treated patients occurred in 3.2%, with 1.5% of events >Grade 3, and 0.4% of events were fatal. Arterial thromboembolic events were reported in 2% of FOTIVDA-treated patients, including death due to ischemic stroke (0.1%).

FOTIVDA has not been studied in patients who had an arterial thrombotic event, myocardial infarction, or unstable angina within the preceding 6 months before FOTIVDA treatment initiation. Closely monitor patients who are at risk for, or who have a history of, these events (such as myocardial infarction and stroke), during treatment with FOTIVDA. Discontinue FOTIVDA in patients who develop any severe or life-threatening arterial thromboembolic event.

5.4 Venous Thromboembolic Events

FOTIVDA can cause serious, sometimes fatal, venous thromboembolic events. Venous thromboembolic events occurred in 2.4% of patients treated with FOTIVDA, including death (0.3%). Closely monitor patients who are at risk for, or who have a history of these events during treatment with FOTIVDA. Discontinue FOTIVDA in patients who develop any severe or life-threatening venous thromboembolic event.

5.5 Hemorrhagic Events

FOTIVDA can cause serious, sometimes fatal, hemorrhagic events. Hemorrhagic events occurred in 11% of patients treated with FOTIVDA, including death (0.2%). FOTIVDA has not been studied in patients with significant bleeding within the preceding 6 months before FOTIVDA treatment initiation. Closely monitor patients who are at risk for or who have a history of bleeding during treatment with FOTIVDA. Discontinue FOTIVDA in patients who develop severe or life-threatening hemorrhagic events.

5.6 Proteinuria

FOTIVDA can cause proteinuria. Proteinuria occurred in 8% of FOTIVDA-treated patients with 2% of events Grade 3. Of the patients who developed proteinuria, 3/81 (3.7%) had acute kidney injury either concurrently or later during treatment. Monitor patients for proteinuria before initiation of, and periodically throughout, treatment with FOTIVDA. For patients who develop moderate to severe proteinuria, reduce the dose or interrupt FOTIVDA treatment. Discontinue FOTIVDA in patients who develop nephrotic syndrome.

5.7 Thyroid Dysfunction

FOTIVDA can cause thyroid dysfunction. Thyroid dysfunction events in FOTIVDA-treated patients occurred in 11%, with 0.3% Grade 3 or 4 events. Hypothyroidism was reported in 8% of patients and hyperthyroidism was reported in 1% of patients. Monitor thyroid function before initiation of, and periodically throughout, treatment with FOTIVDA. Treat hypothyroidism and hyperthyroidism to maintain euthyroid state before and during treatment with FOTIVDA.

5.8 Risk of Impaired Wound Healing

Impaired wound healing can occur in patients who receive drugs that inhibit the vascular endothelial growth factor (VEGF) signaling pathway, such as FOTIVDA. Therefore, FOTIVDA has the potential to adversely affect wound healing. Withhold FOTIVDA for at least 24 days prior to elective surgery. Do not administer for at least 2 weeks following major surgery and until adequate wound healing. The safety of resumption of FOTIVDA after resolution of wound healing complications has not been established.

5.9 Reversible Posterior Leukoencephalopathy Syndrome

Reversible posterior leukoencephalopathy syndrome (RPLS), a syndrome of subcortical vasogenic edema diagnosed by MRI, can occur with FOTIVDA. Perform an evaluation for RPLS in any patient presenting with seizures, headache, visual disturbances, confusion, or altered mental function. Discontinue FOTIVDA in patients who develop RPLS.

5.10 Embryo-Fetal Toxicity

Based on findings from animal studies and its mechanism of action, FOTIVDA can cause fetal harm when administered to a pregnant woman. In embryo-fetal developmental studies, oral administration of tivozanib to pregnant animals during the period of organogenesis caused maternal toxicity, fetal malformations and embryo-fetal death at doses below the maximum recommended clinical dose on a mg/m² basis.

5.11 Allergic Reactions to Tartrazine (FD&C Yellow No. 5)

FOTIVDA 0.89 mg capsule contains FD&C Yellow No. 5 (tartrazine) as an imprint ink which may cause allergic-type reactions (including bronchial asthma) in certain susceptible patients.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are also described elsewhere in the labeling: Hypertension and Hypertensive Crisis, Cardiac Failure, Cardiac Ischemia and Arterial Thromboembolic Events, Venous Thromboembolic Events, Hemorrhagic Events, Proteinuria, Thyroid Dysfunction, Risk of Impaired Wound Healing, Reversible Posterior Leukoencephalopathy Syndrome (RPLS).

6.1 Clinical Trial Experience

The pooled safety population described in WARNINGS AND PRECAUTIONS reflect exposure to FOTIVDA administered at 1.34 mg orally once daily with or without food for 21 days on treatment followed by 7 days off treatment for a 28-day cycle in 1008 patients with advanced RCC in TIVO-3 and five other monotherapy studies. Among 1008 patients who received FOTIVDA, 52% were exposed for 6 months or longer and 34% were exposed for greater than one year.

Relapsed or Refractory Advanced RCC Following Two or More Prior Systemic Therapies

The safety of FOTIVDA was evaluated in TIVO-3, a randomized, open-label trial in 350 patients with relapsed or refractory advanced RCC who received 2 or 3 prior systemic treatments. Patients were randomized (1:1) to receive FOTIVDA 1.34 mg orally once daily for 21 days on treatment followed by 7 days off treatment for a 28-day cycle, or to receive sorafenib 400 mg orally twice a day continuously until disease progression or unacceptable toxicity. Among patients who received FOTIVDA, 53% were exposed for 6 months or longer and 31% were exposed for greater than one year.

Serious adverse reactions occurred in 45% of patients who received FOTIVDA. Serious adverse reactions in >2% of patients included bleeding (3.5%), venous thromboembolism (3.5%), arterial thromboembolism (2.9%), acute kidney injury (2.3%), and hepatobiliary disorders (2.3%). Fatal adverse reactions occurred in 8% of patients who received FOTIVDA, including pneumonia (1.7%), hepatobiliary disorders (1.2%), respiratory failure (1.2%), myocardial infarction (0.6%), cerebrovascular accident (0.6%), and subdural hematoma (0.6%).

Permanent discontinuation of FOTIVDA due to an adverse reaction occurred in 21% of patients. Adverse reactions which resulted in permanent discontinuation of FOTIVDA in >2 patients included hepatobiliary disorders, fatigue, and pneumonia. Dosage interruptions of FOTIVDA due to an adverse reaction occurred in 48% of patients. Adverse reactions which required dosage interruption in >5% of patients included fatigue, hypertension, decreased appetite, and nausea. Dose reductions of FOTIVDA due to an adverse reaction occurred in 24% of patients. Adverse reactions which required dose reductions in >3% of patients included fatigue, diarrhea, and decreased appetite.

The most common (≥20%) adverse reactions were fatigue, hypertension, diarrhea, decreased appetite, nausea, dysphonia, hypothyroidism, cough, and stomatitis, and the most common Grade 3 or 4 laboratory abnormalities (≥5%) were sodium decreased, lipase increased, and phosphate decreased.

Table 2 summarizes the adverse reactions in TIVO-3.

Table 2. Adverse Reactions (≥15%) in Patients Who Received FOTIVDA in TIVO-3

Adverse Reaction	FOTIVDA (n = 173)		Sorafenib (n = 170)	
	All Grades (%)	Grades 3 OR 4 (%)	All Grades (%)	Grades 3 OR 4 (%)
Any	99	67	100	72
General				
Fatigue*	67	13	48	12
Vascular				
Hypertension†	44	24	31	17
Bleeding‡	17	3	12	1
Gastrointestinal				
Diarrhea§	43	2	54	11
Nausea	30	0	18	4
Stomatitis	21	2	23	2
Vomiting	18	1	17	2
Metabolism and nutrition				
Decreased appetite	39	5	30	4
Respiratory, thoracic, and mediastinal				
Dysphonia	27	1	9	0
Cough	22	0	15	1
Dyspnea	15	3	11	1
Endocrine				
Hypothyroidism¶	24	1	11	0
Musculoskeletal				
Back pain	19	2	16	2
Skin and subcutaneous tissue disorders				
Rash*	18	1	52	15
Palmar-plantar erythrodysesthesia syndrome	16	1	41	17
Investigations				
Weight decreased	17	3	22	3

*Includes fatigue and asthenia

†Includes hypertension, blood pressure increased, hypertensive crisis

‡Includes hematuria, epistaxis, hemoptysis, hematoma, rectal hemorrhage, vaginal hemorrhage, contusion, gastrointestinal hemorrhage, hematochezia, intraocular hematoma, melena, metrorrhagia, pulmonary hemorrhage, subdural hematoma, gingival bleeding, hematemesis, hemorrhage intracranial, hemorrhoidal hemorrhage, splinter hemorrhages

§Includes diarrhea and frequent bowel movements

¶Includes hypothyroidism, blood thyroid stimulating hormone increased, tri-iodothyronine decreased, tri-iodothyronine free decreased

*Includes dermatitis, dermatitis acneiform, dermatitis contact, drug eruption, eczema, eczema nummular, erythema, erythema multiforme, photosensitivity reaction, pruritus, psoriasis, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash morbilliform, rash pruritic, seborrheic dermatitis, skin exfoliation, skin irritation, skin lesion, swelling face, toxic skin eruption, urticaria

Clinically relevant adverse reactions in <15% of patients who received FOTIVDA included proteinuria, venous thromboembolism, arterial thromboembolism, hyperthyroidism, hepatobiliary disorders, osteonecrosis, cardiac failure, and delirium.

Table 3 summarizes the laboratory abnormalities in TIVO-3.

Table 3. Select Laboratory Abnormalities (≥10%) That Worsened from Baseline in Patients with Advanced RCC Who Received FOTIVDA

Laboratory Abnormality	FOTIVDA ^a (n = 173)		Sorafenib ^b (n = 170)	
	All Grades (%)	Grades 3 OR 4 (%)	All Grades (%)	Grades 3 OR 4 (%)
Hematology				
Lymphocytes decreased	25	5	42	6
Hemoglobin increased	19	0	8	0
Platelets decreased	19	0	18	1
Hemoglobin decreased	16	1	27	4
Chemistry				
Creatinine	50	0	37	1
Glucose increased	50	3	40	0
Phosphate decreased	38	5	63	31
Sodium decreased	36	9	30	11
Lipase increased	32	9	36	10
ALT increased	30	4	29	2
Alkaline phosphatase increased	30	4	32	2
AST increased	28	1	31	2
Potassium increased	26	3	23	0
Magnesium decreased	26	0	23	1
Amylase increased	23	2	28	3
Calcium increased	15	2	7	2
Bilirubin increased	11	3	11	0
Coagulation				
Activated partial thromboplastin time prolonged	26	1	18	0

^aThe denominator used to calculate the rate varied from 139 to 171 based on the number of patients with a baseline value and at least one post-treatment value.

7 DRUG INTERACTIONS

Avoid concomitant use of strong CYP3A inducers with FOTIVDA.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal studies and its mechanism of action, FOTIVDA can cause fetal harm when administered to a pregnant woman. There are no available data on FOTIVDA use in pregnant woman to inform the drug-associated risk. In embryo-fetal developmental studies, oral administration of tivozanib to pregnant animals during the period of organogenesis caused maternal toxicity, fetal malformations and embryo-fetal death at doses below the maximum recommended clinical dose on a mg/m² basis. Advise pregnant woman of the potential risk to a fetus.

Animal data

In an embryo-fetal developmental study in pregnant rats, daily oral administration of tivozanib at doses ≥0.03 mg/kg/day (0.2 times the maximum recommended clinical dose on a mg/m² basis) during the period of organogenesis resulted in maternal toxicity, increases in early and late resorptions, and an increase in fetal external malformations (body edema, short/kinked tail), and skeletal developmental delays.

In an embryo-fetal developmental study in pregnant rabbits, daily oral administration of tivozanib at 1 mg/kg/day (14.5 times the maximum recommended clinical dose on a mg/m² basis) during the period of organogenesis resulted in fetal malformations including ventricular septal defects and major vessel anomalies. No maternal toxicity was reported at doses up to 1 mg/kg/day.

8.2 Lactation

Risk Summary: There are no data on the presence of tivozanib in human milk, or the effects of tivozanib on the breastfed child, or on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise a lactating woman not to breastfeed during treatment with FOTIVDA and for one month after the last dose.

8.3 Females and Males of Reproductive Potential
FOTIVDA can cause fetal harm when administered to a pregnant woman.

Pregnancy Testing: Verify pregnancy status of females of reproductive potential prior to starting treatment with FOTIVDA.

Contraception: Advise females of reproductive potential to use effective contraception during treatment with FOTIVDA and for one month after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with FOTIVDA and for one month after the last dose.

Infertility: Based on findings in animal studies, FOTIVDA can impair fertility in females and males of reproductive potential.

8.4 Pediatric Use

The safety and effectiveness of FOTIVDA in pediatric patients have not been established.

8.5 Geriatric Use

Of the 1008 patients with advanced RCC treated with FOTIVDA, 29% were ≥65 years of age and 4% were ≥75 years of age. No overall differences in safety were observed between patients ≥65 versus <65 years of age. Of the 175 patients with advanced RCC following two or more prior systemic therapies randomized to FOTIVDA, 44% were ≥65 years of age and 9% were ≥75 years of age. No overall differences in effectiveness were observed between patients ≥65 versus <65 years of age.

8.6 Renal Impairment

No dosage modification is recommended for patients with mild to severe renal impairment (creatinine clearance [CL_{CR}] 15-89 mL/min, estimated by Cockcroft-Gault). The recommended dosage for patients with end-stage renal disease has not been established.

8.7 Hepatic Impairment

Reduce the dosage when administering FOTIVDA in patients with moderate (total bilirubin greater than 1.5 to 3 times ULN with any AST) hepatic impairment. No dosage modification is recommended for patients with mild (total bilirubin less than or equal to ULN with AST greater than ULN or total bilirubin greater than 1 to 1.5 times ULN with any AST) hepatic impairment. The recommended dosage of FOTIVDA in patients with severe (total bilirubin greater than 3 to 10 times ULN with any AST) hepatic impairment has not been established.

10 OVERDOSAGE

Overdosage with FOTIVDA can cause severe hypertension and hypertensive crisis that may result in death.

During clinical studies, three patients inadvertently received doses ≥2.68 mg (≥2 times the recommended dose) of FOTIVDA. One patient who received two daily doses of 8.9 mg of FOTIVDA experienced hypertensive crisis with severe hypertensive retinopathy; a second patient who received three doses of 1.34 mg in one day experienced fatal uncontrolled hypertension; and a third patient who received two doses of 1.34 mg FOTIVDA in one day experienced persistent hypertension lasting over 5 days. There is no specific treatment or antidote for FOTIVDA overdose. In cases of suspected overdose, withhold FOTIVDA, closely monitor patients for hypertension and hypertensive crisis and other potential adverse reactions. Immediately manage signs or symptoms of hypertension and provide other supportive care as clinically indicated.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA approved patient labeling (PATIENT INFORMATION).

Hypertension and Hypertensive Crisis: Inform patients that hypertension or hypertensive crisis may occur during FOTIVDA treatment. Advise patients to undergo routine blood pressure monitoring and to contact their healthcare provider if blood pressure is elevated. Advise patients that if they experience signs or symptoms of hypertension to immediately contact their health care provider.

Cardiac Failure: Advise patients to immediately contact their healthcare provider if they develop symptoms of cardiac failure.

Cardiac Ischemia and Arterial Thromboembolic Events: Inform patients that arterial thromboembolic events (including fatal outcomes) may occur during FOTIVDA treatment. Advise patients to immediately contact their health care provider if new onset of chest discomfort, sudden weakness, or other events suggestive of a thrombotic event occurs.

Venous Thromboembolic Events: Advise patients to immediately contact their healthcare provider if they develop symptoms of dyspnea or localized limb edema.

Hemorrhagic Events: Instruct patients to contact their healthcare provider to seek immediate medical attention for signs or symptoms of unusual bleeding or hemorrhage.

Risk of Impaired Wound Healing: Inform patients that FOTIVDA may impair wound healing. Advise patients that temporary interruption of FOTIVDA is recommended prior to elective surgery. Advise patients to contact their healthcare provider before any planned surgeries, including dental surgery.

Reverse Posterior Leukoencephalopathy Syndrome: Inform patients that RPLS may occur during FOTIVDA treatment. Advise patients to immediately contact their health care provider in the event of seizures, headaches, visual disturbances, confusion, or difficulty thinking.

Overdosage: Instruct patients to contact their healthcare provider immediately if they inadvertently take too much FOTIVDA.

Embryo-Fetal Toxicity: Advise females of reproductive potential of the potential risk to a fetus. Advise patients to inform their healthcare provider of a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with FOTIVDA and for one month after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with FOTIVDA and for one month after the last dose.

Lactation: Advise women not to breastfeed during treatment with FOTIVDA and for one month after the last dose.

Infertility: Advise males and females of reproductive potential that FOTIVDA can impair fertility.

Allergic Reactions to Tartrazine (FD&C Yellow No. 5): FOTIVDA 0.89 mg capsule contains FD&C Yellow No. 5 (tartrazine) as an imprint ink which may cause allergic-type reactions (including bronchial asthma) in certain susceptible patients.

Other Common Events: Advise patients that other adverse reactions with FOTIVDA treatment may include diarrhea, vomiting, dysphonia (hoarseness of voice), fatigue, asthenia and stomatitis (sores in the mouth), and cough.

Important Administration Information: Instruct patient if a dose of FOTIVDA is missed, the next dose should be taken at the regularly scheduled time. Do not take two doses in the same day.

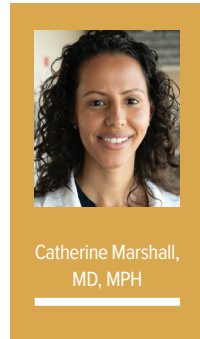
Drug Interactions: Advise patients to inform their healthcare provider of all concomitant medications, vitamins, or dietary and herbal supplements.

This brief summary is based on the FOTIVDA Prescribing Information issued 03/2021

Treatment of Men with Metastatic Hormone-Sensitive Prostate Cancer: Triplet Versus Doublet Therapy

Daniel Tennenbaum, MD

ALTHOUGH MOST CASES of prostate cancer present at an early stage, and often with an indolent course, the disease continues to be the second most common and fifth most deadly cancer in men worldwide. This is because an estimated one-third of men with prostate cancer will develop metastases at some point during the course of their disease. For these reasons, treatment of high-risk and advanced prostate cancer is of critical importance for patients and physicians. For decades, the standard of care treatment for metastatic hormone-sensitive prostate cancer (mHSPC) has been androgen-deprivation therapy (ADT), which reduces the levels of circulating testosterone to prevent



further growth of prostate cancer. With the recent publication of landmark trials, including CHAARTED and STAMPEDE, there has been a recent paradigm shift in the management of advanced prostate cancer. In particular, there have been significant changes in treatment guideline recommendations for mHSPC.

Catherine Marshall, MD, MPH, an assistant professor of oncology at Johns Hopkins Medical Center, and *GU Oncology Now* Editor, helped clarify the recent shifts in management of mHSPC. According to Dr Marshall, when we speak about mHSPC, we really are referring to 2 related entities:

(1) confirmed metastatic disease based on conventional scans (eg, computed tomography [CT] or nuclear bone scans) showing evidence of lymphadenopathy, visceral disease, or bone lesions on bone scan; and

(2) recently diagnosed prostate adenocarcinoma that has not yet been treated with ADT and may still be sensitive to it. With the development and increased use of functional imaging, such as prostate-specific membrane antigen (PSMA) positron emission tomography (PET) CT, Dr Marshall pointed out that upstaging of prostate cancer in patients is likely to increase. Indeed, upstaging of disease that once would have been considered biochemically recurrent accomplished in a patient with rising PSA shown on and negative conventional scans (ie, CT and bone imaging), may have PSMA imaging indicative of metastatic cancer. According to Dr Marshall, this is worth pointing out because the clinical trials that have established benefit of intensification of treatments for men with mHSPC whose was shown but were based on the presence of metastatic disease on conventional imaging.

As mentioned above, ADT has long been the standard of care for treatment of men with mHSPC; it using either a luteinizing hormone-releasing hormone (LHRH) agonist or antagonist alone. Unfortunately, it is almost certain that men with mHSPC treated with ADT will ultimately develop hormone-resistant disease. Over the past decade, efforts have been made to add various antiandrogen therapeutics to the regimen to delay the inevitable creep in onset of hormone resistance. Currently, 4 drugs, previously only being approved for the use of treatment of metastatic hormone-resistant prostate cancer, have become standard of care in the treatment of men with mHSPC. The chemotherapeutic agent docetaxel and the oral antiandrogen

drugs abiraterone, enzalutamide, and apalutamide have been shown in large trials to prolong overall survival when used upfront at the time of diagnosis (ie, when the patient is still sensitive to ADT) instead of waiting for the disease to evolve into metastatic hormone-resistant prostate cancer. Dr Marshall explained that this approach—a regimen of ADT plus 1 of the 4 approved therapeutic agents—is referred to as “doublet therapy” for treatment of men with mHSPC.

If doublet therapy shows a clinical advantage, the obvious question is whether “triplet therapy” would show an even greater one. When *GU Oncology Now* posed the question to Dr Marshall, she was careful to temper expectations. She cited 2 recent randomized trials investigating the benefit of triplet therapy, the PEACE-1 trial and the ARASENS trial. According to Dr Marshall, the real question being asked about triplet therapy is whether “combining chemotherapy with an oral novel hormonal agent improves outcomes compared to chemotherapy and ADT.” PEACE-1 is exploring the addition of ingabiraterone/prednisone and ARASENS is exploring the addition of darolutamide as agents that can be incorporated against the backbone of ADT plus docetaxel. However, Dr Marshall noted some differences in the patient populations of these trials. Patients enrolled in the PEACE-1 had de novo metastatic disease (ie, disease that was metastatic at the time of prostate cancer diagnosis), both (specifically, and + therapy) and (and + + therapy). The results showed that men who received abiraterone with or without radiation in addition to ADT plus docetaxel had improvements in radiologic progression-free survival and overall survival. By contrast, the ARASENS trial compared ADT plus docetaxel with either the antiandrogen darolutamide or placebo. Most, but not all, patients had metastatic disease at the time of diagnosis. ARASENS also showed an overall survival benefit of triplet therapy compared with ADT plus docetaxel, with the risk of death in the darolutamide group found to be 32% lower than in the placebo group. It is important. Neither of these trials evaluated the triplet therapy of ADT and docetaxel plus an oral antiandrogen against a comparator arm of ADT plus an oral antiandrogen alone. For this reason, Dr Marshall points out, we cannot yet say with certainty that triplet therapy is superior to doublet therapy of ADT + oral anti-androgen.

Dr Marshall noted that one of the major concerns about use of triplet therapy is the risk of toxicity to the patient. There have been concerns within the medical community about potential additive toxicity when taking 3 agents simultaneously. Primary among these is concern about the potential exacerbation of fatigue and neuropathy with inclusion of docetaxel. However, according to Dr. Marshall, those because trials showed] “toxicities are what would be expected from the individual agents” if they are taken alone.

As described earlier, the 4 standard of care agents used in addition to ADT were previously only indicated for metastatic

hormone-resistant prostate cancer. When asked how else the treatment of hormone-resistant disease may be impacting the approach to mHSPC, Dr Marshall stressed that deciding on the appropriate sequencing of treatments will continue to be increasingly challenging as more treatments become available in clinical practice and the standard treatments for hormone-resistant disease continue to be used earlier in the prostate cancer course. Further, as the medical community continues to employ novel hormonal agents and chemotherapy in the hormone-sensitive setting, the choice of which treatments to use next—after hormone resistance develops—has become a gray area. Dr Marshall mentioned the CARD trial as a study that provides evidence supporting the use of the chemotherapeutic agent cabazitaxel when there has been disease progression on abiraterone or enzalutamide, plus docetaxel. Results from the CARD trial showed significant improvement in both progression-free survival and overall survival. Dr Marshall also was careful to point out that the medical community will be required to consider when to use newer therapeutic agents, such as radiologic-targeted ones like lutetium-177 PSMA therapy, and immunotherapy and targeted agents, such as PARP (poly adenosine diphosphate-ribose polymerase) inhibitors, for treatment of men who might benefit from those therapies.

GU Oncology Now asked Dr Marshall what the treatment of men with mHSPC might look like in the future. According to her, the future of management likely will include use of more targeted agents at earlier stages of disease. She anticipates that with further drug development and clinical trial progress, the medical community will likely get better at defining who will require the most intensive treatment course and who can still be managed well without the increased morbidity that accompanies treatment intensification.

Ultimately, Dr Marshall stressed, the choice of treatment for men with mHSPC must be tailored to multiple patient- and disease-specific variables. Current treatment of men with mHSPC has moved well beyond the previous standard of ADT alone. The paradigm has shifted as the use of chemotherapy or new antiandrogen agents in conjunction with ADT has demonstrated significant survival benefits compared to ADT alone. Although select individuals may not benefit from doublet therapy because they are too frail to tolerate the second agent, or have other significant comorbidities, it is clear that for many outpatients, there are far more treatment options to choose from in determining how best to approach a patient with a diagnosis of mHSPC.



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Single Versus Multiport Robotic Prostatectomy— An AUA Plenary Debate

Akhil A. Saji, MD

AT THE AMERICAN UROLOGICAL ASSOCIATION (AUA) 2022 meeting in New Orleans, one of the highlights of the plenary session was a debate between Jeffrey A. Cadeddu, MD, of UT Southwestern Medical Center, and Jihad Kaouk, MD, of the Cleveland Clinic, on the subject of single versus multiport robotic prostatectomy (RARP) for patients with prostate cancer. The robotic platform referenced in these discussions was the da Vinci surgical system (Intuitive Surgical). The core components of the system include a surgeon's

console, a 3-dimensional vision system, and proprietary EndoWrist technology that allows for flexible articulation and precision during surgery. A commonly used version of the platform is the da Vinci Xi, which uses up to 4 robotic trocar ports to perform minimally invasive surgery. The most recent iteration of the platform is the single port (SP) robot, which was approved by the US Food and Drug Administration (FDA) in May 2018 for use in urologic surgery. Similar to the da Vinci Xi, the SP platform provides the surgeon with a 3-dimensional high-definition camera and highly articulate instruments through a single incision.

Dr Cadeddu began by defending the view that multiport RARP is superior. The multiport robot is supported by more than 2 decades of literature comparing it to open radical prostatectomy and demonstrating equivalent oncologic outcomes and equivalent, or possibly improved, functional outcomes including reduced blood loss, less pain, and shorter durations of hospital stay. He explained that introduction of the SP platform should begin by demonstrating at least equivalent metrics to justify the higher expense and learning curve associated with switching to SP.

Equivalency can be measured through a concept referred to as “pentafecta,” coined originally by Patel et al,¹ to describe 5 key metrics for RARP. These include complication rates, positive surgical margins, potency, urinary continence, and biochemical recurrence-free rate. Dr Cadeddu asserted that any utility for the SP platform should originate from the ability to demonstrate overall complication rates of <7%, positive surgical margin rates <10%, potency >90%, and urinary continence and biochemical-free rates >96%, all based on the large series presented by Dr Patel. These results are achievable in the hands of an expert robotic surgeon, explained Dr Cadeddu. Furthermore, citing data from Patel et al, he explained that at least 83% percent of patients should achieve trifecta (or 3 of 5 metrics) and at least 71% percent should achieve pentafecta (5 of 5 metrics). If these are not achievable in the hands of an expert surgeon, then the SP platform should not be considered for RARP.

Dr Cadeddu remarked that since the inception of the RARP and its gradual transition to mainstream adoption (90% of radical prostatectomy by 2014²), surgeons have been learning and evolving to achieve pentafecta for their patients. The introduction of a new technology, totally distinct from the multiport robotic approach, risks setting functional outcome progress backward, he explained. Citing an article by Thompson et al³ examining the learning curve for RARP, he explained that surgeons would need to perform at least 100 to 200 prostatectomies to achieve equivalency to open radical prostatectomy outcomes.

Although another selling point for SP RARP is less perceived patient pain, it is well-documented that multiport RARP can be conducted without the use of any opioid analgesics according to Dr Cadeddu. He explained that these clinical pathways often utilize ketorolac, IV acetaminophen and ibuprofen and that up to 95% of patients can be managed without opioids. He noted that the ability to perform outpatient surgery, allowing patients to return home in the same day, is another marketing point for SP RARP but rebutted the point by citing data from Trabulsi et al⁴ and Khalil et al⁵ showing that even with multiport RARP, patients are able to go home the same day. In expert hands, he remarked, patients can be discharged after multiport RARP and have a <3% rate of readmission.⁶

Questioning the intent of the SP robot, Dr Cadeddu asked whether surgeons need a new robot or just better surgical techniques to improve outcomes. He cited prior documented improvements, including Rocco stitches, anterior suspensions, posterior urethral suspensions, bladder neck sparing and membranous urethral sparing approaches. He also highlighted the latest Retzius-sparing approach which, by Rosenberg et al⁷, demonstrated to have a distinct advantage for urinary continence recovery compared to standard RARP.

At this point, Dr Kaouk took the stage to make the case for SP RARP. He began by rebuking the debate topic, explaining that the goal should not be to assert the superiority of a multiple versus single incision, but rather to utilize instruments that allow regionalizing surgical dissection for a procedure and further minimizing the impact of minimally invasive surgery on the patient. As a critical example, he displayed several images showing examples of patients who are ideal candidates for a SP RARP, primarily due to significant prior abdominal surgical history. He explained that the low profile and single port would allow surgeons to perform this lifesaving procedure through an extraperitoneal, transvesical, or even perineal approach, none of which are possible with the multiport robot.

Dr Kaouk emphasized this point by playing a video demonstrating a transvesical RARP where, instead of insufflating the abdomen, the bladder is inflated, allowing surgeons to avoid issues from prior abdominal surgery such as adhesions or frozen pelvises. One limitation of this approach, however, is the limited ability to perform a lymph node dissection. This further supports the idea that it should be considered one among other tools, to be used in selected cases. Dr Kaouk also spoke about the functional outcomes of this approach. He cited data from his institution where among 106 patients undergoing transvesical SP RARP, there was a median catheter time duration of just 3 days and 97% achieved full urinary control by 24 weeks after surgery. He also cited data comparing urinary continence



with the multiport Retzius-sparing approach versus the SP transvesical approach showing SP RARP yielded equivalent, if not superior, urinary control outcomes at 3 and 6 months postoperatively.⁸ To further contest Dr Cadeddu's position, he cited data showing that length of stay for patients receiving SP RARP is also equivalent, if not superior. In his own series of patients, he explained that 87% of those undergoing SP transvesical RARP were discharged home within 4 hours after surgery.

What if surgeons feel uncomfortable or unfamiliar with the transvesical approach to RARP? Dr Kaouk explained that extraperitoneal RARP is also significantly easier with the SP robot because there is only one midline port to place (whereas the multiport extraperitoneal approach requires lateral ports that can be difficult to place). Furthermore, Dr Kaouk explained that while traditional urologic open surgery is primarily extraperitoneal, the majority of multiport approaches to RARP require transperitoneal access. He explained that another benefit of the SP platform is the ability to return to the extraperitoneal space. He noted that despite the increased cost of the SP platform, there has been research demonstrating that the overall cost may be lower due to shorter durations of hospital stay.⁹ Dr Kaouk concluded by emphasizing the importance of seeking innovations that provide value. For the patient, the SP RARP allows for faster return to continence and less morbidity. For the surgeon, it offers an additional approach to treat patients with hospital intraperitoneal cavities.

Finally, for hospital systems, it helps achieve lower costs through outpatient encounters for surgery.

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Safety of Relugolix in Advanced Prostate Cancer—Analysis From the HERO Trial

A Review of Moderated Poster 27-16

David Ambinder, MD

IN THIS MODERATED poster presentation at the American Urological Association (AUA) 2022 meeting, Neal Shore, MD, detailed the safety analysis of the phase 3 HERO trial¹ that ultimately led to the 2020 US Food and Drug Administration (FDA) approval of relugolix, the first and only oral gonadotropin-releasing hormone (GnRH) antagonist.

Patients in HERO were randomized in a 2 to 1 ratio to receive relugolix or leuprolide. Those who met the inclusion criteria were not considered appropriate for treatment with interventional therapy, such as surgery or radiation, but were appropriate candidates for starting androgen-deprivation therapy. Patients had to be treated for at least 1 year. Primary endpoints of the study focused on the efficacy of testosterone suppression. Other secondary endpoints included changes in prostate-specific antigen (PSA). The study also aimed to investigate the safety profile of relugolix.

Dr Shore noted that there has been a long-standing belief that luteinizing hormone–releasing hormone (LHRH) agonists are associated with cardiovascular events. In this vein, the study specifically evaluated the rate of major adverse cardiovascular events (MACE), which include nonfatal myocardial infarction, nonfatal cerebrovascular event, or death from any cause. The investigators examined both the rate of events and the duration of use prior to experiencing an adverse event (AE).

Dr Shore illustrated that patients experienced a higher rate of AEs, such as hot flashes, fatigue, and diarrhea, with oral relugolix compared with leuprolide; however, all AEs were of grade 1 or 2 severity. There was also a slight increase in patients experiencing arthralgias in the oral relugolix arm. He presented a table comparing MACE that showed a significant odds ratio between patients who received an LHRH agonist every 3 months and those who took relugolix daily; the findings showed that MACE tended to occur earlier and at a higher rate in the LHRH group. Dr Shore commented that he believes this difference is likely related to the mechanism of action of an LHRH agonist, when compared to a GnRH antagonist, and that this accounts for the subsequent risk seen in the cardiovascular AE profile and, ultimately, the safety of the drug.

A Review of Podium Discussion 35-08

IN THIS PODIUM discussion at AUA 2022, Dr Shore began by outlining his desire to explain how relugolix (an oral agent that acts as a GnRH antagonist) compares with the standard of care (an LHRH agonist). This study was a pooled safety analysis investigation of 2 randomized controlled trials, the C27002 trial² and the HERO study,¹ that compared daily relugolix with leuprolide given every 3 months.

C27002 was a phase 2, randomized, open-label, parallel-group study of 125 men with advanced prostate cancer who were stratified 2 to 1 to either leuprolide or oral relugolix. Patients in the leuprolide arm received a 22.5-mg subcutaneous injection. The relugolix loading dose was 3 pills on the first day and 120 mg daily thereafter. Patients were given relugolix over 24 weeks. The study reported that these participants had reduced and sustained testosterone-to-castration levels, and that the drug was well-tolerated and had an acceptable safety.

In comparison, HERO was a phase 3, randomized, open-label, parallel-group study in which consistent results showed that use of relugolix led to sustained testosterone suppression over 48 weeks while maintaining an acceptable safety profile. Of particular interest, when compared to leuprolide standard of care, relugolix maintained a 54% decrease in the risk of MACE.

HERO was a pivotal trial that led to the registration and FDA approval of oral relugolix. Its design was similar to the C27002 clinical trial, except it included 934 patients. The primary endpoint for HERO were testosterone suppression; its many secondary endpoints included testosterone recovery, safety, tolerability, and PSA correlates.

Dr Shore focused on the pooled analyses and safety of these 2 landmark trials. Overall, AEs were comparable between the treatments. The rate of serious AEs (grade 3 and higher) was 9.5% in the relugolix arm versus 12% in the leuprolide arm. The rate of AEs leading to discontinuation was 3.6% in the relugolix arm versus 0.3% in the leuprolide arm. Dr Shore also emphasized the reports of MACE, which included nonfatal myocardial infarction, nonfatal cerebrovascular events, or death. For any grade, there was a 2.8% versus 6.3% risk of MACE for

patients receiving relugolix compared to leuprolide; hot flashes (55.2% vs 52.4%) and fatigue (22.3% vs 19.3%) were similar between the 2 groups. Notably both low-grade constipation (11.7% vs 9%) and diarrhea (11.7% vs 6.3%) were worse in the relugolix arm when compared to the leuprolide arm. Dr Shore attributed this finding to relugolix being an oral drug that requires hepatic metabolism, which may contribute to an earlier onset of gastrointestinal symptoms.

Regarding duration and time of onset of AEs overall, patients given relugolix reported earlier experiences of AEs. When looking at MACE and pooling the analysis together in the C27002 phase 2 study, the findings corroborated what was seen in the HERO trial—a 54% reduction in the risk of a patient experiencing a MACE. During the question period, Dr Shore was asked if the patient cohorts were well-balanced in the pretreatment period prior to beginning the investigation of MACE. He answered affirmatively and said that one of the exclusion criteria for the trial was experience of MACE within 6 months of trial eligibility. A total of 15% of patients in each cohort had a history of experiencing a MACE more than 6 months before trial enrollment. He added that demographics were well-balanced between the cohorts, as were other cardiovascular risk factors that may contribute to MACE, such as glycated hemoglobin level and pre-enrollment electrocardiogram results.

Overall, Dr Shore expressed excitement that oral relugolix, a highly selective GnRH antagonist, is the first drug in its class to receive FDA approval. Its convenient once-daily administration, and support from the pooled safety analyses trials help to highlight its potential for improving patient care.

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Focal Therapy for Prostate Cancer: Should it Become a Standard of Care?

David Ambinder, MD

WHERE HAS FOCAL THERAPY found its place in the treatment for prostate cancer? This was discussed at the American Urological Association (AUA) 2022 meeting during the plenary lecture titled, “Second opinion cases: Focal therapy for prostate cancer—Should it replace standard of care?” Michael Koch, MD, of the Indiana University School of Medicine, moderated the session; the panelists were Kelly Stratton, MD (University of Oklahoma School of Medicine), and Scott Eggener, MD (University of Chicago School of Medicine).

Dr Koch began by reviewing the prevalence of prostate cancer in the United States, where nearly 200,000 men continue to be diagnosed annually. The vast majority will survive at least 5 years, and for men with localized prostate cancer, many will live for 10 to 20 years after undergoing treatment. Understanding this is critical when discussing therapy options with patients, as many treatment modalities have consequential permanent side effects. He noted that in the past 10 to 15 years, there has been an increase in the use of active surveillance for patients with low-risk disease and an increase in radical therapy for those with high-risk disease. Trends for the treatment of patients with intermediate-risk disease have been split between surgery (40%) and radiation (40%), with active surveillance used for only a small proportion of these patients. Sadly, Dr Koch painted a picture that showed that for nearly 40 years, there have been no significant changes in the approach to treating patients with intermediate-risk prostate cancer.

A 2017 study that evaluated decisional regret after prostate cancer treatment found that ~15% of patients who underwent surgery or radiation had major decisional regret.¹ This regret was primarily associated with sexual or gastrointestinal dysfunction. This paved the way to consider focal therapy, especially if it reduced the side-effect profile seen with whole gland therapy. This approach, introduced in 2008, was supported by the results of a small study evaluating focal therapy with nearly 5 years follow-up, which reported fairly good oncologic and quality-of-life outcomes.² That same year, a consensus panel organized by *Urology*[®], the “Gold

Journal,” and led by Peter Scardino, MD, of Memorial Sloan Kettering Cancer Center, concluded that focal therapy was a reasonable treatment option that should be explored in clinical trials.

Dr Koch went on to explain why it took so long for focal ablation therapy to become adopted. Initially, the reason was that because prostate cancer is a multifocal disease, the idea of treating an index lesion while leaving residual disease was concerning. However, over time, we have become more aware that the index lesion drives cancer biology. Moreover, advances in multiparametric magnetic resonance imaging (mpMRI), prostate-specific membrane antigen (PSMA), positron emission tomography (PET) imaging, and ablation technology have made the argument for focal therapy stronger. Patients are also becoming more aware of these less morbid approaches and are expressing a desire to pursue them.

Advances in multiparametric magnetic resonance imaging (mpMRI), prostate-specific membrane antigen (PSMA), positron emission tomography (PET) imaging, and ablation technology have made the argument for focal therapy stronger.

So, how effective is focal therapy? The largest cohorts of patients receiving focal therapy ablation are from Europe. A recently reported study that included 1400 men, mostly with intermediate-risk, and some with high-risk disease, attempted to determine which patients did not require whole gland treatment (failure-free survival). Failure was defined as 2 consecutive increases in prostate-specific

antigen (PSA) level followed by magnetic resonance imaging (MRI) and biopsy that then might indicate the need for whole gland therapy. In the study, 70% of patients with intermediate-risk and 30% with high-risk disease were able to avoid whole gland therapy for 7 years while experiencing minimal complications.³ Other researchers have found that quality of life is maintained in patients who undergo focal therapy, and a conglomerate of 3 studies indicates erectile function initially declines but returns almost to baseline by 1 year after treatment.⁴

Dr Koch concluded that the ideal patient for focal therapy has significant disease but is not a candidate for active surveillance. Prospective patients should not have high-risk disease, where a wide resection and/or lymph node dissection would be indicated. Cancer should be confined to a single portion of the prostate, not involve the sphincter, and ideally it should be visible on mpMRI.

Dr Koch next introduced Dr Stratton, who discussed 2 modalities, cryotherapy and high-intensity focused ultrasound (HIFU). Cryotherapy is a thermal ablation of the prostate by placing treatment probes into the prostate. The needles are placed and create an “ice ball.” On follow-up mpMRI, the index lesion is obliterated, and a subsequent biopsy would be negative. Limitations for the use of cryotherapy include large prostates (>80 g), small prostates, the presence of a median lobe, or prior transurethral resection of the prostate (TURP).

By contrast, HIFU allows for precise demarcation of an ablation zone. Again, posttreatment mpMRI would show obliteration of the index lesion. Challenges with HIFU technology include a rigid probe focal length, which means the prostate must be manipulated to ensure the focal length is correct. Limitations for use include prostate height, an enlarged prostate (>40 g), and apical tumors. Other limitations include prostate calcifications and brachytherapy seeds, as they inhibit the high-intensity ultrasound. Cryotherapy and HIFU have similar efficacy in treating prostatic base tumors. However, if the index tumor is more apical, there may be a higher risk of recurrence with use of HIFU. Dr Stratton concluded that focal therapy can be considered the standard of care for patients with intermediate-risk prostate cancer.

Dr Koch then introduced Dr Eggener, who discussed MRI-guided laser ablation and transurethral ultrasound ablation. MRI-guided laser ablation uses transperineal access and is done with real-time MRI feedback. It is best used to treat small visible lesions seen on mpMRI. Data on its effectiveness are limited. The largest study included a population in which one-third of patients had Gleason 3+3 disease. Patients were monitored and had a follow-up biopsy at 1 year after treatment. However, only one-third of the patients in this study received a follow-up biopsy. Of those who underwent a biopsy, nearly 40% of patients still had relevant pattern

4 disease. Side effects included hematuria (7.4%), erectile dysfunction (5%), and urinary retention (4.1%), and, notably, 2 patients developed a rectourethral fistula.⁵

MRI-guided transurethral ultrasound ablation differs from HIFU in that it works by emitting ultrasound waves in a radial fashion. Initially it was only available to use as whole gland therapy, but now it can be also used for focal therapy. It is capable of treating large and small prostates. In a phase 2 multicenter trial evaluating 115 patients, two-thirds of whom had intermediate-risk disease, the primary endpoints were safety and changes in PSA level.⁶ In patients who underwent whole gland treatment, the median PSA reduction was 95% and average gland size shrank significantly (from 37 g to 3 g). Posttreatment biopsy at 1 year showed that 75% to 80% of patients had a lower level or similar level of disease, compared to the initial biopsy, while 65% of patients had no evidence of disease. At the 3-year follow-up, approximately 13% of men required additional therapy. The side-effect profile was quite favorable in this patient population and, when compared to traditional treatment approaches, there was a better toxicity profile. A small percentage of patients experienced adverse effects from the treatment, including worsening of urinary symptoms, such as irritative voiding symptoms or urinary incontinence. Additionally, 25% of patients experienced erectile dysfunction, although many of these patients responded successfully to oral erectile dysfunction pharmaceutical treatment.

Dr Eggener concluded that although only very short-term follow-up and early outcomes data are available for these focal therapy technologies, it is reasonable to consider them for treatment of highly selected patients. Such patients can benefit from the significant improvement in treatment-related toxicity effects. It is important to keep in mind that these technologies require the use of an MRI machine and a skilled radiology team, can be expensive, and may require out-of-pocket costs for patients.

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Women and Underrepresentation in Urologic Oncology

Akhil Saji, MD

AT THE AMERICAN UROLOGICAL ASSOCIATION (AUA) 2022 meeting in New Orleans, Eila C. Skinner, MD, of Stanford Health Care, chaired the presentation on women in urologic oncology. The presentation was divided into segments with Cheryl T. Lee, MD, of Ohio State Medical Center, providing an overview of the history of women in the field. Sarah Psutka, MD, MSc, of the University of Washington, spoke on the history of the organization Women in Urologic Oncology (WUO), a section of the Society of Urologic Oncology (SUO). Kristen Scarpato, MD, MPH, of Vanderbilt University Medical Center, discussed the process of creating a pipeline for the production of urologic oncologists. Finally, Sima Porten, MD, MPH, of University of California San Francisco, explained the importance of supporting women healthcare professionals in urologic oncology, as well as promoting underrepresented minorities in achieving careers in the field.

Dr Lee began her presentation by outlining the history of the founding of SUO, where in May 1984, the founders sought to create an identity for AUA members that focused on urologic oncology. They sought to bring urologic oncology “to the table” by gaining representation in important government organizations, such as at the

National Cancer Institute, and pushing the field forward by obtaining funding for clinical trials. Dr Lee identified parallels in the founding of the WUO, which tailored its focus to the needs of women urologic oncologists and female urologic oncology patients. She highlighted the contributions of several trailblazers, including Dr Elisabeth Pickett, the first female urologic oncologist trained by the late Dr Willet Whitmore, former chief of urology at Memorial Sloan Kettering Cancer Center.

Dr Lee also explained why adequate female representation in the SUO and WUO is important for patient care. She cited an article by Siegel et al,¹ which estimates a total of ~445,000 patients with genitourinary cancer in the United States of whom approximately 11% (~49,700) are female. Therefore, Dr Lee recommended that at least 11% of the active SUO membership should be female, to ensure fair representation and patient care. Citing additional data from a report by Wallis et al,² she noted that when female urologic oncologists treated patients with radical cystectomy, there was a slightly lower rate of complications and hospital readmissions compared with their male counterparts, although this finding was not statistically significant.

Next, Dr Psutka discussed the process for creating a diverse and equitable community in urologic oncology. She began by citing data demonstrating that, although more than 50% of current medical students are women, fewer than 10% of female urology residents ultimately apply for fellowship training. She noted that fewer than 3% of female urologists hold full professorships in urology compared with 12% of their male counterparts. Then she began to speak briefly about the history of the WUO, which went from informal meetings of the female urologic oncologists in 2015 to formal application for recognition in 2019. According to Dr Psutka, the process of forming such affinity groups results in networking opportunities for professionals from underrepresented populations and ultimately leads to the equity that creates value. She reviewed the goals of the WUO, including providing representation to female members through mentorship and advocacy, and promoting recruitment and retention of its members. To highlight her point, she presented data showing that since the creation of the WUO, SUO membership has risen steadily from 78 members in 2021 to 91 members in 2022. Furthermore, more female physicians are attending the SUO annual meeting and have joined in leadership positions at the SUO.

Dr Porten advised all individuals to recognize and unlearn prior biases and to advocate for their peers. She also noted the critical role of sponsorship.

Succeeding Dr Psutka, Dr Scarpato talked about addressing the training pipeline for women in urologic oncology. Citing a study by Netter et al,³ Dr Scarpato explained that, compared with their male counterparts, very small numbers of women enter the urologic oncology subspecialty; however she noted that the high numbers of women who choose to specialize in female pelvic reconstruction and pediatric urology suggest more work could be done to encourage interest. She cited additional statistics, such as that while roughly 11% of practicing urologists are female, only 4% of them focus on oncology. In regard to those in training, Dr Scarpato explained that between 2011 and 2017, the number of women applying to SUO-accredited oncology fellowships was in the single digits, although it has slowly started to rise, with 17 applicants in 2021. To underscore her point,

she cited data obtained from the AUA 2020 urology match survey showing that female and underrepresented minority (URM) applicants were more likely to rank a program highly if female or URM faculty were present in the leadership. Dr Scarpato gave the audience tips for promoting female and URM involvement in urology, including encouraging awareness of the issue through discussion, offering mentorship, diversifying the workforce, and promoting a supportive work environment by offering policies such as parental leave and pay equality.

At the end of the plenary session, Dr Porten discussed the future of women and URMs in urologic oncology. She spoke first about finding success, distilling the process down to several key steps, including finding a passion within urologic oncology and then building a network of mentors to help guide the candidate through their career. She emphasized the importance of meeting new colleagues and taking risks throughout one's career.

How can one support their female or URM colleagues? She advised all individuals to recognize and unlearn prior biases and to advocate for their peers. She also noted the critical role of sponsorship. Distinct from mentors, sponsors are individuals who have only intermittent transactional relationships with a candidate but can significantly promote their career advancement. She commented that mentors can also serve as sponsors if they have access to resources the candidate would require for career advancement.

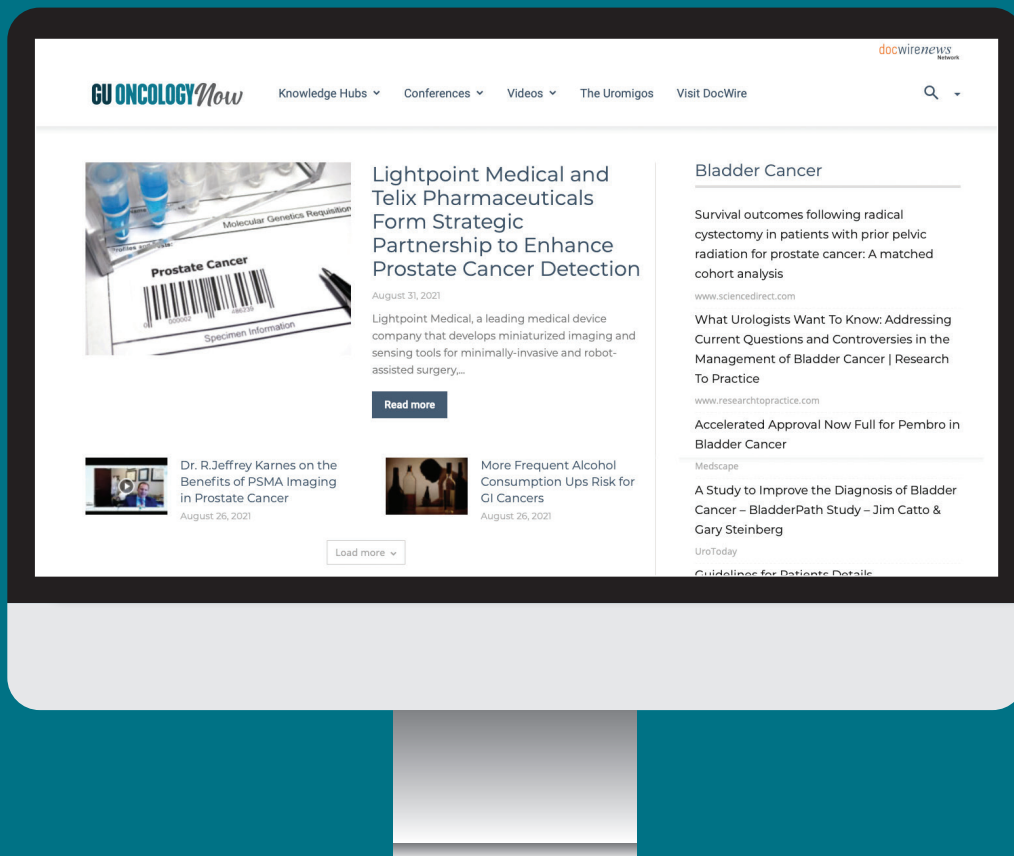
She emphasized that mentorship is itself a critical component of the career advancement process. Specifically, a good mentor will share his or her own career trajectory, and provide the candidate with guidance, motivation, and emotional support. Specific examples of mentor functions include reviewing grants, reviewing papers, and providing feedback. She emphasized that a good mentor-mentee relationship is reciprocal, and that most good relationships will be ones where the pair share mutual goals and needs. Together, the strategies shared by the panelists to help promote greater diversity in the urologic oncology workforce were well-received by a wide audience of AUA attendees.

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