Prostate Cancer Highlights at ASCO 2022 p.26

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ASCO ANNUAL MEETING COVERAGE



Profiles in GU Oncology

Michael J. Morris, MD

Michael J. Morris, MD, Section Head, Prostate Cancer at Memorial Sloan Kettering Cancer Center (MSKCC), describes how his early work experiences informed his decision to pursue clinical research in the diagnosis and treatment of prostate cancer. *p.16*

ALSO...

Editor's Talk:
Dr. Cathy Marshall on Highlights of ASCO 2022 *p.22*

Role of 3D Modeling in Treatment of Renal Tumors *p.28*

REDUCING OPIATE USE IN UROLOGIC SURGERY

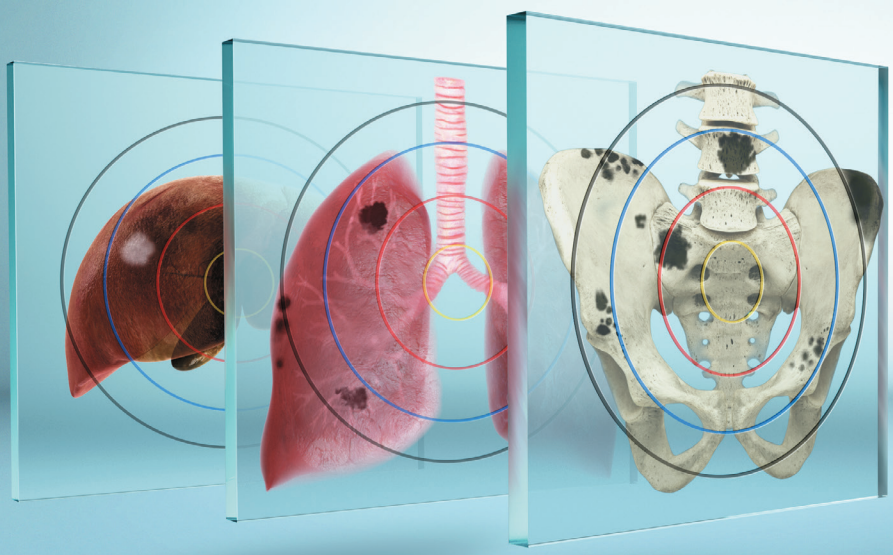
An Interview with Benjamin Davies, MD, Professor at University of Pittsburgh School of Medicine, Chief of Urology at UPMC Shadyside *p.11*



NOW APPROVED

PLUVICTO™
lutetium Lu 177 vipivotide tetraxetan
INJECTION FOR INTRAVENOUS USE

Target PSMA+ mCRPC wherever it goes—bone, nodal, or visceral metastases[1]





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 alone[1-4]:

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 rPFS[3]

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

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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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 CLcr, 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 ≥ 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 (≥ 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 (≥ 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 (≥ 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 ≥ 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 (≥ 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.
[a]Peripheral edema includes peripheral edema, fluid retention, and fluid overload.
[b]Dry mouth includes dry mouth, aptyalism, and dry throat.
[c]Vomiting includes vomiting and retching.
[d]Abdominal pain includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, abdominal tenderness, and gastrointestinal pain.
[e]Urinary tract infection includes urinary tract infection, cystitis, and cystitis bacterial.
[f]Acute kidney injury includes blood creatinine increased, acute kidney injury, renal failure, and blood urea increased.
[g]Dysgeusia 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.
[a]The 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.
[b]The 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.
[c]No 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.

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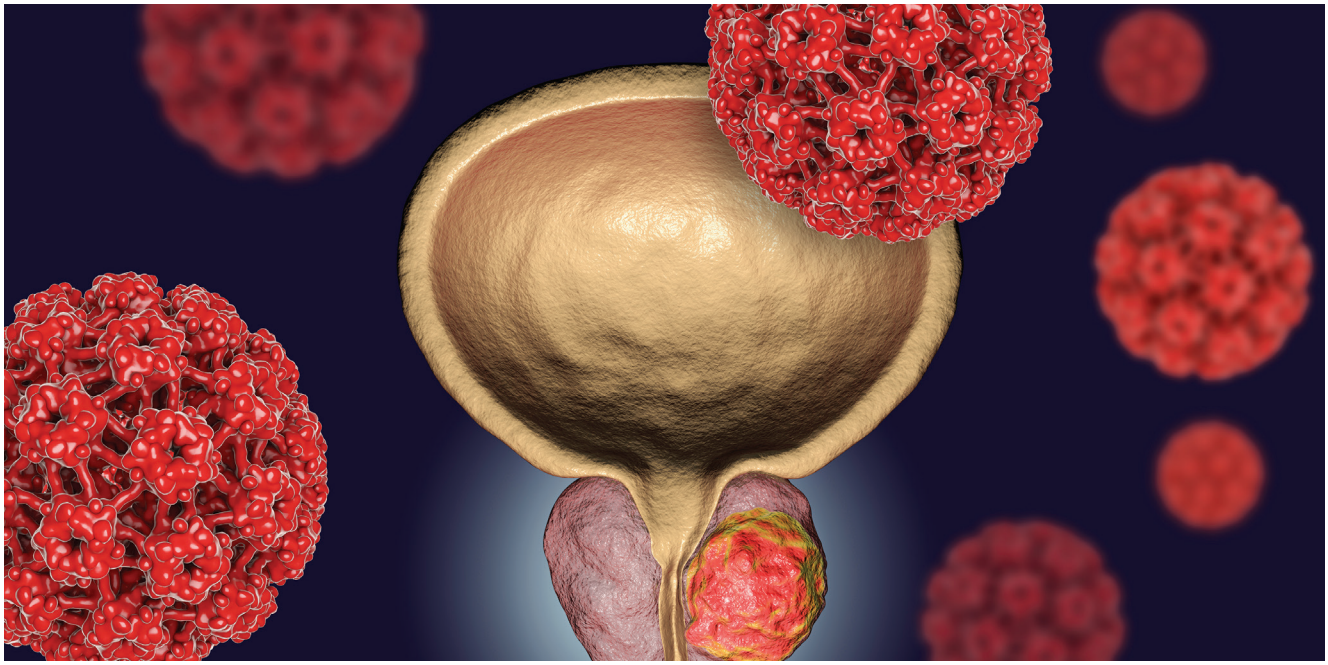
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Review: En Bloc Versus Conventional Transurethral Resection of Bladder Tumors

Daniel Tennenbaum, MD



Daniel Tennenbaum, MD

TRANSURETHRAL RESECTION of bladder tumor (TURBT) remains the standard of care for diagnosis and staging of bladder cancers. Although the surgery is often considered a basic urologic procedure, there often are drastic differences in quality of resection and staging.[1,2] This discordance speaks to the significant technical demands of performing the procedure properly and adequately: without obtaining muscularis propria (MP) in the specimen, one cannot ensure adequate depth of resection. This critical depth of resection is paramount to proper clinical staging, as it is part of what classifies a patient's risk stratification and subsequent treatment options and needs. Absence of MP from TURBT specimens has been reported in up to 35% of cases.[3]

Classically, TURBT is performed by resecting the tumor piece by piece, eventually resecting the tumor at its base, where there may be muscle invasion. However, there are theoretical concerns with this technique, namely the loss of tumor integrity and concern for possible tumor seeding within the bladder. Because of this, there has been a recent push toward "en bloc resection" TURBT, wherein the bladder tumor is resected away from the bladder wall in its entirety. This type of resection aims to obtain tissue comprising both its exophytic and endophytic parts, which reduces tumor cell dispersion, allows precise resection, facilitates detrusor muscle (DM) sampling in proximity to the tumor base, and yields a more informative pathological specimen. Several retrospective studies have suggested there is benefit to en bloc resection, although there has not yet been a prospective study. A recent report by Gallioli et al, published in *European Urology Oncology* sought to provide the highest level of evidence to date,

comparing en bloc TURBT to conventional TURBT, via a prospective randomized control trial.[4]

Investigators consisted of 7 senior urologic oncologists and 4 junior urologic oncologists (<5 years' experience) at a single center who prospectively randomized 300 patients with bladder tumors <3 cm, with R3 tumors, without evidence of ureteral disease, and no evidence of muscle-invasive bladder cancer (MIBC). The study was designed as a noninferiority study, to evaluate a multitude of perioperative and clinical outcomes. The procedure was performed with monopolar or bipolar energy for both classic or en bloc TURBT, or in the case of en bloc resection, a thulium laser was also used for resection in some cases.

In what is thought to be the first prospective randomized control trial comparing classic TURBT to en bloc TURBT, Gallioli et al did not find many differences between the 2 study groups.

The only significant finding from the analysis was the ability to pathologically substage pT1 tumors, with all en bloc resections able to be substaged, whereas only 80% of classic TURBTs were able to be substaged. T1 substaging is defined as T1a (tumor invasion into the lamina propria without infiltration into the muscularis mucosa) and T1b (tumor invasion into the lamina propria, with infiltration of the muscularis mucosa).5 That is, the ability to differentiate a tumor's invasion into the muscularis mucosa (as opposed to pT2 invasion into the MP) was found to be significantly improved with en bloc resection. There was no difference between the classic approach compared with en bloc resection in terms of the length of catheterization or irrigation time, median length of hospitalization, planned adjuvant treatment, experiencing obturator reflex during resection, or complication rate. Notably, 5 of the 6 patients randomized to en bloc resection who ultimately underwent classic resection had anterior tumors that were not amenable to en bloc resection. With a median follow-up of 15 months, there was no survival difference between either group.

In what is thought to be the first prospective randomized control trial comparing classic TURBT to en bloc TURBT, Gallioli et al did not find many differences between the 2 study groups, demonstrating noninferiority of en bloc TURBT compared to classic TURBT. However, the one difference between the groups found to be statistically significant was the ability to better substage T1 disease via en bloc resection than by classic resection. While only a single significant data point, it is of crucial importance, as numerous studies have demonstrated meaningful differences in survival prognostics based on T1 substaging.[6,7] Although the data did not show a survival advantage, it should be noted that the follow-up was relatively small in the setting of smaller, mostly low-risk bladder tumors. Otherwise, the benefit of one approach compared with the other remains controversial.

There are reports within the literature demonstrating conflicting perioperative advantages with either approach. The data from these retrospective studies, when combined with the outcomes from what is thought to be the first prospective study evaluating the difference between these 2 approaches, help to further solidify that outside of the ability to substage T1 disease, there is little difference between classic and en bloc TURBT. Thus, with either approach, it is important to stress the importance of the fundamental principles of bladder tumor resection: one must clear all visible disease, resect to the level of the MP, and avoid perforation. When the operative surgeon adheres to these foundational principles, the choice of one approach over the other is likely to be of little consequence.

Daniel Tennenbaum, MD is a urology resident at Maimonides Medical Center in Brooklyn, NY. His interests include surgical education and GU oncology with a focus on pediatric malignancies.

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Review of Article:

Active Surveillance Plus Enzalutamide Monotherapy Vs. Active Surveillance Alone in Patients with Low-risk or Intermediate-risk Localized Prostate Cancer

David Ambinder, MD

IN A RECENTLY PUBLISHED REPORT in *JAMA Oncology,* Shore et al evaluated the addition of enzalutamide to the current standard of care for patients with low- or intermediate-risk prostate cancer.[1] According to the current National Comprehensive Cancer Network® (NCCN) guidelines, active surveillance (AS) is the current preferred recommendation for patients with very-low-risk and low-risk prostate cancer. For patients with intermediate-risk disease, AS is recommended, but not necessarily preferred over definitive therapy such as surgery or radiation.[2] AS has gained significant traction, due to both good long-term oncologic outcomes and, in part, as a strategy to reduce the adverse effects of definitive therapies. The REDEEM trial found that dutasteride, a 5-α-reductase inhibitor, significantly reduced the risk of progression by 38%.[3] Shore et al commented that prior to this study, "there are few publications prospectively assessing pharmacological interventions to delay prostate cancer progression in the AS population."[1]

Enzalutamide is a potent oral androgen receptor inhibitor that has been shown in numerous studies to be effective in patients with localized[4] and advanced prostate cancer.[5] This in part inspired the current study. "The ENACT randomized clinical trial compared the efficacy and safety of treatment with enzalutamide monotherapy versus AS alone in patients with clinically localized low-risk or intermediate-risk prostate cancer."

ENACT was a multicenter, randomized, open label, phase 2 trial that enrolled patients from June 2016 to August 2020 and included patients with low- or intermediate-risk prostate cancer diagnosed on biopsy within 6 months of screening and who were undergoing AS with an expected life expectancy of r5 years. In addition, patients needed to not have received prior local or systemic therapy for prostate cancer, oral glucocorticoids within 1 month of screening, or a 5-α-reductase inhibitor within 1 month of screening, or for >3 months within the 2 years before screening. The trial also ensured that patients with very-low-risk prostate cancer were excluded from the study.

Patients were randomized to either receive 1 year of treatment with enzalutamide 160 mg daily or AS alone, stratified by low or intermediate risk, and whether or not biopsy included targeted multiparametric magnetic resonance imaging (mpMRI). Patients were monitored for 24 months. Patients who experienced a grade r3 adverse event (AE) were paused from treatment for 1 week or until the AE improved to grade R2. At that point, treatment either continued at the regular dose or a reduced dose of 80 to 120 mg daily. Doses were also reduced to manage gynecomastia or breast complications. Transrectal ultrasound–guided prostate biopsies (with or without mpMRI targeted biopsies) were performed at the 12- and 24-month time points.

Enzalutamide is a potent oral androgen receptor inhibitor that has been shown in numerous studies to be effective in patients with localized and advanced prostate cancer.

The primary endpoints were time to pathological (increase in primary or secondary Gleason pattern by r1 or more or a higher proportion of cancer-positive cores with 15% increase) or therapeutic (earliest occurrence of surgery, radiation, focal or systemic therapy) progression. Secondary endpoints included negative biopsies at 12 and 24 months, percentage of cancer-positive cores at 1 and 2 years, time to prostate-specific antigen (PSA) progression, and incidence of a rise in PSA levels at 1 and 2 years. PSA progression was defined as an increase in PSA of r25% above the nadir or an

absolute increase of r2 ng/mL. Patient-reported outcomes were assessed via questionnaires, and AEs were monitored throughout the study.

The study included 227 patients, of whom 53% had low-risk prostate cancer and 47% had intermediate-risk disease. Most patients (76%) underwent mpMRI targeted follow-up biopsies. A total of 114 patients underwent treatment with enzalutamide; 75% completed 1 year of AS, 61% completed 1 year of follow-up, and 51% had 1 year of continued follow-up. The full trial was completed by 47% of patients in the enzalutamide arm and 35% in the AS arm. Disease progression and patient withdrawal from the study were the most commonly cited reasons for patient discontinuation in both arms. Median follow-up time for patients on enzalutamide was ~500 days, compared with 270 days in the AS arm. The median duration of actively taking enzalutamide was 352 days. Treatment was disrupted in 13% and reduced in 12% of patients, typically owing to AEs.

Disease progression was seen in 28% of patients in the enzalutamide arm versus 37.2% in the AS arm. Although the time to pathological or therapeutic progression was not reached, there was a significant 46% reduced risk of progression in the enzalutamide arm compared with the AS arm. At 1 year, the incidence of pathological or therapeutic progression was 8% with enzalutamide arm versus 23% with AS; however, at 2 years, this difference was not seen (16% vs 16.4%). Odds of a negative biopsy were significantly increased with enzalutamide compared with AS at one year (OR, 3.5; 95% CI, 1.76-6.92; $P< .001$), but this difference was not appreciated at 2 years. The trend was similar for the percentage of positive cores on biopsy and the secondary rise in serum PSA levels. There was clinically significant sexual and physical function reported in patients taking enzalutamide, but this resolved at 2 years, after ending treatment.

In the enzalutamide arm 92% of patients experienced an AE, compared with 55% of patients in the AS arm. Both arms had decreased numbers of AEs in the second year of the trial compared to the first. Serious AEs were low in both treatment arms. Commonly reported AEs with enzalutamide included fatigue (55%), gynecomastia (37%), nipple pain (30%) or breast tenderness (26%), and erectile dysfunction (18%). Only hypertension was noted to occur in r5% of patients in the AS arm. Enzalutamide-associated AEs were seen in 88% of patients, but only 2.7% were considered serious and 7.1% led to patients discontinuing enzalutamide. A total of 9.8% of enzalutamide-related AEs were grade r3, and the authors note that only fatigue was reported by multiple patients. Other grade 3 enzalutamide-attributed AEs were gait disturbance, gynecomastia, myocardial infarction, and syncope. No deaths were considered to be related to treatment or disease progression.

Shore et al began the discussion of their investigation by emphasizing that, "in the phase 2 ENACT randomized clinical trial, treatment with enzalutamide monotherapy significantly reduced the risk of prostate cancer and PSA progression compared to AS in patients with low-risk or intermediate-risk prostate cancer."[1] In addition, there were several secondary endpoints, including odds of a negative biopsy, reduction in percentage of positive cores, and odds of a secondary rise in PSA at 1 year that also improved with enzalutamide. The drug was well tolerated and consistent with other trials investigating enzalutamide. The observed 46% risk reduction seen in this study was similar to the 38% reduced risk seen with dutasteride in the REDEEM trial. Limitations of the study included generalizability regarding race (90% of patients identified as white) and the results of the additional analyses (not discussed in this review), which should be interpreted with caution, given that the study was not designed or powered for those analyses.

The authors concluded that the ENACT trial is the first of its kind to evaluate a novel androgen receptor antagonist as monotherapy, compared with AS in patients with low- or intermediate-risk prostate cancer. In this study, enzalutamide showed a significant response, was well tolerated, and the "results suggest that enzalutamide may offer an alternative short-term treatment option for this patient population, potentially reducing the need for more aggressive treatment approaches."[1]

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David Ambinder, MD is a urology resident at New York Medical College / Westchester Medical Center. His interests include surgical education, GU oncology and advancements in technology in urology. A significant portion of his research has been focused on litigation in urology.

AUA 2022:
Late-Breaking Plenary Highlights

Akhil A. Saji, MD

AT THE AMERICAN UROLOGICAL ASSOCIATION (AUA) 2022 meeting in New Orleans, the Friday plenary session highlighted 3 key late-breaking abstracts that warrant awareness by all practicing clinicians treating patients with urologic malignancy.

The first abstract, entitled "IL-15RαFc superagonist N-803 with BCG in BCG unresponsive non-muscle invasive bladder cancer (nMIBC) CIS and papillary cohorts,"[1] was presented by Karim Chamie, MD, associate professor of urology at UCLA. Dr Chamie explained that the current standard of care for high-risk patients with nMIBC is bacillus Calmette-Guérin (BCG), due to its ability to induce trained immunity of T cells and natural killer (NK) cells. Anktiva (N-803 compound; ImmunityBio) is a superagonist complex[2] composed of an interleulin-15 (IL-15)-like peptide and a fusion protein, allowing for stimulation of activation of T cells and NK cells. Dr Chamie explained that the concept explored in the QUILT 3032 trial was to identify if addition of N-803 to BCG in patients with BCG-unresponsive disease would result in improved results.

The trial enrolled patients with histologically confirmed disease recurrence after BCG therapy and stratified patients into carcinoma in situ (CIS) and papillary cohorts. According to Dr Chamie, BCG-unresponsive disease was defined as persistent or recurrent CIS with or without Ta/T1 disease within 12 months of BCG therapy. The patients enrolled in the trial received BCG 50 mg plus N-803 compound intravesically instilled weekly for 6 weeks. The investigators sought to identify several parameters, including safety of the compound as well as a primary endpoint of complete response (CR) and secondary endpoints of duration of complete response, time to cystectomy, and cystectomy avoidance. Dr Chamie explained that the mean age of all patients was approximately 72 years of age, with the majority (>70%) of patients being male and with good performance status. In reviewing the safety outcomes, Dr Chamie explained that overall, N-803 was very well tolerated, with only 1% of the patient population experiencing treatment-related adverse events (AEs). The majority of AEs were low-grade issues such as dysuria, and no patients were found to have elevated systemic IL-15 levels, noted Dr Chamie.

The clinical results of the trial were promising. For cohort A (patients with CIS), Dr Chamie explained that 71% of patients experienced a CR, with a median CR duration of 24.1 months. Furthermore, patients who experienced therapeutic response had a lower cystectomy rate than those who did not (7% vs 15%). Most patients experienced progression-free survival (PFS) of 91% at 24 months. Even more impressively, Dr Chamie presented a forest plot demonstrating that the improvement in response was sustained throughout all subgroup analyses (ie, age, race, gender). For cohort B (patients with papillary recurrence), Dr Chamie explained that investigators focused on disease-free survival (DFS) because these patients mostly had transurethral resections for definitive therapy. A median DFS was 23.6 months, with a DFS rate of 57% at 12 months and 48% at 24 months. Most patients (73 of 77) were spared radical cystectomy. Dr Chamie concluded by reiterating that the outcomes of this trial were favorable, with 100% and 98% rates overall survival at 2 years for both the CIS and papillary cohorts, respectively.

The second abstract highlighted was "Impact of ^{18}F-rhPSMA-7.[3] PET on upstaging of patients with prostate cancer recurrence: results from the prospective, phase 3 multicenter SPOTLIGHT study,"3 which was presented by Mark Fleming, MD, of Virginia Oncology Associates.

Dr Fleming began by explaining the molecular advantages of ^{18}F-rhPSMA-7.3, a fluorine-18 (^{18}F)-based high-affinity prostate-specific membrane antigen (PSMA)-targeted PET pharmaceutical. He specifically cited 2 features: low bladder activity and improved spatial resolution of positron emission tomography (PET) images compared with gallium-68 (^{68}Ga) PSMA scans.[4] Dr Fleming also cited production advantages of ^{18}F as well as the ability to produce it in larger quantities, with a longer half-life for clinical use than its comparators. Additionally,

he remarked that the compound also can be bound to α- or ß-emitted radiopharmaceuticals for theranostics therapy.

The SPOTLIGHT study (NCT04186845)[5] sought to investigate the utility of ^{18}F-rhPSMA-7.3 diagnostic scans in patients who had received prior localized therapy for prostate cancer (ie, prostatectomy or radiation) and subsequently experienced rising PSA levels that were considered suspicious for biochemical recurrence (BCR). All patients enrolled in the study had negative results on conventional imaging. Dr Fleming explained that the scans were obtained approximately 50 to 70 minutes after injection of the radiotracer, and all images were evaluated by 3 radiologists. The findings on diagnostic PET scan were confirmed by biopsy or by confirmation on conventional imaging modalities such as computed tomography (CT) or magnetic resonance imaging (MRI). The investigators sought to identify patients with true- positive disease recurrence that led to upstaging in patients who had negative baseline findings on conventional imaging.

In reviewing the results, Dr Fleming explained that ultimately, 389 patients underwent ^{18}F-rhPSMA-7.3 PET/CT imaging. The mean age of the population was 68.4 years, and the median BCR suspicion PSA was 1.27. The majority of the cohort comprised patients with Gleason grade group 3 disease. Of these patients, 366 had enough data for the exploratory analysis, with Dr Fleming reporting a corrected detection rate of 57% for patients receiving this scan. A total of 68% of the patients in the analysis had negative baseline conventional imaging results before therapy. Subsequent imaging with ^{18}F-rhPSMA-7.3 PET/CT at the time of concern for BCR resulted in a corrected detection rate ranging from 45% to 47%, suggesting that despite negative conventional imaging, these patients were upstaged to locally advanced or metastatic disease based on the findings of the PET/CT scan. The results of the exploratory analysis were substratified by anatomic region by Dr Fleming. In the prostate bed, detection rates were markedly higher for those patients who had undergone radiotherapy (39%-41%) compared with prostatectomy (3.5%-8%); however, this difference was diminished in the pelvic lymph node region (18%-21% vs 6.5%) and extrapelvic regions (21%-26% vs 20%-30%).

In concluding remarks, Dr Fleming summarized that the rhPSMA scan often detected upstaging of prostate cancer stage, especially after negative findings on conventional imaging. This effect was markedly notable in patients who had undergone radiotherapy compared with prostatectomy. According to Dr Fleming, before therapy for BCR, the utility of the ^{18}F-rhPSMA-7.3 scan may allow clinicians to localize areas of disease and help guide treatment decisions.

The third abstract highlighted was "Efficacy and safety of a novel gene therapy (URO-902; pVAX/hSlo) in female patients with overactive bladder and urge urinary incontinence: results from a phase 2a trial"[6] presented by Kenneth M. Peters, MD, of Oakland University William Beaumont School of Medicine.

Dr Peters briefly explained the mechanism of URO-902, a novel gene therapy that, when injected into the detrusor muscle, is posed to reduce bladder hypercontractility by increasing potassium channel expression. The results of an interim analysis of an ongoing multicenter randomized controlled trial evaluating the efficacy of URO-902 were reviewed. Dr Peters explained that the trial sought to enroll women patients between 40 and 79 years of age with overactive bladder (OAB) and urge urinary incontinence (UUI) refractory to oral medications. Patients enrolled in this trial were randomized to URO-902 instillation of 24 mg or 48 mg, or placebo.

The mean age of patients enrolled was 64.7 years. Most patients had >3 urge urinary incontinence episodes per day and had received prior onabotulinum toxin injection. Although not final, the exploratory analysis of this trial demonstrated several promising markers for URO-902 as a treatment option for patients with OAB and UUI. Dr Peters remarked that patients receiving treatment with URO-902, regardless of dose, had a statistically significant decrease in OAB-q symptom bother score. The safety profile of the URO-902 therapy was also very favorable, with no patients experiencing AEs leading to discontinuation. Although this was a preliminary exploratory analysis of this medication, the early results of this trial demonstrate that URO-902 may be an emerging effective therapy for patients with refractory OAB.

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Reducing Opiate Use in Urologic Surgery



An Interview with Benjamin Davies, MD

by David Ambinder, MD

MANAGEMENT OF PAIN is a central concern of physicians and their patients preparing to undergo conventional or minimally invasive procedures. This interview with **Benjamin Davies, MD** in the field of urologic surgery explores how surgeons may be proactive in addressing their challenges and responsibilities for helping to mitigate the current opioid addiction crisis and looks toward a future where opiate-free robotic surgery may become the standard of care. Dr Davies is a professor at University of Pittsburgh School of Medicine, chief of urology at UPMC Shadyside, and program director of the Urologic Oncology Fellowship at UPMC. He has published extensively on several aspects of urology.

Continued on next page

David Ambinder, MD: You have published significantly on several topics, including covering opiate trends and opiate-reduction strategies in urologic surgery. Can you tell us some of the motivations that compelled you to pursue research in this arena?

Benjamin Davies, MD: There were many contributing factors. I always tell the story that, when I was in medical school, my best friend died as a result of a drug overdose. I later found out that he was initially introduced to, and became dependent on, opioids after a back injury. I didn't know at the time that he had any substance abuse disorder.



Benjamin Davies, MD

When I became an attending physician, I already had a research interest in health services. I then read some works by Chad Brummett, who is a professor of anesthesiology and pain specialist at the University of Michigan. He wrote a great article in 2017, published in the *Journal of the American Medical Association*, on persistent opioid use after surgical procedures. It was then that I became really jazzed about the topic.

I noticed that after robotic surgery, patients were going home with significant doses of oxycodone, and I questioned this practice, asking if it was necessary for 4 tiny incisions. I also practice in a region that has one of the highest overdose rates in the country, where patients frequently share terrible stories about their loved ones dying because of an overdose. All these factors came together to inspire me to research and help change practice patterns.

Can you briefly review some of the major concepts surrounding the harmful effects of opioid use and how surgery contributes to its impact?

The first concept to understand is diversion. Drugs that you give your patients may well have no effect, and they may not directly cause an opiate use disorder. We take for granted that patients will throw away the medication they don't use, but in fact many patients don't discard their opiates. Many people who develop substance abuse disorders first obtain the drugs from family members and loved ones. An example of diversion is when a physician gives a pain medication to a patient, and the patient doesn't take it, but it's taken by another person living in their home. This could be a child, parent, sibling, housekeeper—anyone with access to the pills. This should be at the forefront of our minds, because that is how substance abuse disorders start in more than 80% of cases. As a surgeon, this is important to know, because you want to avoid giving your patients any more opiates than they need.

The second concept is that persistent opioid use can begin with even a very small prescription of painkillers. Approximately 1% to 1.5% of patients who are drug naive when they receive a prescription of opiates for 7 days or more will have persistent opioid use 1 year out. So, to summarize, concerns about diversion and persistence are reasons we should be very careful about the drugs we prescribe to our patients.

What role can surgeons play in reducing opiate use?

The role is simply to help reduce it, and there have been inroads made. Several studies in the past few years have indicated that surgeons have radically decreased the amount of pain medications administered to patients. Moreover, there have been many state-led initiatives. In Pennsylvania, for example, you cannot prescribe more than a set amount of medication to patients undergoing specific surgeries without requesting approval. However, if you dig deep using large insurance-based databases, use of opiates by urologists is still higher than it ought to be. So, we can't just rest on our laurels and say, "the AUA put out a position paper, we are good now." Penetration [of ideas] in medicine is very challenging. We must keep hammering the message home, and eventually we'll get somewhere.

As early as 2019, you began discussing the idea of opiate-free robotic surgery. It was an even more novel concept then than it is now. What is the typical pain regimen you currently prescribe for patients receiving robotic surgery?

That's simple and straightforward. Preoperatively, patients receive a paravertebral block, gabapentin, and intravenous (IV) anesthesia. Postoperatively, lidocaine is administered around just the incisions, which may be overkill because they have a block anyway, and patients are given 1 full dose of IV ketorolac (Toradol®) as they are waking up. Acetaminophen (preferably administered IV, if possible) and ketorolac are given for the first 6 hours. Oral ibuprofen and acetaminophen are then given after the first IV doses. Of course, if patients continue to experience pain, IV morphine can be dosed in small quantities, if necessary. Most patients are accepting of the typical regimen if it is explained to them beforehand. It is important to counsel patients before surgery and discuss expectations, including what to expect in terms of pain and pain control.

If patients have a history of chronic pain issues, we usually consult chronic pain specialists and consider stronger opiates, if necessary. However, this is rare. It's important to mention that if patients are taking opiates chronically, we continue their current pain regimen. We're not here to change their pain regimen.

How would you respond to physicians who are uncomfortable prescribing ketorolac in the immediate postoperative period?
I have reviewed the urology data ad nauseam, and I have yet to see any convincing evidence that it's going to harm the patient. For the most part, in patients with normal kidney function undergoing a robotic prostatectomy, a full dose of ketorolac is fine. I have never had a patient experience a bleeding problem.

What do you think are some barriers to surgeons implementing opiate-reducing strategies in practice?
There are several significant barriers to change. Of course, there is always physician education, but I think we do a good enough job with new trainees in terms of creating awareness. I think many surgeons become comfortable with the approaches they have used for many years. This contributes to inertia. They may think they have been giving great care for many years, and that it has worked, so deviating away from their standard approach would result in worse quality of care. This means there may be little incentive to make a change. I think continuing discussion and implementing practice-changing policies may help many physicians revise their approaches for the better.

What would you most like to see altered in the next 10 years in terms of how we think about postoperative pain management?
I believe that changes may be industry driven. Pain management is a billion-dollar industry. There is a lot of research investigating narcotic antagonists that do not have addictive potential, and therefore cannot be abused. There already are products evolving around this space. I suspect that several of these agents will become available in the next few years.

Are there any publications you would recommend as reading for someone interested in learning more about the topic?
I believe the best article is the American Urological Association position paper on opioids that was released last year, written by a task force led by Dr Jennifer Robles.1 It has everything in it. It goes through all the data and really looks at specific details that are important to review, including several aspects we have discussed, such as optimal pain management strategies and questions about ketorolac and bleeding risk. For anyone who is interested, it's an excellent readily available resource to explore.

There is a lot of research investigating narcotic antagonists that do not have addictive potential, and therefore cannot be abused. There already are products evolving around this space.

–Benjamin Davies, MD



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Long-Term Data from ENZAMET Reconfirm Survival Benefit With Enzalutamide in mHSPC But Role of Docetaxel Remains Uncertain

Linda Brookes, MSc

DURING THE 2022 Annual Meeting of the American Society of Clinical Oncology (ASCO), 3-year follow-up data were presented from the ENZAMET (Enzalutamide in First Line Androgen Deprivation Therapy for Metastatic Prostate Cancer) trial by **Ian Davis, MB BS, PhD,** medical oncologist and Professor of Medicine and Head of Eastern Health Clinical School, Monash University and Eastern Health, Melbourne, Australia.[1] The new data reconfirmed findings of overall survival (OS) benefit with enzalutamide added to testosterone suppression in metastatic hormone-sensitive prostate cancer (mHSPC) from an interim analysis reported in 2019.[2]

Thomas Powles, MBBS, MD, (Barts Cancer Centre, London, UK) and **Brian Rini, MD** (Vanderbilt University, Nashville, TN) invited Dr Davis to review the ENZAMET trial and discuss the implications of the latest analysis. Dr Davis is co-chair of ENZAMET, along with Christopher Sweeney, MBBS (Dana-Farber Cancer Institute, Boston), and chair of the Australian and New Zealand Urogenital and Prostate Cancer Trials Group Ltd (ANZUP), the primary sponsor of ENZAMET.

ENZAMET is an ongoing phase 3, randomized, open-label study in patients with mHSPC who were first treated with testosterone suppression. "It was a very simple question when the study began," Dr Davis explained, "Could we improve outcomes, particularly overall survival by adding enzalutamide 160 mg/day upfront compared to a standard nonsteroidal antiandrogen drug such as bicalutamide, nilutamide, or flutamide?" A total of 1125 men were entered into the trial at 83 sites in Australia, New Zealand, Canada, UK, and Ireland between March 2014 and March 2017.

At the first interim analysis in February 2019, after 235 deaths and a median follow-up of 34 months, enzalutamide was shown to significantly improve OS. "At that time, we had a hazard ratio for death of 0.67 for patients on the enzalutamide arm, which was very exciting," Dr Davis recalled. This finding aligned with data already reported from the CHAARTED[3] and STAMPEDE[4] trials, for docetaxel, and from the STAMPEDE[5] and LATITUDE[6] trials, for abiraterone, he noted. Improved radiographic progression-free survival (rPFS) was reported with enzalutamide in the ARCHES trial[7] and significantly longer OS and rPFS with apalutamide in the TITAN trial.[8] ENZAMET differed from these two trials, however, in that docetaxel was allowed at investigative discretion. "We opened ENZAMET at the beginning of 2014, just before the CHAARTED data were presented," Dr Davis explained. "Then after the CHAARTED results came out, literally overnight in Australia, people were filling up prescription pads with docetaxel. So our study was dead in the water unless we amended it very rapidly to allow docetaxel." Docetaxel use was not randomized in ENZAMET, but it was stratified. Overall about 45% of patients on the study received concurrent docetaxel.

"There was lot of interest about whether the triplet therapy would be of additional benefit compared with testosterone suppression plus enzalutamide alone," Dr Davis recalled. "We really wanted to answer this question, but that would have made it a much larger study and we didn't have the resources to do that," he admitted. A compromise was reached by allowing docetaxel at investigator discretion and about 45% of patients overall eventually received docetaxel, predominantly those with high-volume disease compared with those with low-volume disease "We believe that this was probably related to clinical factors that led the investigators to conclude this was something that these participants should receive," Dr Davis said. The question of whether patients with low volume disease were less suitable for docetaxel remained controversial.

The updated ENZAMET survival data reconfirmed the earlier findings. After a median of 68 months of follow up, the benefit of enzalutamide persisted, with a hazard ratio for OS of 0.70 (95%CI 0.58 to 0.84), still statistically significant ($P<0.001$). The estimated median survival was 73 months for the control group and not reached for the enzalutamide group, and 5-year survival was 57% and 67%, respectively. The control group "did very well," Dr Davis noted. "It's gratifying that this does represent the best international standard of care for the outcomes of the control group, and even with that, we're still seeing the

benefit of enzalutamide as the alternative," he remarked.

"We are now able to do some exploratory analysis looking at subgroups of prognostic significance," Dr Davis continued. "When we looked at the patients with high or low volume disease and those with synchronous de novo metastatic disease versus those with metachronous or relapsed metastatic disease, a few messages emerged," he said. First, "it is very clear that weak androgen deprivation therapy (testosterone suppression) as active control is not the best approach." They also found that across the board, enzalutamide alone with testosterone suppression, or docetaxel, or in combination of both had similar outcomes. "That leads to the question of whether the docetaxel might be needed, and I think raises the hypothesis that the greatest benefits of triple therapy might be limited to those patients with the poorest prognosis disease, especially those with synchronous and high volume disease," Dr Davis suggested. "So if you've got low volume disease, you probably don't need docetaxel."

Asked by Dr Powles whether ENZAMET has changed thinking, Dr Davis referred to the more recent results of the PEACE-1 and ARASENS trials.[9,10] The ARASENS data strongly suggested that all patients should be getting triple therapy, he comments. "But we have to remember that ARASENS was a different, very high-risk population, with around 86% of patients having synchronous metastases and 65% visceral metastases, and it was considered necessary for them all to get docetaxel. The ENZAMET population contained a mix of prognostic groups and more closely reflected the spectrum of patients that come through our clinic," he pointed out.

"What ENZAMET suggests to us is that we know what not to do, which is testosterone suppression by itself in a patient who's fit to get anything," he asserted. "Metachronous low volume disease is the group that does best and should still have intensification of testosterone suppression but probably does not need to have triple therapy. High volume disease is probably the subset where triple therapy should be considered most seriously."

ENZAMET hasn't answered the clinical question of who needs docetaxel, Dr Rini pointed out "That is still the biggest gap in this area, and as a statistical purist and clinical trialist, I would say that's the study that we need," Dr Davis replied. "On the other hand, ENZAMET now has a median 68 months of follow up and the data are very mature, and there are some very clear messages about how well addition of enzalutamide only is doing compared with the other study groups," he said. "We know that the addition of enzalutamide gives very good results, comparable to those in patients who've received docetaxel or the triplet. If you're going to choose any subgroup to receive triplet therapy, you could probably use these data to justify giving it to those at highest risk," he concluded.

Linda Brookes, MSc is a freelance medical writer/editor based in New York and London.

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Brian Rini, MD

Taking the Road Less Traveled Toward Clinical Research in Prostate Cancer



Michael J. Morris, MD, Section Head, Prostate Cancer and attending physician at Memorial Sloan Kettering Cancer Center (MSKCC), is well known for his work in the development of targeted radioimaging and theranostic agents, including his leading role in the Phase 3 clinical trials, OSPREY and CONDOR.

Linda Brookes, MSc

IN AN INTERVIEW WITH *GU Oncology Now,* Dr Morris described how he followed a less conventional path through the study of medicine and how that and his early work experiences informed his decision to pursue clinical research in the diagnosis and treatment of prostate cancer.

Almost the whole of Dr Morris' personal and professional life has been based in New York City, "a great place to live and practice medicine," he asserts. In a typical week, Dr Morris devotes around 2 days to seeing patients in the clinic and the rest of his week on research, mentoring, and education, taking care of protocol work and administrative responsibilities. "Some of the research is my own work and some of it is making sure that I am facilitating the work of others and advancing the field for the next generation," he explains. He also makes time for the Prostate Cancer Clinical Consortium (PCCTC) and the Alliance for Clinical Trials in Oncology, a National Cancer Institute (NCI)-funded cooperative group, for which he serves, respectively, as medical director and GU Committee Chair. "You work a lot of hours, but they are good hours," he says.

"I was born and bred in New York, and most of my family is still here," Dr Morris explains. Growing up, none of his immediate family were physicians, but they valued scientific and other inquisitiveness, he acknowledges. The only extended time Dr Morris has spent outside New York to date was during his undergraduate years at Harvard and subsequent 3-years' employment in a research laboratory in Boston. Unusually, for a premed student, Dr Morris majored in English and Literature, while spending his summers fulfilling the prerequisites for medical school. He chose this path, he says, because of his broad interests and desire to maintain an intellectual balance. He graduated with a BA in 1987. He explains that the aim of then taking on laboratory work was to get some scientific experience before applying to medical school. "The greatest use of it was convincing me that I really wanted to work with people and that my research interests were clinically oriented," he recalls. "I appreciate the discipline of science, but I gravitated much more toward the human end of it, so I decided that my laboratory would involve actual people, as opposed to bacteria or rodents."

"So, I had a rather serendipitous way of making my way, ultimately, to medical school," he says, "but I think that it gave me more valuable life experience and also an appreciation for the road less traveled and feeling comfortable doing that, and I think that that ultimately translated into how I approached my research." He returned to New York in 1990 to matriculate at Icahn School of Medicine at Mt. Sinai in New York, and he received his MD in 1994.

It was during Dr Morris's residency at New York-Presbyterian Columbia University Irving Medical Center that he became interested in oncology. "What I really enjoyed about oncology was that at that time [the 1990s], cancer was still a great unknown, with few therapies," he recalls. "It seemed like a challenging, wide-open space where discovery was ripe and, as they say, 'in the land of the blind, the one-eyed man is king,' so even incremental changes could be very important in terms of influencing patient lives." He

discovered that he especially enjoyed taking care of patients who face acutely challenging illnesses.

Dr Morris looks back with satisfaction at the "sea change" that has taken place so rapidly in oncology in general over the past several decades. "I wasn't disappointed by my choice," he says. "I caught the field right at the time when biologic understanding was picking up and so it was a very opportune time to join the world of oncologic study. The science, of course, translated into drug development shortly afterwards."

He attributes stimulation of his interest in prostate cancer in large part to the mentorship of Howard I. Scher, MD, during his fellowship at MSKCC. Dr Scher is currently Head of the Biomarker Development Program and Chair in Urologic Oncology at MSKCC and Professor of Medicine at Weill Medical College. "He captured my imagination about prostate cancer because he had a long-term view of where the disease was going and what needed to be done to develop new drugs to treat the disease, not just the biology and not just the drugs that matched that biology, but the entire framework of how to do trials in prostate cancer," he recalls. "He also found a unique niche for me, introducing me to the concept of bridging medical oncology and nuclear medicine." Dr Morris' mentor in nuclear medicine was Stephen M. Larson, MD, whom Dr Morris refers to as "one of the greats of nuclear medicine." Dr Larson is currently Hedvig Hricak Chair in Radiology and Lab Head of the Molecular Pharmacology Program at MSKCC.

Dr Morris is very appreciative of the opportunities that MSKCC has afforded him professionally. "One of the great things about MSKCC is that it tends to support unusual careers," he asserts. "There is so much expertise and mentorship there that you can usually find the people that you need to support you within that really fertile environment."

So he was able to study the development of drugs and imaging biomarkers from a nuclear medicine/radiology perspective, but within the field of medical oncology. "It's been a very long road," he admits," but in the course of it, we've done so much to advance the field, not only in therapeutics, but on the imaging side as well, with new imaging modalities and also very importantly, standardizing how to image prostate cancer patients for clinical trials so that drugs can be developed that much more quickly and efficiently."

There is a lot of cross-fertilization between projects, he notes. He cites as an example how, during the development of androgen-receptor targeted therapies, they used a novel form of PET/CT scanning that they had also been working on with fluoro dihydrotestosterone (F18 [18F]-FDHT)), "a type of radioactive testosterone," as part of dose-finding clinical trials of drugs like enzalutamide and apalutamide.

Development of novel imaging methods and treatments requires a team effort by medical oncologists, nuclear medicine doctors, radiologists, and laboratory chemists, Dr Morris stresses. "I can't overemphasize enough the collaborative and multidisciplinary nature of the work." he says. "It's the communications and problem-solving from different aspects and different disciplines and different knowledge bases that make every day interesting."
The development of theranostics has been a global collaboration, especially among centers like MSKCC in the US and other countries. "There's a huge amount of global enthusiasm in which MSKCC shares, especially for a new therapy for a disease that afflicts men in all corners of the world," Dr Morris acknowledges.

He is unstinting in his praise of MSKCC as "one of the best cancer centers in the world, and I say that having worked at a number of different hospitals and seen how they care for patients and what their level of dedication is," he declares. "MSKCC takes really, really good care of cancer patients from top to bottom, whether that's at the administrative, nursing, maintenance, or technical level. Patient care is at the top of everybody's agenda," he asserts. He adds, "Our institutional mission is to develop new drugs, so when patients seek us out, it is not just because we provide excellent care, but because we specifically focus on offering the next generation of drugs that will be at the center of care tomorrow."

Dr Morris has no hesitation in recommending clinical research in oncology to medical graduates considering a career in the field, "It's a great career because you get to see patients not only for who they are and the problems that you need to solve for them, but also for the new ways that you are thinking about for treating the disease and having the patients participate in that. Each patient is part of answering the questions that will ultimately benefit the next generation while your patients are benefitting from the patients that you treated on trials a few years before." That perspective is meaningful, he says. "The whole endeavor of taking care of patients and working closely with colleagues to solve the problems that will define therapy for the future is extremely rewarding."

Linda Brookes, MSc is a freelance medical writer/editor based in New York and London.

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- **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.



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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 (≥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.

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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/m^2 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[1] (n = 173)		Sorafenib[1] (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

[1] The 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/m^2 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/m^2 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/m^2 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 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 [CLcr] 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

AVEO ONCOLOGY

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Highlights of ASCO 2022

Catherine Handy Marshall, MD





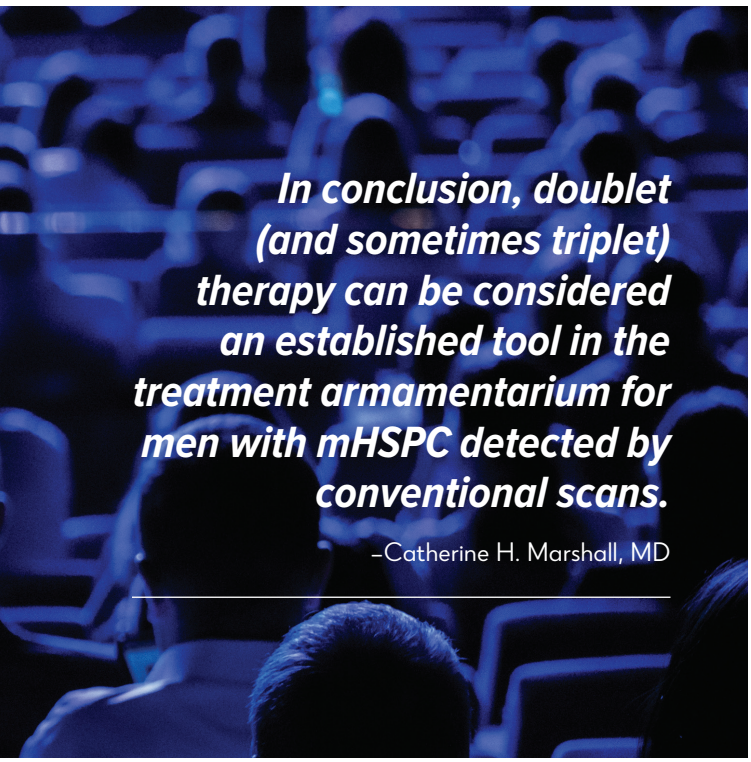
Catherine Handy Marshall, MD, MPH

MISSED ASCO 2022 THIS YEAR? Data presented at the 2022 annual meeting of the American Society of Clinical Oncology (ASCO 2022) solidified the role of doublet therapy—androgen-deprivation therapy (ADT) combined with a novel oral antiandrogen drug—for treatment of men with metastatic hormone-sensitive prostate cancer (mHSPC). Additional data were also presented on lutetium-177 prostate-specific membrane antigen (^{177}Lu-PSMA), which can be used to facilitate treatment sequencing decisions and patient selection for men with metastatic castration resistant prostate cancer (mCRPC).

The first presentation detailed results from the CHART trial, a study of 654 men with high-volume de novo mHSPC. The definition of high-volume disease in this trial was consistent with that in prior studies, ie, visceral disease or disease in which the patient had r4 bone metastases. A total of 20% of the study population had visceral disease and 46% had >20 bone lesions. Patients were randomized 1:1 to receive standard ADT (ie, luteinizing hormone-releasing hormone agonists or antagonists, or surgical castration) plus either SHR3680 (a novel second-generation antiandrogen given orally once daily; treatment arm) or bicalutamide (control arm). The primary endpoints of the study were radiographic progression-free survival (rPFS) and overall survival (OS).

The study met its primary endpoint. At 2 years, 72% of men in the treatment arm were free from radiographic progression, compared with 50% of men in the control arm (hazard ratio [HR] for rPFS, 0.44; 95% confidence interval [CI], 0.33–0.58). Additionally, 81% of men in the treatment arm remained alive compared with 70% of men in the control arm (HR for OS, 0.58; 95% CI, 0.44–0.77). SHR3680 was also associated with a longer time

to the next skeletal-related event (median not reached in the treatment arm vs 38.7 months in the control arm), longer time to prostate-specific antigen (PSA) progression (median not reached in the treatment arm vs 11 months in the control arm), and had a higher PSA undetectable rate (68% in the treatment arm vs 33% in the control arm).



Side effects of treatment for patients in the SHR3680 treatment arm were similar to what was seen in the control arm, and similar to the side effect profiles for the antiandrogen drug class. The most common morbidities were weight gain, hypertriglyceridemia, hypercholesterolemia, and aspartate aminotransferase elevation. This highlights the point that cardiometabolic health is a key consideration in the ongoing care of patients with advanced prostate cancer. Data collected using quality of life (QOL) measures suggest that QOL was better for patients in the treatment arm than for those in the control arm. It is important to note that this study and the development of SHR3680 were conducted entirely outside of the United States, and the drug is not currently available in the United States. Its future availability remains to be seen.

Updated data from ENZAMET were also presented. ENZAMET was a study of 1,125 men with mHSPC who were randomized 1:1 to ADT combined with enzalutamide (treatment arm). or a nonsteroidal antiandrogen (bicalutamide, nilutamide, or flutamide) in the control arm.

In the treatment arm, 67% of men were alive at 5 years compared with 57% in the control arm (HR, 0.70; 95% CI, 0.58–0.84). A benefit was seen in men with both low-volume and high-volume disease. Taken together with the results from CHART, these studies highlight that intensification of ADT produces long-term survival benefits for men with mHSPC. While the ENZAMET investigators also conducted exploratory analysis in men who were also prescribed docetaxel, there was no significant benefit seen with the combination of ADT and enzalutamide plus docetaxel. However, the study was not designed to answer the question of whether or not enzalutamide should be added to ADT and docetaxel. Therefore, this study cannot be used to draw conclusions in support of or against the use of triplet therapy.

Additional data presented on the use of 177Lu-PSMA-617 therapy came from reports on the THERA-P and VISION trials. THERA-P trial is a phase 2 randomized controlled trial in men previously treated with docetaxel. The study randomized 200 men 1:1 to ^{177}Lu-PSMA-617 (up to 6 cycles) or intravenous cabazitaxel (20 mg/m2 every 3 weeks, up to 10 cycles). The authors had previously presented data on the primary endpoint showing increased PSA response with ^{177}Lu-PSMA-617 compared with cabazitaxel. After a median of 3 years, however, they found no difference in OS between the 2 groups. Notably, however, there were fewer adverse events and better patient-reported outcomes in the ^{177}Lu-PSMA-617 treatment group compared with the cabazitaxel group. The researchers posited that, based on these data, it seems reasonable to use ^{177}Lu-PSMA-617 in the post-docetaxel, post-androgen receptor–targeting agent setting, before cabazitaxel chemotherapy.

Data presented from the VISION trial focused on patient selection. They reported that patients who are likely to have the best response to ^{177}Lu-PSMA-617 in that trial are those whose disease has a high mean standardized uptake value (SUV), ie >10, on PSMA–positron emission tomography/computed tomography. Those whose disease has a low mean SUV have a less robust response to ^{177}Lu-PSMA-617 treatment.

In conclusion, doublet (and sometimes triplet) therapy can be considered an established tool in the treatment armamentarium for men with mHSPC detected by conventional scans. ^{177}Lu-PSMA-617 is most beneficial for those whose disease has a high SUV on PSMA PET/CT. Although it does not prolong OS compared with cabazitaxel, it results in better patient-reported outcomes and fewer side effects, making it a reasonable treatment option before second line chemotherapy.

Catherine H. Marshall, MD, MPH, is assistant professor of oncology at The Johns Hopkins School of Medicine, Baltimore, Maryland.



Intravesical Bacillus Calmette-Guérin (BCG) is the Current Standard of Care Treatment for Patients with NMIBC

David Ambinder, MD

DURING THE FRIDAY MORNING plenary session of the 2022 American Urological Association (AUA) annual meeting, Karim Chamie, MD, associate professor of medicine at UCLA, began by reviewing that intravesical bacillus Calmette-Guérin (BCG) is the current standard of care treatment for patients with high grade non–muscle-invasive bladder cancer (NMIBC). BCG induction is believed to work by impacting and training macrophages that then cause a release of cytokines and tumor necrosis factor. Subsequently, natural killer (NK) cells and T cells are activated, and target bladder cancer cells, ultimately leading to death of bladder cancer cells. The combination of NK cells1 and T cells[2] is essential to be effective against bladder cancer cells. Based on animal models, investigators hypothesized that the combination of BCG and interleukin-15 (IL-15) would further augment the efficacy of T-cell and NK-cell response, resulting in activation of memory T cells, which would in turn create an immune memory response with the potential to increase disease-free survival (DFS).

Dr Chamie explained that this hypothesis led to the design of the phase2/phase 3 QUILT 3032 trial. The trial

aimed to assess the safety and efficacy of adding N-803 (an IL-15 superagonist complex) to BCG. Enrolled patients had NMIBC with carcinoma in situ with or without (CIS ffl) papillary disease and had previously received BCG but were unresponsive to treatment. Patients were stratified into 2 cohorts, one with CIS ffl papillary tumor, and one with papillary disease alone (papillary cohort). Inclusion criteria included histologic confirmation of NMIBC with persistent or recurrent CIS ffl papillary disease, with recurrence limited to within 12 months before enrollment.

All patients enrolled in the trial received intravesical BCG 50 mg plus N-803 400 µg instilled once weekly for 6 weeks, followed by maintenance therapy for patients who had an initial complete response (CR). Patients who had only a partial response were offered the option for reinduction. Safety endpoints were aimed at identifying potential serious adverse events (SAEs) and immune-related adverse events (irAEs). Efficacy endpoints were based on US Food and Drug Administration guidance to evaluate for a CR at any time, with the lowest 95% confidence limit at >20%. Secondary endpoints included duration of CR, whether patients underwent subsequent cystectomy, and the time to cystectomy.

There was a total of 83 patients in the CIS ffl papillary cohort and 77 patients in the papillary cohort. The median age in both cohorts was 72 years, and 87% of patients in the CIS ffl papillary and 74% in the papillary cohort identified as male. Eastern Cooperative Oncology Group (ECOG) performance status was 0 for most patients, indicating full activity. Importantly, there was a mean of 4 transurethral resections of bladder tumor for both cohorts. Mean prior administrations of intravesical BCG were 16.6 in the CIS ffl papillary cohort and 12.3 in the papillary cohort.

Dr Chamie then reviewed the safety profile of N-803, explaining that the risk for treatment-related SAEs was 1% and the rate of irAEs was 0%; the treatment-related discontinuation rate was 3%. No treatment-related grade 4 or grade 5 AEs were reported. The most common grade 1 and grade 2 morbidities included dysuria, urinary frequency, hematuria, and urgency. The incidence of grade 3 AEs was <1% overall. Dr Chamie concluded that these safety profile findings were consistent with the hypothesis that N-803 activity acts locally without having a significant IL-15 systemic effect.

Next, Dr Chamie focused on the efficacy data. Based on CR rates of the CIS ffl papillary cohorts, 71% of patients had a CR at any time, and the median duration of that response was approximately 2 years. The CR rate was 62% at 12 months, 55% at 18 months, and 52% at 24 months. The cystectomy rate was 7% for those who responded initially, and 15% for all patients (including those who did or did not respond). Bladder cancer-specific progression-free survival was 91% at 2 years, while the overall survival rate in this cohort was 100%. The median follow-up time was 2 years. This efficacy was maintained when accounting for the multiple variables and demographics evaluated, including age, race, gender, presence of CIS ffl papillary disease, previous prior therapy, and whether patients had undergone reinduction. All patients benefited from the combination of N-803 plus BCG, and patients were followed for nearly 2 years (23.6 months). In the papillary cohort, median DFS was similar to that in the CIS group at 12 months (57%), 18 months (53%), and 2 years (48%). The primary endpoint was met for 73 patients, and 95% avoided a radical cystectomy. The median follow-up time was 21 months. Similar to the CIS ffl cohort, efficacy was retained even when accounting for multiple variables and demographics including age, gender, race, and tumor histology.

According to Dr Chamie, this study evaluating the addition of intravesical N-803 to BCG for the treatment of patients with high-grade NMIBC with CIS showed a clinically meaningful benefit without compromising safety or tolerability.

Dr Chamie concluded that this study evaluating the addition of intravesical N-803 to BCG for the treatment of patients with high-grade NMIBC with CIS showed a clinically meaningful benefit without compromising safety or tolerability. Indeed, the tolerability of the drug combination was consistent and similar to that in patients who received BCG alone in other studies (SAEs of 1% in QUILT 3032 vs 2% in other studies, and 3% treatment-related discontinuations of 3% vs 2% in other studies). In patients with papillary tumors, the rate of DFS was 56% at 12 months and 48% at 2 years. Overall bladder cancer-specific survival was reported in 99% of patients, and 96% avoided cystectomy at 2 years while maintaining good tolerability and a low rate of AEs.

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Prostate Cancer Highlights at ASCO 2022

Akhil A. Saji, MD

AT THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO) 2022 meeting in early June 2022, several important abstracts pertaining to prostate, bladder, and kidney cancer were presented. Several interesting abstracts within the prostate cancer sphere were presented, of which a few will be highlighted in this article.

In the sphere of metastatic hormone-sensitive prostate cancer (mHSPC), several medications including abiraterone (LATITUDE trial[1]), apalutamide (TITAN trial[2]), and enzalutamide (ENZAMET trial[3]) have been approved in recent years for use in combination with androgen- deprivation therapy (ADT). Ian Davis, MD, presented updated overall survival (OS) outcomes from the ENZAMET trial.[4] To review, the original results in 2019 demonstrated that in 1125 patients with mHSPC enrolled in the randomized clinical trial, the 36-month OS in the experimental arm showed an 8% improvement in OS (80% vs 72%) as well as a favorable hazard ratio (HR) of 0.67. Dr Davis briefly reviewed the existing knowledge compiled by several trials, including those referenced above. Specifically, he explained that patients with low-volume mHSPC tend to do well with testosterone-suppressive therapies alone, whereas patients with higher volumes of disease may benefit from addition of docetaxel, stronger combinations of testosterone-suppressive therapies, or even radiation therapy delivered to the primary tumor.

Dr Davis briefly reviewed the ENZAMET trial design. He explained that patients were stratified by volume of metastatic disease, use of docetaxel, and Eastern Cooperative Oncology Group (ECOG) performance scores among other variables prior to randomization, to receive standard ADT plus placebo or ADT plus enzalutamide. He also referenced the original data presented in 2019, taking care to remark that despite the overall OS improvement for the entire cohort, subgroup analysis of patients receiving docetaxel did not demonstrate an OS benefit. Dr Davis noted that updated data after a longer median follow-up time of 68 months may offer further insights into the use of enzalutamide in the mHSPC population. The primary goal of the updated analysis was to study the results of enzalutamide use in patients who had nonmetastatic (M0) versus metastatic (M1) disease at diagnosis, as well as the presence of high-volume disease at trial entry.

The overall cohort analysis for OS demonstrated a sustained survival benefit (favorable HR of 0.70; $P<0.001$), with 10% improvement in OS at 60 months (67% vs 57%) in the experimental arm. Before presenting data on the subcohort analyses, Dr Davis reiterated that use of docetaxel in the enrolled patients was solely at the discretion of each investigator, with 45% of the population ultimately planned to undergo concurrent docetaxel therapy. Presentation of the OS analysis stratified by subgroups demonstrated some interesting findings. Dr Davis explained that the effect of enzalutamide was most prominent in patients with low-volume disease (HR, 0.54 vs 0.79l; $P=0.06$) and those with no docetaxel exposure (HR, 0.60 vs 0.82; $P=0.09$). Overall, the updated results demonstrated that no statistically significant differences were found between subgroups with use of enzalutamide; however, use of enzalutamide appears particularly useful

in patients with low-volume mHSPC. In concluding remarks, Dr Davis further noted that addition of enzalutamide in patients with mHSPC receiving ADT shows a clinically significant improvement in OS.

Several developments related to prostate-specific membrane antigen (PSMA) were also presented at ASCO 2022, including updated results from the TheraP phase II trial (NCT03392428)[5] exploring the utility of lutetium-177 (^{177}Lu)-PSMA-617 compared with cabazitaxel therapy in patients with metastatic castration-resistant prostate cancer (mCRPC). The TheraP trial enrolled 200 patients (291 originally screened) with mCRPC demonstrable on positron emission tomography (PET) imaging, with 99 patients randomized to ^{177}Lu-PSMA-617 and 101 randomized to cabazitaxel therapy. The original results published in 2021,[6] demonstrated that patients randomized to ^{177}Lu-PSMA-617 had a higher rate of PSA response compared with the cabazitaxel arm (66% vs 37%) as well as having a lower rate of significant (grade 3/4) adverse events (AEs; 33% vs 53%).

Michael S. Hoffman, MBBS, lead author for the original publication from the Peter MacCallum Cancer Centre in Melbourne, Australia, reported on longer-term follow-up outcomes for this trial. PSA progression free survival (PFS) in the ^{177}Lu-PSMA-617 arm was improved compared with the cabazitaxel arm (HR, 0.63; *P*=0.007), with a 2.1-month improvement (7.1 vs 5 months). Despite these promising results, no significant difference in OS was noted between the 2 arms. Updated data on AEs were also presented and demonstrated a consistent rate of lower grade 3/4 AEs with ^{177}Lu-PSMA-617 compared with cabazitaxel (32% vs 49%). The updated data from the TheraP trial demonstrate that due to improvements in PFS and an improved safety profile, ^{177}Lu-PSMA-617, despite having no demonstrable OS benefit compared with cabazitaxel, can still serve as a therapy of choice in mCRPC that is refractory to treatment (docetaxel, androgen pathway inhibition). Furthermore, the favorable administration schedule (6 weeks vs 3 weeks for cabazitaxel) may provide an already frail patient population further flexibility.

Another important abstract related to ^{177}Lu-PSMA-617 was presented by Andrew Armstrong, MD, MSc, of Duke University, on behalf of author Philip Kuo, MD, exploring the utility of gallium-68 (^{68}Ga)-PSMA-11 PET imaging for prognostic ability in patients receiving 177Lu-PSMA-617 therapy for mCRPC.[7] Dr Armstrong briefly reviewed the results of the VISION trial,[8] originally published in 2021, demonstrating statistically significant improvements in radiographic PFS (rPFS; HR, 0.40; 8.7 vs 3.4 months) and OS (HR, 0.72; 15.3 vs 11.3 months) in the ^{177}Lu-PSMA-617 arm of patients with refractory mCRPC. The purpose of this VISION trial subanalysis was to elucidate associations between pretreatment PET/computed tomography (CT; ^{68}Ga-PSMA-11) imaging and clinical outcomes from ^{177}Lu-PSMA-617 therapy (ie, rPFS and OS).

The subcohort analysis included 548 of 551 patients for evaluation of OS and 382 patients for evaluation of rPFS and PSA response. Dr Armstrong explained that the mean standard uptake volume (SUV_{mean}; ie, mean counts of detectable lesions across the entire body) was found to be a significant predictor of important treatment indicators, such as rPFS, OS, and PSA response. In regard to rPFS, Dr Armstrong explained that patients with the highest SUV_{mean} values tended to receive the greatest rPFS benefit from ^{177}Lu-PSMA-617 therapy, with values >10.2 having a median rPFS of 14.1 months. This is in comparison to SUV_{max} (region with highest detectable counts), which was found to not be a significant predictor of any endpoints. Finally, in regard to OS, SUV_{mean} was again demonstrated to be a statistically significant predictor (HR, 0.92; *P*<0.001).

In concluding remarks, Dr Armstrong explained that this analysis of the VISION trial data supports the idea that patients with treatment-refractory mCRPC should undergo ^{68}Ga-PSMA-11 PET/CT to help identify which individuals would benefit most from PSMA-directed radioligand therapy such as ^{177}Lu-PSMA-617. Information such as SUV_{mean} values garnered from these scans can help clinicians predict radioligand treatment outcomes.

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Role of 3D Modeling in Treatment of Renal Tumors

Akhil A. Saji, MD

IT IS ESTIMATED THAT IN 2022, nearly 79,000 cases of kidney cancer will be diagnosed in the United States, leading to nearly 14,000 estimated kidney cancer-related deaths.[1] Partial nephrectomy is the current preferred modality for treatment of most T1 and T2 renal masses.[2] The trifecta of partial nephrectomy—defined as absence of perioperative complications, warm ischemia time <30 minutes (renal artery clamping), and no positive surgical margins—has been found to have equivalent outcomes with robotic, laparoscopic, and open approaches.[3] Furthermore, urologists across the world increasingly have been utilizing minimally invasive partial nephrectomy, either robotically or laparoscopically, to reduce the morbidity traditionally associated with open abdominal surgery.

Use of the robotic option for partial nephrectomy in particular offers surgeons an enhanced 3-dimensional (3D) view of the kidney[4] and the tumor in question. To facilitate higher rates and more appropriate use of nephron-sparing techniques such as partial nephrectomy, nomograms such as the PADUA classification system,[5] C-index,[6] and RENAL Nephrometry score[7,8] were created shortly after the mainstream introduction of robotic surgery in the early- to mid-2000s. Such tools have enabled surgeons to better counsel patients on whether nephron-sparing partial nephrectomy would be an option or whether radical nephrectomy is likely to be required. Moreover, their use has been demonstrated to successfully predict perioperative outcomes. In addition to helping the surgeon classify tumors, patients also can gain a better understanding of the 3D anatomy of their tumors. Silberstein, et al, demonstrated the value of creating physical models of the tumors to enhance patient understanding.[9] In a series of 5 patients, they created physical models of the tumors that were found to be helpful for increasing patients' understanding of the anatomic and surgical goals of their care.

Despite these developments, translation of scoring systems into 3D understanding of tumor structure and its relationship to segmental vessels, collecting system involvement, and even live utility during surgery is limited. On a surgical level, until recently, there have been very few tools available to actively assist surgeons in preparing to perform a nephron-sparing partial nephrectomy. This article provides a brief overview of the climate of virtual 3D reconstructions of renal tumors in various settings, including patient counseling prior to surgery, intraoperative assistance, and training of future urologists.

Partial nephrectomy can be an incredibly challenging procedure, depending on the complexity of the tumor as described by a nephrometry score or other scoring systems. Use of virtual reconstructions of the intended renal mass for excision has demonstrated various benefits across several documented studies. For example, in a study of 15 patients undergoing robot- assisted partial nephrectomy (RPNx), the assistance of 3D models within the robotic console facilitated a faster time to identification of the renal vasculature and faster selective clamping of the target artery.[10] Providing further support, a large retrospective propensity-matched series compared patients who underwent RPNx with and without 3D model reconstructions. The authors found that patients who had reconstructions completed had a higher rate of partial nephrectomy trifecta, lower rate of postoperative complications, and a closer-to-target estimated glomerular filtration rate.[11]

Another interesting platform that has recently gained momentum is Iris, from Intuitive Surgical, creators of the popular da Vinci robotic surgery platform. Iris functions by providing virtual 3D reconstructions of the tumor in question, allowing the surgeon to plan a surgical approach, review the computed tomography images from the convenience of the robotic console, and even view the virtual model within the robot console using da Vinci TilePro technology. An initial review[12] of the Iris technology demonstrated that surgeons found it to be helpful in improving procedure efficiency by up to 73%. Iris has also shown benefits in improving rates of nephron-sparing surgery. In a recent study of 462 cases using Iris technology, the authors demonstrated that surgeons using the platform were 16.5% more likely to change the procedure from radical nephrectomy

to partial nephrectomy after reviewing the Iris 3D reconstruction.[13] Similar to Iris, but applicable to all clinicians who review imaging, SYNAPSE VINCENT (Fujifilm Corporation) has also shown promise. In addition to 3D reconstruction, SYNAPSE VINCENT also provides a suite of image analysis products for clinicians to use. A group based in Japan reported success in conducting 26 clampless partial nephrectomies using preoperative planning with SYNAPSE VINCENT software.[14]

Virtual reality may be the next true foray into 3D reconstruction before surgery. Despite exponential improvements over the past 2 decades, current graphics processing units are not capable of providing the level of performance required to achieve true virtual reality or even augmented reality. It is estimated that the human eye would require nearly 100.8 megapixels per eye for the field of view to achieve true parity with real life.[15] Current graphics solutions do not have such capabilities, but it is estimated that they may become realized over the next decade. Publications on applications of such techniques are sparse compared with the literature on use of 3D reconstruction, but many authors have tried to demonstrate their promise. Shirk, et al, conducted a randomized clinical trial to investigate the role of virtual reality in patients planned to undergo RPNx using Google Cardboard virtual reality headsets.[16] The investigators demonstrated that use of the virtual reality technology demonstrated lower blood loss, warm ischemia time, overall lower operative time, and shorter hospital stay durations.

Despite the promising published results supporting use of virtual or augmented reality reconstruction of renal tumors, there are notable limitations to these technologies. The first is the lack of standardization across technologies. For a given modality, whether it be virtual reconstruction or augmented virtual reality, several types of software and reconstruction techniques exist, many of which are proprietary and do not immediately provide insight into how the technology functions. The second limitation is the lack of a standardized prospective clinical trial to study the benefits of augmenting care for patients with renal masses with virtual reality prohibits the drawing of any strong conclusions. Nevertheless, widespread adoption of 3D reconstruction, regardless of modality, will likely offer some benefits, including providing enhanced guidance to trainees and early career surgeons and giving patients a tool to better understand their planned procedure. This may facilitate enhanced preoperative counseling for patients and help them better understand the risks that surgeons are explaining to them.

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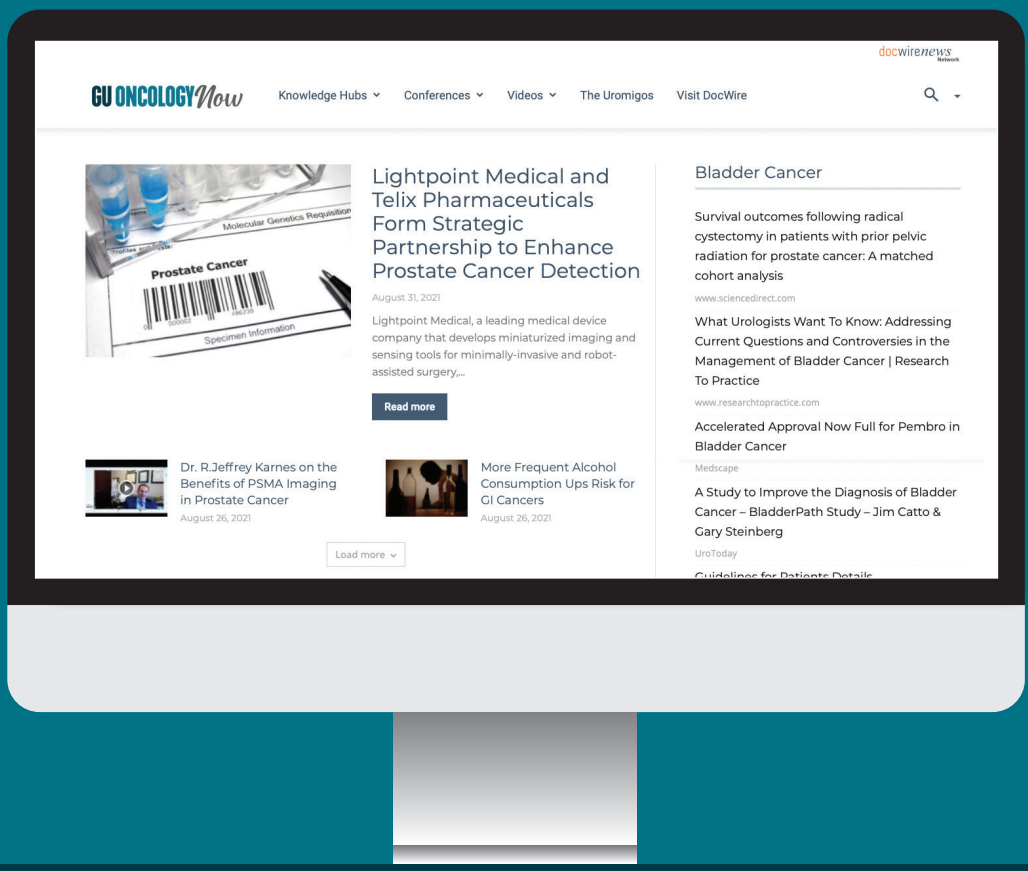
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Akhil Abraham Saji, MD is a urology resident at New York Medical College / Westchester Medical Center. His interests include urology education and machine learning applications in urologic care. He is a founding and current member of the EMPIRE Urology New York AUA section team.

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