American Urological Association

AUANews

OCTOBER 2023

VOLUME 28 | ISSUE 10

AUANews.net

THE OFFICIAL NEWSMAGAZINE OF THE AMERICAN UROLOGICAL ASSOCIATION

– FOCUS ISSUE –

Clinical Trials

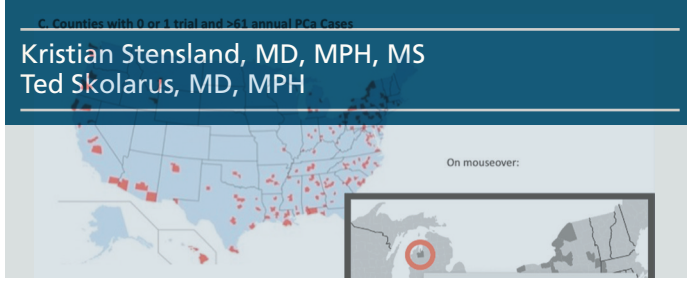
EDITOR: Stacy T. Tanaka, MD, MS, FACS, *University of Alabama at Birmingham*
GUEST EDITORS: Khurshid R. Ghani, MBChB, MS, FRCS, *University of Michigan*
Charles D. Scales Jr, MD, MSHS, *Duke Clinical Research Institute and Department of Urology*
Neal D. Shore, MD, FACS, *Carolina Urologic Research Center*

The Legacy of Black Urologists in America

Arthur L. Burnett, MD, MBA

Improving Clinical Trials With Implementation Science

Kristian Stensland, MD, MPH, MS
Ted Skolarus, MD, MPH



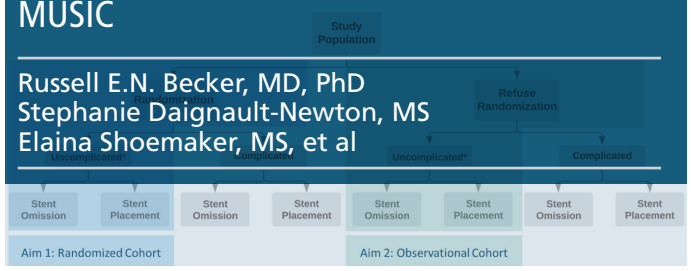
PARTIAL, a Randomized Controlled Trial Comparing Pelvic Fascia-sparing and Conventional Radical Prostatectomy

Mary Oakley Strasser, MD, MBA
Andrew Vickers, PhD
Edward M. Schaefer, MD, PhD, et al

Figure 1. PFS-RP (right) leaves pelvic fascia, comprised of puboprostatic ligament and detrusor apron, and dorsal vascular complex intact vs. conventional RP (left). Anterior approach (white

Leveraging Quality Improvement Networks for Clinical Trials: Making BLUES and SOUL MUSIC

Russell E.N. Becker, MD, PhD
Stephanie Daignault-Newton, MS
Elaina Shoemaker, MS, et al



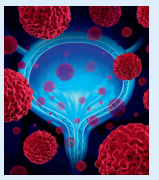
Coming up in the October Issue of AUANews Extra

Clinical Trials for Patients With Stones From the United Kingdom

Matthew Bultitude, MBBS, MSc, FRCS(Urol)

COMING SOON IN THE OCTOBER ISSUE OF *AUANewsExtra*

Embarking Upon a Clinical Research Enterprise in the Independent Private Practice Setting



Why Consider Genitourinary Oncology Research in the Community?

How to Incorporate Urologic Oncology Fellowship Learnings When Starting Practice

CLINICAL TRIALS

Patient and Stakeholder Engagement to Support Clinical Trial Development in Kidney Stone Research: A Roadmap to Success

Patients as Partners in the Modern Clinical Trial Landscape

Addressing Overuse Through De-implementation Trials and Practice

Patient Engagement in a Bladder Cancer Clinical Trial

SipIT Behavioral Intervention Clinical Trial to Increase Fluid Intake for Kidney Stone Prevention

Behavioral Modification Trials in Urology

Why Is It So Hard to Accrue to Randomized Surgical Trials and What Can Be Done About It?

ASCO ANNUAL MEETING RECAPS

Highlights of Genitourinary Cancer: Prostate and Testicular Cancer

Combination Therapies Come of Age in Kidney Cancer

First-line Lenvatinib + Pembrolizumab Treatment Across Nonclear Cell Renal Cell Carcinomas

Standard vs Extended Lymphadenectomy Performed at Radical Cystectomy for Muscle-invasive Urothelial Cancer

Personalizing Androgen Deprivation Therapy in Patients With High-risk Localized Prostate Cancer Using Artificial Intelligence

Patient-reported Quality of Life and Survival Outcomes: CHAARTED Trial in Prostate Cancer

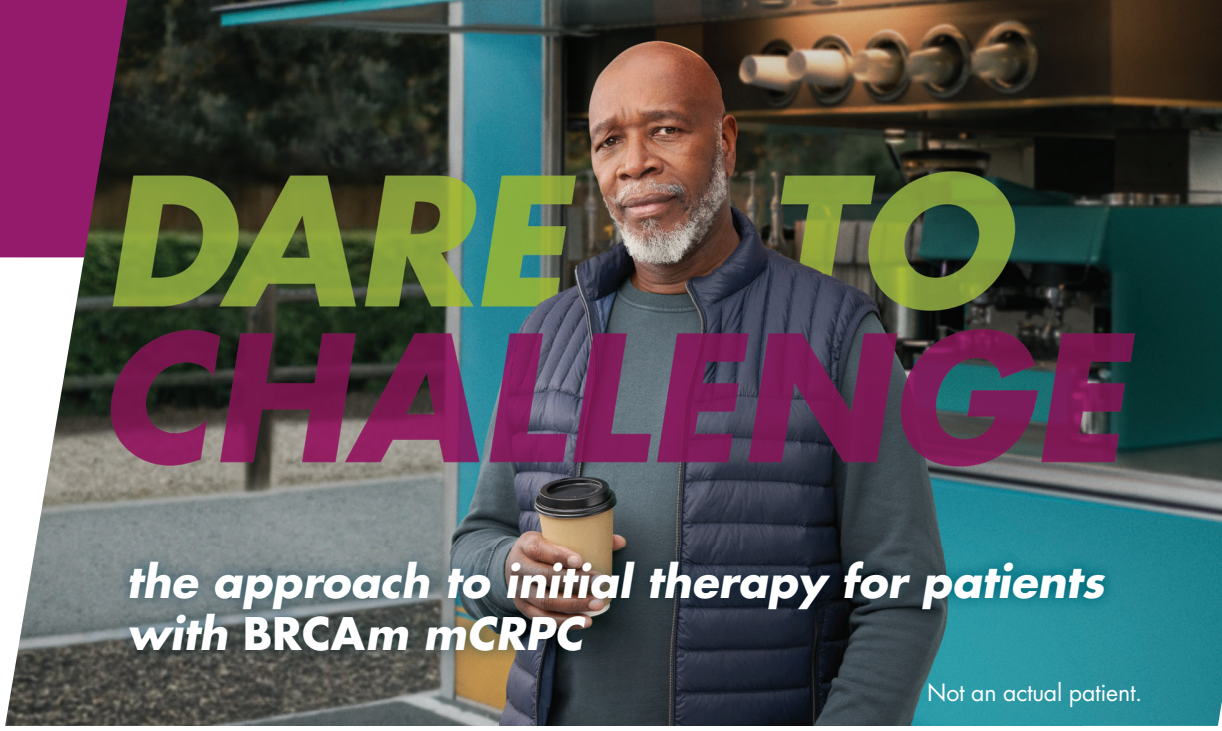
NON-PROFIT ORG.
U.S. POSTAGE
PAID
PERMIT NO. 797
RICHMOND, VA

American Urological Association
1000 Corporate Boulevard
Linthicum, Maryland 21090

Lynparza®
olaparib
tablets 150 mg

NOW APPROVED

LYNPARZA: the FIRST PARPi approved in combination with abiraterone plus prednisone or prednisolone (abi/pred) as initial therapy for *BRCA*m mCRPC[1-4]



INDICATION

LYNPARZA is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated in combination with abiraterone and prednisone or prednisolone (abi/pred) for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCA*m) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic for LYNPARZA.

PROpel: A phase 3 trial

PROpel examined the efficacy of LYNPARZA + abi/pred vs placebo + abi/pred (active comparator) upon mCRPC diagnosis[1,5]

- PROpel was a randomized, double-blind, placebo-controlled, multicenter, phase 3 trial
- ITT population (N=796): mCRPC with or without HRR mutations
  - **FDA approval of LYNPARZA + abi/pred was based on an exploratory *BRCA*m subgroup (n=85)**
- Patients were randomized 1:1 to receive either LYNPARZA (300 mg BID) + abiraterone (1000 mg QD) with prednisone or prednisolone (5 mg BID) (n=399) or placebo + abiraterone (1000 mg QD) with prednisone or prednisolone (5 mg BID) (n=397). LYNPARZA was continued until objective radiological disease progression determined by investigator or unacceptable toxicity. All patients received a GnRH analog or had prior bilateral orchiectomy
- Patients were stratified by metastatic site and whether they received prior docetaxel at mHSPC stage. *BRCA*m status was not a stratification factor. Prior abiraterone was not allowed

Trial endpoints:

- Primary endpoint (ITT): rPFS by investigator assessment*
- Additional efficacy outcome measure (ITT): Overall survival
- Safety and tolerability
- **Exploratory *BRCA*m subgroup analyses**
  - Investigator-assessed rPFS* and OS in patients with *BRCA*m mCRPC (n=85)
  - Sensitivity analysis of rPFS by BICR

*BRCA*m status was assessed after randomization and before primary analysis by both NGS-based tumor tissue and ctDNA tests. *BRCA*m classification criteria in line with the FDA-approved assays were used to determine the deleterious and suspected deleterious somatic or germline mutation status of patients.

*Radiological progression-free survival (rPFS) assessed by investigator per RECIST v1.1 (soft tissue) and PCWG3 (bone) criteria.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

There are no contraindications for LYNPARZA.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia (MDS/AML): Occurred in approximately 1.5% of patients exposed to LYNPARZA monotherapy, and the majority of events had a fatal outcome. The median duration of therapy in patients who developed MDS/AML was 2 years (range: <6 months to >10 years). All of these patients had previous chemotherapy with platinum agents and/or other DNA-damaging agents, including radiotherapy.

Do not start LYNPARZA until patients have recovered from hematological toxicity caused by previous chemotherapy (≤Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt LYNPARZA and monitor blood count weekly until recovery.

If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. Discontinue LYNPARZA if MDS/AML is confirmed.

Pneumonitis: Occurred in 0.8% of patients exposed to LYNPARZA monotherapy, and some cases were fatal. If patients present with new or worsening respiratory symptoms such as dyspnea, cough, and fever, or a radiological abnormality occurs, interrupt LYNPARZA treatment and initiate prompt investigation. Discontinue LYNPARZA if pneumonitis is confirmed and treat patient appropriately.

Venous Thromboembolism (VTE): Including severe or fatal pulmonary embolism (PE) occurred in patients treated with LYNPARZA. In the combined data of two randomized, placebo-controlled clinical studies (PROfound and PROpel) in patients with metastatic castration-resistant prostate cancer (N=1180), VTE occurred in 8% of patients who received LYNPARZA, including pulmonary embolism in 6%. In the control arms, VTE occurred in 2.5%, including pulmonary embolism in 1.5%. Monitor patients for signs and symptoms of venous thrombosis and pulmonary embolism, and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

Embryo-Fetal Toxicity: Based on its mechanism of action and findings in animals, LYNPARZA can cause fetal harm. Verify pregnancy status in females of reproductive potential prior to initiating treatment.

Females

Advise females of reproductive potential of the potential risk to a fetus and to use effective contraception during treatment and for 6 months following the last dose.

Males

Advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of LYNPARZA and to not donate sperm during this time.

ADVERSE REACTIONS—Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

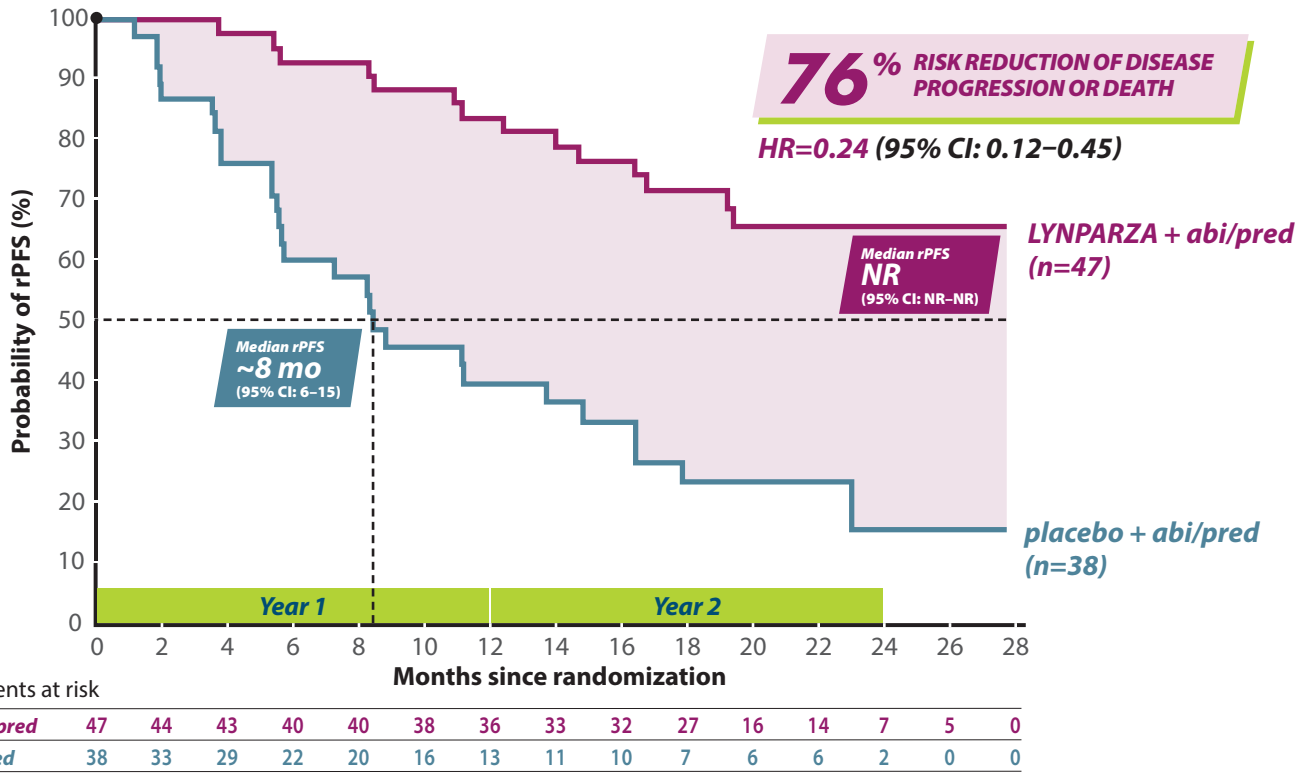
Most common adverse reactions (Grades 1-4) in ≥10% of patients who received LYNPARZA/abiraterone with a difference of ≥5% compared to placebo for **PROpel** were: anemia (48%), fatigue (including asthenia) (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), dizziness (14%), and abdominal pain (13%).

Most common laboratory abnormalities (Grades 1-4) in ≥20% of patients who received LYNPARZA/abiraterone for **PROpel** were: decrease in hemoglobin (97%), decrease in lymphocytes (70%), decrease in platelets (23%), and decrease in absolute neutrophil count (23%).

FDA approval of LYNPARZA + abi/pred was based on an exploratory **BRCAm** *subgroup*

LYNPARZA + abi/pred demonstrated improvement in rPFS vs placebo + abi/pred in patients with BRCAm *mCRPC*[1,5]

rPFS BY INVESTIGATOR ASSESSMENT IN EXPLORATORY *BRCA*m SUBGROUP



Number of patients at risk

LYNPARZA + abi/pred	47	44	43	40	40	38	36	33	32	27	16	14	7	5	0
placebo + abi/pred	38	33	29	22	20	16	13	11	10	7	6	6	2	0	0

***BRCA*m subgroup (n=85)**
rPFS events, n (%): 14/47 (30) with LYNPARZA + abi/pred and 28/38 (74) with placebo + abi/pred
- Results from the BICR assessment were consistent with the investigator-assessed rPFS results

OS analysis: 70% reduction in risk of death (HR=0.30 [95% CI: 0.15–0.59]) for LYNPARZA + abi/pred vs placebo + abi/pred. OS events, n (%): 13/47 (28) and 25/38 (66), respectively

*BRCA*m status was not a stratification factor in PROpel, and analysis was not controlled for Type 1 error

ITT population (n=796)
Statistically significant improvement in rPFS* was observed for LYNPARZA + abi/pred compared with placebo + abi/pred. OS for LYNPARZA + abi/pred compared to placebo + abi/pred did not reach statistical significance in the ITT population

Patients without an identified *BRCA*m (n=711)
Results from exploratory analyses in this subgroup (rPFS: HR=0.77 [95% CI: 0.63–0.96] and OS: HR=0.92 [95% CI: 0.74–1.14]) indicated that the improvement in the ITT population was primarily attributed to the results seen in the *BRCA*m subgroup

IMPORTANT SAFETY INFORMATION (Cont'd)

DRUG INTERACTIONS

Anticancer Agents: Clinical studies of LYNPARZA with other myelosuppressive anticancer agents, including DNA-damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

CYP3A Inhibitors: Avoid coadministration of strong or moderate CYP3A inhibitors when using LYNPARZA. If a strong or moderate CYP3A inhibitor must be coadministered, reduce the dose of LYNPARZA. Advise patients to avoid grapefruit, grapefruit juice, Seville oranges, and Seville orange juice during LYNPARZA treatment.

CYP3A Inducers: Avoid coadministration of strong or moderate CYP3A inducers when using LYNPARZA.

USE IN SPECIFIC POPULATIONS

Lactation: No data are available regarding the presence of olaparib in human milk, its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infant, advise a lactating woman not to breastfeed during treatment with LYNPARZA and for 1 month after receiving the final dose.

Pediatric Use: The safety and efficacy of LYNPARZA have not been established in pediatric patients.

Hepatic Impairment: No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C).

Renal Impairment: No dosage modification is recommended in patients with mild renal impairment (CLcr 51-80 mL/min estimated by Cockcroft-Gault). In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the dose of LYNPARZA to 200 mg twice daily. There are no data in patients with severe renal impairment or end-stage renal disease (CLcr ≤30 mL/min).

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.FDA.gov/medwatch or call 1-800-FDA-1088.

Choose LYNPARZA + abi/pred as initial therapy for BRCAm mCRPC to help give your patients more time without disease progression

References: 1. LYNPARZA® (olaparib) [prescribing information]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2023. **2.** Rubraca® (rucaparib) [prescribing information]. Boulder, CO: Clovis Oncology, Inc.; 2022. **3.** Talzenna® (talazoparib) [prescribing information]. New York, NY: Pfizer Inc.; 2021. **4.** Zejula® (niraparib) [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2023. **5.** Clarke NW, Armstrong AJ, Thiery-Vuillemin A, et al. Abiraterone and olaparib for metastatic castration-resistant prostate cancer. *NEJM Evid*. Published online June 3, 2022. doi:10.1056/EVIDoa2200043

abi/pred=abiraterone plus prednisone or prednisolone; BICR=blinded independent central review; BID=twice daily; *BRCA*m=*BRCA*-mutated or *BRCA* mutation; CI=confidence interval; ctDNA=circulating tumor DNA; GnRH=gonadotropin-releasing hormone; HR=hazard ratio; HRR=homologous recombination repair; ITT=intent-to-treat; mCRPC=metastatic castration-resistant prostate cancer; mHSPC=metastatic hormone-sensitive prostate cancer; NGS=next-generation sequencing; NR=not reached; OS=overall survival; PARPi=poly (ADP-ribose) polymerase inhibitor; PCWG3=Prostate Cancer Working Group 3; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; rPFS=radiological progression-free survival.

LYNPARZAprhcp.com to explore additional data from the PROpel trial

MERCK AstraZeneca

LYNPARZA® (olaparib) tablets, for oral use

Initial U.S. Approval: 2014

Brief Summary of Prescribing Information. For complete prescribing information consult official package insert.

INDICATIONS AND USAGE

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Lynparza is indicated for the treatment of adult patients with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer (mCRPC) who have progressed following prior treatment with enzalutamide or abiraterone. Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

Treatment of *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with deleterious or suspected deleterious *BRCA*-mutated (*BRCAm*) metastatic castration-resistant prostate cancer (mCRPC). Select patients for therapy based on an FDA-approved companion diagnostic for Lynparza *[see Dosage and Administration (2.1) in the full Prescribing Information]*.

DOSAGE AND ADMINISTRATION

Patient Selection

Information on FDA-approved tests for the detection of genetic mutations is available at http://www.fda.gov/companiondiagnostics.

Select patients for treatment with Lynparza based on the presence of deleterious or suspected deleterious HRR gene mutations, including *BRCA* mutations, or genomic instability based on the indication, biomarker, and sample type (Table 1).

Table 1 Biomarker Testing for Patient Selection*

Indication	Biomarker	Sample type		
		Tumor	Blood	Plasma (ctDNA)
Germline or somatic HRR gene-mutated metastatic castration-resistant prostate cancer	*ATM*m, *BRCA1*m, *BRCA2*m, *BARD1*m, *BRIP1*m, *CDK12*m, *CHEK1*m, *CHEK2*m, *FANCL*m, *PALB2*m, *RAD51B*m, *RAD51C*m, *RAD51D*m, *RAD54L*m	X		
	g*BRCA1*m, g*BRCA2*m		X	
	*ATM*m, *BRCA1*m, *BRCA2*m			X
BRCA-mutated metastatic castration-resistant prostate cancer in combination with abiraterone and prednisone or prednisolone	*BRCA1*m, *BRCA2*m	X	X	X

* Where testing fails or tissue sample is unavailable/insufficient, or when germline testing is negative, consider using an alternative test, if available.

Recommended Dosage

The recommended dosage of Lynparza is 300 mg taken orally twice daily, with or without food.

If a patient misses a dose of Lynparza, instruct patient to take their next dose at its scheduled time. Instruct patients to swallow tablets whole. Do not chew, crush, dissolve, or divide tablet.

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

Continue treatment until disease progression or unacceptable toxicity for:

- HRR gene-mutated metastatic castration-resistant prostate cancer

BRCA-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

Continue treatment until disease progression or unacceptable toxicity.

When used with Lynparza, the recommended dose of abiraterone is 1000 mg taken orally once daily. Abiraterone should be given in combination with prednisone or prednisolone 5 mg orally twice daily. Refer to the Prescribing Information for abiraterone for dosing information.

Patients with mCRPC should also receive a gonadotropin-releasing hormone (GnRH) analog concurrently or should have had bilateral orchiectomy.

Dosage Modifications for Adverse Reactions

To manage adverse reactions, consider interruption of treatment or dose reduction. The recommended dose reduction is 250 mg taken twice daily.

If a further dose reduction is required, then reduce to 200 mg taken twice daily.

Dosage Modifications for Concomitant Use with Strong or Moderate CYP3A Inhibitors

Avoid concomitant use of strong or moderate CYP3A inhibitors with Lynparza.

If concomitant use cannot be avoided, reduce Lynparza dosage to:

- 100 mg twice daily when used concomitantly with a strong CYP3A inhibitor.
- 150 mg twice daily when used concomitantly with a moderate CYP3A inhibitor.

After the inhibitor has been discontinued for 3 to 5 elimination half-lives, resume the Lynparza dose taken prior to initiating the CYP3A inhibitor *[see Drug Interactions (7.2) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Dosage Modifications for Renal Impairment

Moderate Renal Impairment

In patients with moderate renal impairment (CLcr 31-50 mL/min), reduce the Lynparza dosage to 200 mg orally twice daily *[see Use in Specific Populations (8.6) and Clinical Pharmacology (12.3) in the full Prescribing Information]*.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Myelodysplastic Syndrome/Acute Myeloid Leukemia

Myelodysplastic syndrome (MDS)/Acute Myeloid Leukemia (AML) has occurred in patients treated with Lynparza and some cases were fatal.

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1) in the full Prescribing Information]*, the cumulative incidence of MDS/AML was approximately 1.5% (43/2901). Of these, 51% (22/43) had a fatal outcome. The median duration of therapy with Lynparza in patients who developed MDS/AML was 2 years (range: < 6 months to > 10 years). All of these patients had received previous chemotherapy with platinum agents and/or other DNA damaging agents including radiotherapy.

Do not start Lynparza until patients have recovered from hematological toxicity caused by previous chemotherapy (≤ Grade 1). Monitor complete blood count for cytopenia at baseline and monthly thereafter for clinically significant changes during treatment. For prolonged hematological toxicities, interrupt Lynparza and monitor blood counts weekly until recovery. If the levels have not recovered to Grade 1 or less after 4 weeks, refer the patient to a hematologist for further investigations, including bone marrow analysis and blood sample for cytogenetics. If MDS/AML is confirmed, discontinue Lynparza.

Pneumonitis

In clinical studies enrolling 2901 patients with various cancers who received Lynparza as a single agent *[see Adverse Reactions (6.1) in the full Prescribing Information]*, the incidence of pneumonitis, including fatal cases, was 0.8% (24/2901). If patients present with new or worsening respiratory symptoms such as dyspnea, cough and fever, or a radiological abnormality occurs, interrupt Lynparza treatment and promptly assess the source of the symptoms. If pneumonitis is confirmed, discontinue Lynparza treatment and treat the patient appropriately.

Venous Thromboembolism

Venous thromboembolism (VTE), including severe or fatal pulmonary embolism (PE), occurred in patients treated with Lynparza *[see Adverse Reactions (6.1) in the full Prescribing Information]*.

In the combined data of two randomized, placebo-controlled clinical studies (PROfound and PROpel) in patients with metastatic castration-resistant prostate cancer (N=1180), VTE occurred in 8% of patients who received Lynparza, including pulmonary embolism in 6%. In the control arms, VTE occurred in 2.5% including pulmonary embolism in 1.5%.

Monitor patients for clinical signs and symptoms of venous thrombosis and pulmonary embolism and treat as medically appropriate, which may include long-term anticoagulation as clinically indicated.

Embryo-Fetal Toxicity

Lynparza can cause fetal harm when administered to a pregnant woman based on its mechanism of action and findings in animals. In an animal reproduction study, administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily. Apprise pregnant women of the potential hazard to a fetus and the potential risk for loss of the pregnancy. Advise females of reproductive potential to use effective contraception during treatment and for 6 months following the last dose of Lynparza. Based on findings from genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1, 8.3) in the full Prescribing Information]*.

ADVERSE REACTIONS

The following adverse reactions are discussed elsewhere in the labeling:

- Myelodysplastic Syndrome/Acute Myeloid Leukemia *[see Warnings and Precautions (5.1) in the full Prescribing Information]*
- Pneumonitis *[see Warnings and Precautions (5.2) in the full Prescribing Information]*
- Venous Thromboembolism *[see Warnings and Precautions (5.3) in the full Prescribing Information]*

Clinical Trial 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.

Unless otherwise specified, the data described in the WARNINGS AND PRECAUTIONS reflect exposure to Lynparza as a single agent in 2901 patients; 2135 patients with exposure to 300 mg twice daily tablet dose including five controlled, randomized, trials (SOLO-1, SOLO-2, OlympiAD, POLO, and PROfound) and to 400 mg twice daily capsule dose in 766 patients in other trials that were pooled to conduct safety analyses. In addition to the 2901 patients, certain subsections in the WARNINGS AND PRECAUTIONS include adverse reactions observed with exposure to Lynparza with abiraterone (n=398) in PROpel. All patients with metastatic castration resistant prostate cancer received concomitant ADT or previous bilateral orchiectomy.

In the pooled safety population, 56% of patients were exposed for 6 months or longer and 28% were exposed for greater than one year in the Lynparza group.

In this pooled safety population, the most common adverse reactions in ≥10% of patients were nausea (60%), fatigue (55%), anemia (36%), vomiting (32%), diarrhea (24%), decreased appetite (22%), headache (16%), dysgeusia (15%), cough (15%), neutropenia (14%), dyspnea (14%), dizziness (12%), dyspepsia (12%), leukopenia (11%), and thrombocytopenia (10%).

HRR Gene-mutated Metastatic Castration-Resistant Prostate Cancer

PROfound

The safety of Lynparza as monotherapy was evaluated in patients with mCRPC and HRR gene mutations who have progressed following prior treatment with enzalutamide or abiraterone in PROfound *[see Clinical Studies (14.7) in the full Prescribing Information]*. This study was a randomized, open-label, multi-center study in which 386 patients received either Lynparza tablets 300 mg orally twice daily (n=256) or investigator's choice of enzalutamide or abiraterone acetate (n=130) until disease progression or unacceptable toxicity. Among patients receiving Lynparza, 62% were exposed for 6 months or longer and 20% were exposed for greater than one year.

Fatal adverse reactions occurred in 4% of patients treated with Lynparza. These included pneumonia (1.2%), cardiopulmonary failure (0.4%), aspiration pneumonia (0.4%), intestinal diverticulum (0.4%), septic shock (0.4%), Budd-Chiari Syndrome (0.4%), sudden death (0.4%), and acute cardiac failure (0.4%).

Serious adverse reactions occurred in 36% of patients receiving Lynparza. The most frequent serious adverse reactions (≥2%) were anemia (9%), pneumonia (4%), pulmonary embolism (2%), fatigue/asthenia (2%), and urinary tract infection (2%).

Dose interruptions due to an adverse reaction of any grade occurred in 45% of patients receiving Lynparza; dose reductions due to an adverse reaction occurred in 22% of Lynparza patients. The most frequent adverse reactions leading to dose interruption of Lynparza were anemia (25%) and thrombocytopenia (6%) and the most frequent adverse reaction leading to reduction of Lynparza was anemia (16%). Discontinuation due to adverse reactions occurred in 18% of Lynparza. The adverse reaction that most frequently led to discontinuation of Lynparza was anemia (7%).

Tables 16 and 17 summarize the adverse reactions and laboratory abnormalities, respectively, in patients in PROfound.

Table 16 Adverse Reactions* Reported in ≥10% of Patients in PROfound

Adverse Reactions	Lynparza tablets n=256		Enzalutamide or abiraterone n=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and lymphatic disorders				
Anemia†	46	21	15	5
Thrombocytopenia‡	12	4	3	0
Gastrointestinal disorders				
Nausea	41	1	19	0
Diarrhea	21	1	7	0
Vomiting	18	2	12	1
General disorders and administration site conditions				
Fatigue (including asthenia)	41	3	32	5
Metabolism and nutrition disorders				
Decreased appetite	30	1	18	1
Respiratory, thoracic, and mediastinal disorders				
Cough	11	0	2	0
Dyspnea	10	2	3	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
† Includes anemia and hemoglobin decreased.
‡ Includes platelet count decreased and thrombocytopenia.

Clinically relevant adverse reactions that occurred in <10% of patients receiving Lynparza were neutropenia (9%), VTE (7%), dizziness (7%), dysgeusia (7%), dyspepsia (7%), headache (6%), pneumonia (5%), stomatitis (5%), rash (4%), blood creatinine increase (4%), pneumonitis (2%), upper abdominal pain (2%), and hypersensitivity (1%).

Table 17 Laboratory Abnormalities Reported in ≥25% of Patients in PROfound

Laboratory Parameter*	Lynparza tablets n†= 256		Enzalutamide or abiraterone n†=130	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	98	13	73	4
Decrease in lymphocytes	62	23	34	13
Decrease in leukocytes	53	4	21	0
Decrease in absolute neutrophil count	34	3	9	0

* Patients were allowed to enter clinical studies with laboratory values of CTCAE Grade 1.
† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Treatment of *BRCA*-mutated Metastatic Castration-Resistant Prostate Cancer in Combination with Abiraterone and Prednisone or Prednisolone

PROpel

The safety of Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of patients in the first-line mCRPC setting was investigated in PROpel *[see Clinical Studies (14.8) in the full Prescribing Information]*. Patients were randomized to receive either Lynparza tablets 300 mg orally twice daily plus abiraterone tablets 1000 mg once daily (Lynparza/abiraterone) (n=398), or placebo plus abiraterone 1000 mg once daily (placebo/abiraterone) (n=396) until disease progression or unacceptable toxicity. Patients in both arms also received either prednisone or prednisolone 5 mg twice daily.

Fatal adverse reactions occurred in 6% of patients, including COVID-19 (3%) and pneumonias (0.5%).

Serious adverse reactions occurred in 39% of patients. Serious adverse reactions reported in > 2% of patients included anemia (6%), COVID-19 (6%), pneumonia (4.5%), pulmonary embolism (3.5%), and urinary tract infection (3%).

Permanent discontinuation of Lynparza due to adverse reactions occurred in 16% of patients treated in the Lynparza with abiraterone arm. The most common adverse reactions which resulted in permanent discontinuation of Lynparza were anemia (4.3%) and pneumonia (1.5%).

Dosage interruption of Lynparza due to adverse reactions occurred in 48% of patients treated in the Lynparza with abiraterone arm. The most common (>2%) adverse reactions requiring dosage interruption of Lynparza were anemia (16%), COVID-19 (6%) fatigue (3.5%), nausea (2.8%), pulmonary embolism (2.3%), and diarrhea (2.3%).

Dose reduction of Lynparza due to adverse reactions occurred in 21% of patients treated in the Lynparza with abiraterone arm. The most common (>2%) adverse reactions requiring dosage reductions of Lynparza were anemia (11%) and fatigue (2.5%).

The most common adverse reactions (≥10%) in patients who received Lynparza/abiraterone were anemia (48%), fatigue (38%), nausea (30%), diarrhea (19%), decreased appetite (16%), lymphopenia (14%), abdominal pain (13%), and dizziness (14%).

Tables 18 and 19 summarize adverse reactions and laboratory abnormalities in PROpel, respectively.

Table 18 Adverse Reactions (≥10%) in Patients Who Received Lynparza (with a Difference of ≥5% Compared to Placebo) in PROpel

Adverse Reactions*	Lynparza/abiraterone n=398		Placebo/abiraterone n=396	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Blood and Lymphatic Disorders				
Anemia†	48	16	18	3.3
Lymphopenia‡	14	5	6	1.8
General Disorders and Administration Site Conditions				
Fatigue (including asthenia)	38	2.3	30	1.5
Gastrointestinal Disorders				
Nausea	30	0.3	14	0.3
Diarrhea	19	1	10	0.3
Abdominal pain$^{\alpha}$	13	0	7	0.5
Metabolism and nutrition disorders				
Decreased appetite	16	1	7	0
Nervous System Disorders				
Dizziness$^{\beta}$	14	0.3	7	0

* Graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.
† Includes anemia, anemia macrocytic, and red blood cell count decreased
‡ Includes lymphocyte count decreased and lymphopenia
$^{\alpha}$ Includes abdominal discomfort, abdominal pain, abdominal pain upper, and abdominal pain lower
$^{\beta}$ Includes dizziness and vertigo.

Clinically relevant adverse reactions that occurred in <10% for patients receiving Lynparza plus abiraterone were headache (9%), VTE (8%), rash (7%), dysgeusia (6%), acute kidney injury (3%), and stomatitis (2.5%).

Table 19 Selected Laboratory Abnormalities Reported in ≥20% of Patients in PROpel

Laboratory Parameter	Lynparza/abiraterone n=398†		Placebo/abiraterone n=396†	
	Grades 1-4 (%)	Grades 3-4 (%)	Grades 1-4 (%)	Grades 3-4 (%)
Decrease in hemoglobin	97	12	81	1.3
Decrease in lymphocytes	70	23	49	11
Decrease in platelets	23	1.2	20	0.3
Decrease in absolute neutrophil count	23	5	6	0

† This number represents the safety population. The derived values in the table are based on the total number of evaluable patients for each laboratory parameter.

Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Lynparza. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Immune System Disorders: Hypersensitivity including angioedema.

Skin and subcutaneous tissue disorders: Erythema nodosum, rash, dermatitis.

DRUG INTERACTIONS

Use with Anticancer Agents

Clinical studies of Lynparza with other myelosuppressive anticancer agents, including DNA damaging agents, indicate a potentiation and prolongation of myelosuppressive toxicity.

Effect of Other Drugs on Lynparza

Strong and Moderate CYP3A Inhibitors

Coadministration of CYP3A inhibitors can increase olaparib concentrations, which may increase the risk for adverse reactions *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Avoid coadministration of strong or moderate CYP3A inhibitors. If the strong or moderate inhibitor must be coadministered, reduce the dose of Lynparza *[see Dosage and Administration (2.4) in the full Prescribing Information]*.

Strong and Moderate CYP3A Inducers

Concomitant use with a strong or moderate CYP3A inducer decreased olaparib exposure, which may reduce Lynparza efficacy *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*. Avoid coadministration of strong or moderate CYP3A inducers.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action *[see Clinical Pharmacology (12.1) in the full Prescribing Information]*, Lynparza can cause fetal harm when administered to a pregnant woman. There are no available data on Lynparza use in pregnant women to inform the drug-associated risk. In an animal reproduction study, the administration of olaparib to pregnant rats during the period of organogenesis caused teratogenicity and embryo-fetal toxicity at exposures below those in patients receiving the recommended human dose of 300 mg twice daily *(see Data)*. Apprise pregnant women of the potential hazard to the fetus and the potential risk for loss of the pregnancy.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. The estimated background risk in the U.S. general population of major birth defects is 2-4%; and the risk for spontaneous abortion is approximately 15-20% in clinically recognized pregnancies.

Data

Animal Data

In a fertility and early embryonic development study in female rats, olaparib was administered orally for 14 days before mating through to Day 6 of pregnancy, which resulted in increased post-implantation loss at a dose level of 15 mg/kg/day (with maternal systemic exposures approximately 7% of the human exposure ($AUC_{0\text{-}24h}$) at the recommended dose).

In an embryo-fetal development study, pregnant rats received oral doses of 0.05 and 0.5 mg/kg/day olaparib during the period of organogenesis. A dose of 0.5 mg/kg/day (with maternal systemic exposures approximately 0.18% of human exposure ($AUC_{0\text{-}24h}$) at the recommended dose) caused embryo-fetal toxicities including increased post-implantation loss and major malformations of the eyes (anophthalmia, microphthalmia), vertebrae/ribs (extra rib or ossification center; fused or absent neural arches, ribs, and sternebrae), skull (fused exoccipital), and diaphragm (hernia). Additional abnormalities or variants included incomplete or absent ossification (vertebrae/sternebrae, ribs, limbs) and other findings in the vertebrae/sternebrae, pelvic girdle, lung, thymus, liver, ureter, and umbilical artery. Some findings noted above in the eyes, ribs, and ureter were observed at a dose of 0.05 mg/kg/day olaparib at lower incidence.

Lactation

Risk Summary

No data are available regarding the presence of olaparib in human milk, or on its effects on the breastfed infant or on milk production. Because of the potential for serious adverse reactions in the breastfed infants from Lynparza, advise a lactating woman not to breastfeed during treatment with Lynparza and for one month after receiving the last dose.

Females and Males of Reproductive Potential

Lynparza can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1) in the full Prescribing Information]*.

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating treatment with Lynparza.

Contraception

Females

Advise females of reproductive potential to use effective contraception during treatment with Lynparza and for 6 months following the last dose.

Males

Based on findings in genetic toxicity and animal reproduction studies, advise male patients with female partners of reproductive potential or who are pregnant to use effective contraception during treatment and for 3 months following the last dose of Lynparza. Advise male patients not to donate sperm during therapy and for 3 months following the last dose of Lynparza *[see Use in Specific Populations (8.1) and Nonclinical Toxicology (13.1) in the full Prescribing Information]*.

Pediatric Use

Safety and effectiveness of Lynparza have not been established in pediatric patients.

Geriatric Use

Of the 2901 patients with advanced solid tumors who received Lynparza as a single agent, 680 (23%) patients were aged ≥65 years, and this included 206 (7%) patients who were aged ≥75 years. Thirteen (0.4%) patients were aged ≥85 years.

Of the 535 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with bevacizumab (PAOLA-1), 204 (38%) patients were aged ≥65 years, and this included 31 (6%) patients who were aged ≥75 years.

Of the 398 patients with advanced solid tumors who received Lynparza tablets 300 mg orally twice daily in combination with abiraterone and prednisone or prednisolone (PROpel), 268 (67%) patients were aged ≥65 years, and this included 95 (24%) patients who were aged ≥75 years.

No overall differences in the safety or effectiveness of Lynparza were observed between these patients and younger patients.

Renal Impairment

No dosage modification is recommended in patients with mild renal impairment (CLcr 51 to 80 mL/min estimated by Cockcroft-Gault). Reduce Lynparza dosage to 200 mg twice daily in patients with moderate renal impairment (CLcr 31 to 50 mL/min) *[see Dosage and Administration (2.5) in the full Prescribing Information]*. There are no data in patients with severe renal impairment or end-stage disease (CLcr ≤30 mL/min) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Hepatic Impairment

No adjustment to the starting dose is required in patients with mild or moderate hepatic impairment (Child-Pugh classification A and B). There are no data in patients with severe hepatic impairment (Child-Pugh classification C) *[see Clinical Pharmacology (12.3) in the full Prescribing Information]*.

Distributed by:
AstraZeneca Pharmaceuticals LP
Wilmington, DE 19850

05/23 US-63563 6/23

AUA TAKE 5

THE TOP 5 AUA HAPPENINGS THIS MONTH!

1

Whether you are a resident who wants to get started as a peer reviewer, a current reviewer interested in honing your approach, or even a seasoned reviewer interested in mentoring new reviewers, check out this free webinar series, featuring editorial leaders from around the urological world. Sponsored by *The Journal of Urology*® and hosted by Dr George Koch, there is something for everyone in this fun and informative webinar series.

AUAnews.net/PeerReview

2

Check out our new Webinar on submitting a successful abstract to the AUA Annual Meeting. Deadline to submit AUA2024 abstracts is November 9.

AUAnet.org/2024

3

It's time to renew your AUA Membership and continue accessing your exclusive member benefits in 2024!

AUAnet.org/Renew

4

Showcase Your Urologic Innovation at the 2024 Innovation Nexus Conference! Apply today for the opportunity to pitch your concept to a panel of seasoned investors and successful innovators during the world's premier urology innovation and research incubator conference.

AUANexus.org/Showcase

5

Incorporating the AUA/SUO Guideline on Advanced Prostate Cancer into Practice. Stream this FREE CME course anytime, anywhere to receive an in-depth update on the most recent clinical guideline for the management of advanced prostate cancer. This course is also available in Spanish and Portuguese!

AUAnet.org/APC

AUANews
October 2023, Volume 28 | Issue 10

PUBLICATIONS DEPARTMENT
American Urological Association
publications@AUAnet.org

PRODUCTION
KnowledgeWorks Global Ltd.
2905 Byrdhill Road, Richmond, VA 23228

ADVERTISING SALES
The Walchli Tauber Group
(443) 512-8899
stephen.tauber@wt-group.com

AUANews is the official newsmagazine of the American Urological Association, located at 1000 Corporate Blvd., Linthicum, MD 21090, and is a function of the AUA Education and Research, Inc. AUANews is published 24 times a year by the American Urological Association. Published free of charge for AUA membership. Annual non-member subscription rates: individual $110 ($155 foreign); institution $135 ($180 foreign); industry $65 ($135 foreign). U.S. POSTMASTER: Send address changes to *AUANews*, American Urological Association, 1000 Corporate Blvd., Linthicum, MD 21090. Library of Congress ISSN: 1088-7350. All correspondence on editorial matters should be addressed to: Executive Editor, American Urological Association, 1000 Corporate Boulevard, Linthicum, MD 21090.

The Legacy of Black Urologists in America

Arthur L. Burnett, MD, MBA
The Johns Hopkins University School of Medicine, Baltimore, Maryland

Wednesday, June 14, 2023, was a historic day in American urology. This date marked a special event honoring living legends in our specialty: Dr Melvin Hollowell, Dr Isaac J. Powell, Dr Ray Littleton, and Dr Conrad Maitland (see Figure). The event, entitled "Onwards and Upwards: The Legacy of Black Urologists in America," was momentous in recognizing these individuals whose achievements in their urological careers are both remarkable and inspirational. Hosted by the Department of Urology at the Henry Ford Health Systems in Detroit, Michigan, the event was staged as a prelude for the upcoming AUA History Exhibit that will celebrate African American urologists, to be held at the organization's national meeting in San Antonio, Texas, in May 2024.

The honorees were the centerpiece of the publicly attended event, which was simultaneously webcast. To begin the program, I was privileged to deliver a Grand Rounds presentation which centered on the progress and value of African American physicians and urologists in the context of organized medicine in the United States. The traditions of organized medicine in America have shaped the medical training and professional practices of Black physicians, both positively and negatively. As well, this institution has been a factor in the underrepresentation of the Black physician workforce and the inequitable conditions of health care delivery in this country.

Dr Linda McIntire, who served superbly as master of ceremonies, then led a high-spirited and enthralling panel discussion, during which the honorees were able to share their extraordinary personal and professional life stories. We learned about the unique challenges and influences they experienced in the course of their urological careers, and how they drew strength and resilience to succeed along the way. The honorees also participated in individual interviews later in the day, which were recorded as audiovisual productions for inclusion in the History Exhibit and for future viewing as museum displays.

It is hardly excessive to establish the relevance of these forefathers, as for other early African American pioneers in urology. In the context of the broad urological community, African American urologists have contributed profoundly to the progress of urology in America. Such figures have well demonstrated their commitment and excellence in diverse ways, perhaps most exceptionally by way of humanitarian service. Within the Black community, they further represent true role models who have paved the way for successors to enter and succeed in urology.

The essence of this festive event is expected to carry over to the History Exhibit of the 2024 AUA national meeting. Featured elements of the exhibit will be topics comprising the past experiences (Legacy), present endeavors (Journey), and future expectations (Destiny) of Black urologists in America. Legacy topics will include the systemic effects of organized medicine; structural racism; early African American pioneers in urology; and the origins of the R. Frank Jones Urological Society (the African American urological society). Journey topics will include African American urologists in nontraditional leadership roles, as premier academicians, and as innovators; African American women in urology; African American researchers in prostate cancer; the African American urological workforce; microaggressions; and social determinants of health. Destiny topics will include purposes of mentorship and leadership; curriculum applications toward diversity, equity, and inclusion; and actionable interventions to improve the African American urology workforce and address health care disparities. The topics will be crafted into text panels for the exhibit and expanded as enduring chapters of an historical book.

Figure. Participants in the Legacy Event, shown left to right, are Linda McIntire, MD, Melvin Hollowell, MD, Ray Littleton, MD, Isaac J. Powell, MD, Conrad Maitland, MD, and Arthur Burnett, MD.

> "In the context of the broad urological community, African American urologists have contributed profoundly to the progress of urology in America. Such figures have well demonstrated their commitment and excellence in diverse ways, perhaps most exceptionally by way of humanitarian service."

> "As a theme celebrating African American urologists, the 2024 AUA History Exhibit importantly reflects the foresight of the AUA. By this, the organization timely recognizes the historical contributions of African American urologists whose influences are often underrecognized."

As a theme celebrating African American urologists, the 2024 AUA History Exhibit importantly reflects the foresight of the AUA. By this, the organization timely recognizes the historical contributions of African American urologists whose influences are often underrecognized. It also reveals an understanding that the richness of the history of urology in America culminates from and rests on the accomplishments of urologists representing diverse backgrounds and origins.

The success of both the legacy event and the exhibit owes enormously to many individuals who have volunteered graciously for this purpose. I extend much appreciation to the curator team, consisting of Arthur L. Burnett, Pamela Coleman, Tracy Downs, Linda McIntire, and Bart Ragon. I am thankful for the rather large group of contributors of text panels and associated book chapters. I also thank the AUA History Committee and the museum team of the William P. Didusch Center for Urologic History for their service. ■

CLINICAL TRIALS

Improving Clinical Trials With Implementation Science

Kristian Stensland, MD, MPH, MS
University of Michigan, Ann Arbor

Ted Skolarus, MD, MPH
University of Chicago, Illinois

Clinical Trials: Beyond the Plenary Stage

The thought of engaging with clinical trials can be daunting. It often seems trials are meant only for AUA plenary sessions and high-impact journal publications, but clinical trials should be for everyone. As we look to improve care for our patients, we should be aiming to increase the availability and accessibility of clinical trials by making clinical trials easier to run and participate in for all patients, providers, and practices, for multiple reasons.

Clinical trials have massive benefits to science, society, and individuals. For some conditions like cancer, clinical trials can be considered standard of care. For example, the National Comprehensive Cancer Network clearly states in all its clinical practice guidelines "the best management for any patient with cancer is in a clinical trial."[1] But historically clinical trials have been difficult to implement and improve, creating hurdles preventing patient and provider participation, with some groups more impacted than others. The resulting gaps in clinical knowledge and equity have real implications for patients and our practice. We must find ways to overcome these barriers to make clinical trials more efficient and equitable.

There has been an increasing effort to address these issues and engage urologists and patients in clinical trials. Sessions at our AUA and Society of Urologic Oncology meetings focused on engaging with clinical trials are a good start. However, expanding our approach to how we design and implement trials–that is, the science of clinical trials–holds promise as an opportunity to improve clinical trials themselves. This article will give an overview of how we are applying implementation science concepts to facilitate this process, and ultimately aim to make it easier for all to engage in clinical trials.

Is There Really a Problem With Clinical Trials Now?

In addition to anecdotal difficulties, clinical trials suffer from high documented failure rates. Urologic oncology trials struggle with both enrollment and completion, with 1 in 6 trials failing to reach the primary end point, mostly due to poor enrollment, and one-third of even "completed" trials failing to get close to anticipated end points.[2,3] Similar issues are faced by other urological subspecialties, and in other cancer types.[4,5] Thousands of patients are enrolled in trials that ultimately fall short, with loss of the promised benefits to science promised as part of the trials consent process. Further, these trial failures and inefficiencies contribute to, and waste part of, the over $200 billion spent annually on clinical trials.[6]

Considering these shortcomings, the extant science of trial improvement is lacking. For example, existing strategies to improve trial enrollment have limited evidence, small effect sizes, and uncertain methods of scaling for broad application.[7] Further, these approaches are generally not theory informed, making it difficult to compare approaches and adapt existing methods to more efficiently develop clinical trials science and generalizability of findings.

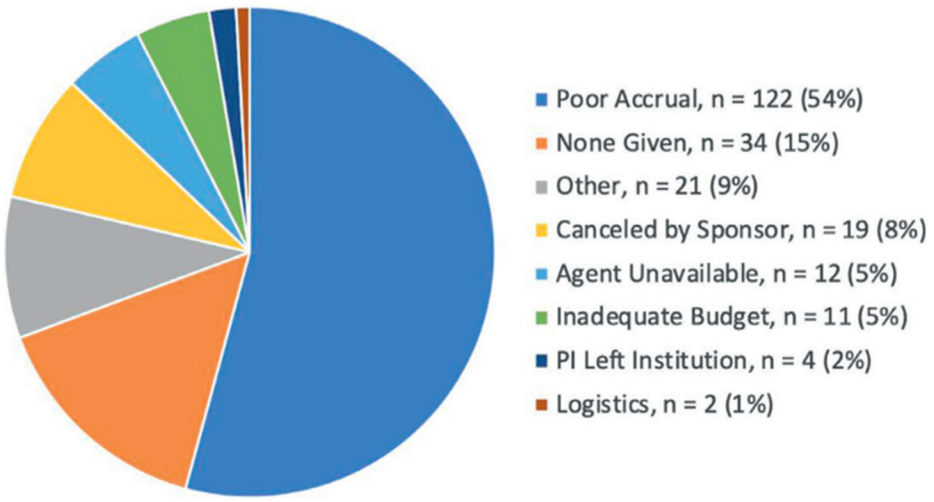


Figure 1. Reasons for urologic oncology trial termination. PI indicates principal investigator. Reprinted with permission from Stensland KD et al. *Urol Oncol.* 2021;39:154-160.[3]

Interfacing Implementation Science and Trial Improvement

To address these problems, we have proposed using implementation science to improve clinical trials by considering clinical trials per se as evidence-based interventions.[8] Similar to other evidence-based interventions, like smoking cessation or vaccines, clinical trials have huge benefits but often suffer from suboptimal implementation. By applying techniques including rigorous context assessment before and during trial implementation, implementation outcome evaluation for a given trial, and targeted intervention development to improve trial implementation, we can build new trial improvement science on the platform of existing implementation and behavior change science.

A major advantage of this approach is that it emphasizes the importance of making trials easier (ie, more feasible and acceptable) for physicians and other providers in addition to patients. While improving the scientific value of trials is important, ensuring trials can be delivered effectively and applied in real-world settings is critical and well supported by the principles of implementation science. For example, barriers to urological cancer trials in rural communities have been explored using these approaches.[9] In our own work, we have incorporated qualitative methods to ensure our concepts and approaches are acceptable, applicable, and well

→ Continued on page 9

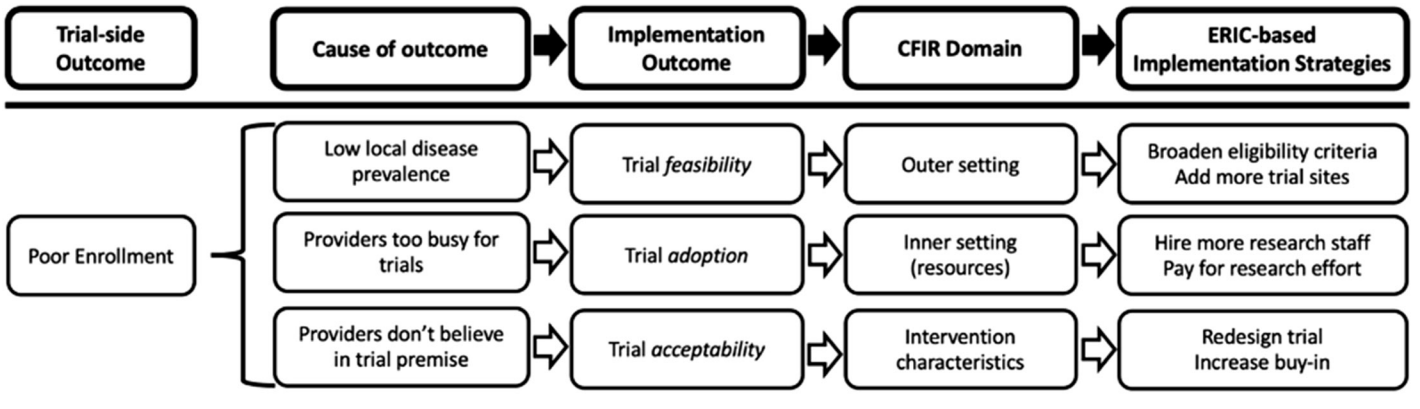


Figure 2. Adapted Implementation Research Logic Model applied to the clinical trial-side outcome of poor enrollment. CFIR indicates Consolidated Framework for Implementation Research; ERIC, Expert Recommendation for Implementing Change. Reprinted with permission from Stensland KD et al. *Implement Sci Commun.* 2022;3(1):109.[11]

IMPROVING CLINICAL TRIALS WITH IMPLEMENTATION SCIENCE

→ Continued from page 8

understood by physicians and other stakeholders.[10]

Applying the Science of Implementation to the Trials Context

The basic implementation science approach is to define outcomes to evaluate how well an evidence-based practice is being implemented, identify barriers and facilitators to the uptake of the practice, and then design implementation strategies to overcome the identified barriers. In other words: why isn't something being used, how do we measure how and why people aren't using it, and what can we do to get people to use it?

We adapted existing frameworks to structure this approach specifically for clinical trials.[11] We used the Consolidated Framework for Implementation Research to identify barriers and facilitators to trial uptake, adapted Proctor's implementation outcomes to evaluate how well trials are being implemented, and linked these to implementation strategies from the Expert Recommendation for Implementing Change compilation, all through an adaptation of the Implementation Research Logic Model.[12-15] This process allows for linking root causes of problems to targeted improvement interventions with a higher chance of working to improve problems like poor enrollment or representation in trials. Laying this approach out also could explain why some trial improvement interventions are unsuccessful: they target the wrong problem.

> "We used the Consolidated Framework for Implementation Research to identify barriers and facilitators to trial uptake, adapted Proctor's implementation outcomes to evaluate how well trials are being implemented, and linked these to implementation strategies from the Expert Recommendation for Implementing Change compilation, all through an adaptation of the Implementation Research Logic Model."

For example, a prostate cancer trial struggling to enroll patients has multiple options for improvement. Hiring more research staff or developing an electronic medical record system alert could enhance the penetration to eligible prostate cancer patients. However, if there are only 10 eligible prostate cancer patients presenting to a clinic every year, there is no amount of research staff hiring that can increase enrollment to 100 patients annually. Instead, in this case identifying new trial sites would be a more rational enrollment improvement intervention.

Similarly, this approach can highlight new research directions. Continuing the question of available eligible patients (ie, trial feasibility), we developed a tool to identify areas with many incident prostate cancer cases but few available trials, as we found trials were more likely to be successful in areas of higher cancer incidence.[16] This tool, or similar analyses, could be helpful in selecting future prostate cancer clinical trial sites, especially for trials struggling with enrollment specifically due to low local prostate cancer incidence or competing trials.

The Path Forward: A Trail to Trials

Moving forward, we hope to expand efforts to improve clinical trials, and reduce barriers to trial implementation and participation through feasible, acceptable interventions. We encourage participation in clinical trials when possible, and to consider applying implementation science approaches to make and measure outcomes of targeted improvements to ongoing trials adding to trial success and generalizable knowledge. ■

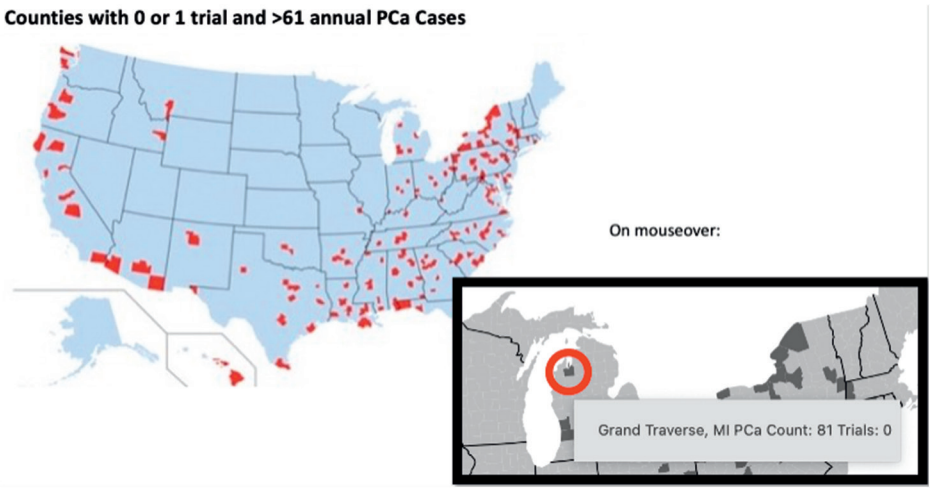


Figure 3. Tool identifying areas with many prostate cancer (PCa) cases but few clinical trials. Adapted with permission from Stensland et al. *Contemp Clin Trials*. 2021;111:106600.[16]

> "We encourage participation in clinical trials when possible, and to consider applying implementation science approaches to make and measure outcomes of targeted improvements to ongoing trials adding to trial success and generalizable knowledge."

1. National Comprehensive Cancer Network. *NCCN Clinical Practice Guidelines in Oncology. Version 3.2023–Bladder Cancer.* 2023. https://www.nccn.org/guidelines
2. Stensland K, Kaffenberger S, Canes D, et al. Assessing genitourinary cancer clinical trial accrual sufficiency using archived trial data. *JCO Clin. Cancer Inform.* 2020;4:614-622.
3. Stensland KD, DePorto K, Ryan J, et al. Estimating the rate and reasons of clinical trial failure in urologic oncology. *Urol Oncol.* 2021;39:154-160.
4. Bandari J, Theisen KM, Maganty A, et al. Clinical trials in urology: predictors of successes and failures. *J Urol.* 2020;204(4):805-810.
5. Stensland KD, McBride RB, Latif A, et al. Adult cancer clinical trials that fail to complete: an epidemic?. *J Natl Cancer Inst.* 2014;106(9): dju229.
6. Grand View Research. *Clinical Trials Market Size, Share & Trends Analysis Report by Phase (Phase I, Phase II, Phase III, Phase IV), by Study Design (Interventional, Observational, Expanded Access), by Indication, by Region, and Segment Forecasts, 2021-2028.* 2023. Accessed July 30, 2021. https://www.grandviewresearch.com/industry-analysis/global-clinical-trials-market
7. Treweek S, Pitkethly M, Cook J, et al. Strategies to improve recruitment to randomised trials. *Cochrane Database Syst Rev.* 2018;2:MR000013.
8. Stensland KD, Damschroder LJ, Sales AE, Schott AF, Skolarus TA. Envisioning clinical trials as complex interventions. *Cancer.* 2022;128(17):3145-3151.
9. Ellis SD, Geana M, Mackay CB, Moon DJ, Gills J, Zganjar A. Science in the heartland: exploring determinants of offering cancer clinical trials in rural-serving community urology practices. *Urol Oncol.* 2019;37(8):529.e9-529.e18.
10. Stensland KD, Sales AE, Vedapudi VK, Damschroder LJ, Skolarus TA. Exploring implementation outcomes in the clinical trial context: a qualitative study of physician trial stakeholders. *Trials.* 2023;24(1):297.
11. Stensland KD, Sales AE, Damschroder LJ, Skolarus TA. Applying implementation frameworks to the clinical trial context. *Implement Sci Commun.* 2022;3(1):109.
12. Proctor E, Silmere H, Raghavan R, Hovmand P, Aarons G, Bunger A. Outcomes for implementation research: conceptual distinctions, measurement challenges, and research agenda. *Adm Policy Ment Health.* 2011;38(2):65-76.
13. Damschroder LJ, Aron DC, Keith RE, et al. Fostering implementation of health services research findings into practice: a consolidated framework for advancing implementation science. *Implement Sci.* 2009;4(1):50.
14. Powell BJ, Waltz TJ, Chinman MJ, et al. A refined compilation of implementation strategies: results from the Expert Recommendations for Implementing Change (ERIC) project. *Implement Sci.* 2015;10:21.
15. Smith JD, Li DH, Rafferty MR. The Implementation Research Logic Model: a method for planning, executing, reporting, and synthesizing implementation projects. *Implement Sci.* 2020;15:84.
16. Stensland KD, Kaffenberger SD, George AK, Morgan TM, Miller DC, Salami SS. Prostate cancer clinical trial completion: the role of geography. *Contemp Clin Trials.* 2021;111:106600.

CLINICAL TRIALS

PARTIAL, a Randomized Controlled Trial Comparing Pelvic Fascia-sparing and Conventional Radical Prostatectomy

Mary Oakley Strasser, MD, MBA
New York-Presbyterian/Weill Cornell Medicine, New York

Andrew Vickers, PhD
Memorial Sloan Kettering Cancer Center, New York, New York

Edward M. Schaefer, MD, PhD
Northwestern University, Chicago, Illinois

Mohamad Allaf, MD
Johns Hopkins University, Baltimore, Maryland

Douglas Scherr, MD
New York-Presbyterian/Weill Cornell Medicine, New York

Keith Kowalczyk, MD
Georgetown University, Washington, DC

Jim C. Hu, MD, MPH
New York-Presbyterian/Weill Cornell Medicine, New York

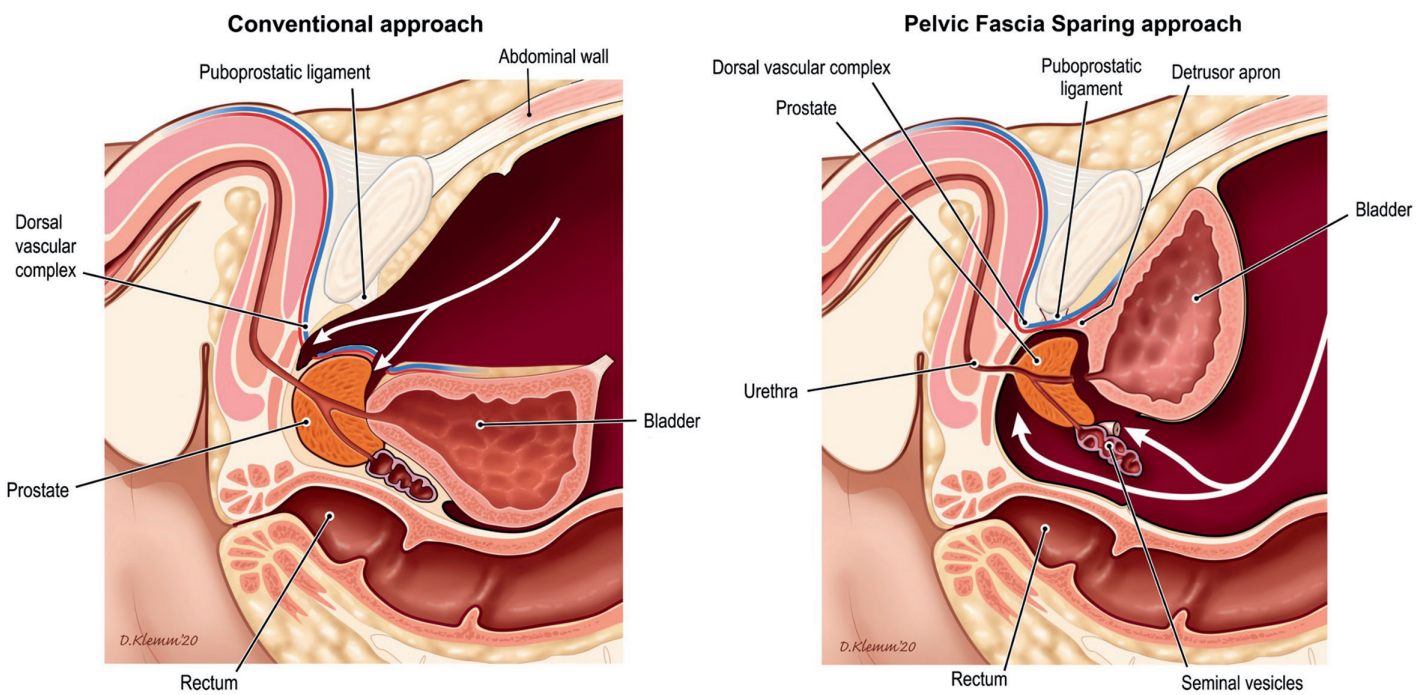


Figure 1. Pelvic fascia-sparing radical prostatectomy (right) leaves pelvic fascia, comprised of puboprostatic ligament and detrusor apron, and dorsal vascular complex intact vs conventional radical prostatectomy (left). Anterior approach (white arrows) to radical prostatectomy dissects the bladder from the anterior abdominal wall and causes inguinal hernia risk, which is avoided with posterior approach of pelvic fascia-sparing radical prostatectomy.

More than 60,000 men undergo robotic-assisted radical prostatectomy (RP) each year in the United States as treatment for localized prostate cancer.[1] The long-term risks of RP include life-long urinary incontinence and erectile dysfunction, as well as penile shortening and deformity (Peyronie's disease) and inguinal hernias. The pelvic fascia-sparing approach to radical robotic-assisted prostatectomy is a novel surgical technique first described in 2010.[2] This posterior approach better preserves native anatomy, including the dorsal vascular complex, nerves, and fascial support structures overlying the anterior prostate, which are severed and removed during conventional RP (Figure 1). Retrospective studies demonstrated lower rates of penile shortening and deformity, attributable, perhaps, to maintaining arterial flow to the penis by preserving the dorsal vascular complex; lower rates of inguinal hernias, attributable to the posterior surgical approach behind the bladder (instead of separating it from the abdominal wall); and more rapid return of urinary continence, attributable to preservation of pelvic fascial support structures.[3] An anterior approach to pelvic fascia-sparing has also been described.[4] However, preserving the tissue overlying the anterior prostate may risk more positive surgical margins and worse cancer control, especially for men with anterior tumor locations, which is more common in African American patients.[5]

Currently, evidence quality for pelvic fascia-sparing radical prostatectomy (PFS-RP) is low-grade and largely retrospective. Our published, prospective, parallel comparison of 70 PFS-RPs vs 70 RPs demonstrated that PFS-RP is associated with a lower risk of: urinary incontinence (2% vs 19%); penile shortening (39% vs 67%; $P = .02$); penile deformity (0% vs 9%; $P = .05$); and inguinal hernia adverse events requiring surgical repair (0% vs 16%; $P < .01$). PFS-RPs had similar risk for ED, positive surgical margins, and 12-month prostate-specific antigen recurrence.[6] Adequately powered, multisurgeon, multicenter randomized controlled trials (RCT) with longitudinal follow-up are needed to compare the functional and oncologic outcomes of RP and PFS-RP. PFS-RPs currently account for <10% of prostate cancer surgeries, therefore the timing for a multicenter RCT is ideal to evaluate outcomes prior to widespread adoption without sound evidence.[7]

Historically, standards of surgical care have been accepted without rigorous evidence. While medical and radiation oncologists conduct RCTs comparing various radiotherapy and chemotherapy regimens to iteratively improve outcomes, in surgical oncology, improvements in technique are typically developed by individual surgeons and published as retrospective case series. Unfortunately, randomized comparisons of surgical approaches are challenging to conduct for a variety of reasons. Accrual is often slow and difficult since many patients decline to participate in RCTs, preferring to choose their treatment modalities or finding RCT consents confusing or distressing. Surgeon equipoise may also be difficult to attain, and there may be significant technical variation within a specific technique being compared in contrast to a standard dose of chemotherapy or intensity of radiotherapy. Slow accrual has plagued at least 11 RCTs of novel interventions for prostate cancer that were forced to close prematurely, for example accruing 56 out of a targeted 1,980 patients.[8] High trial costs, inadequate research infrastructure for data collection and follow-up, scarcity of funding, and need for large sample sizes are also significant barriers to surgical RCTs.[9] In particular, surgical RCTs intended to demonstrate superiority for health-related quality of life (HRQoL) and noninferiority for oncologic outcomes must be powered and large enough to capture small differences in recurrence

→ Continued on page 11

PARTIAL, A RANDOMIZED CONTROLLED TRIAL COMPARING PELVIC FASCIA-SPARING

→ Continued from page 10

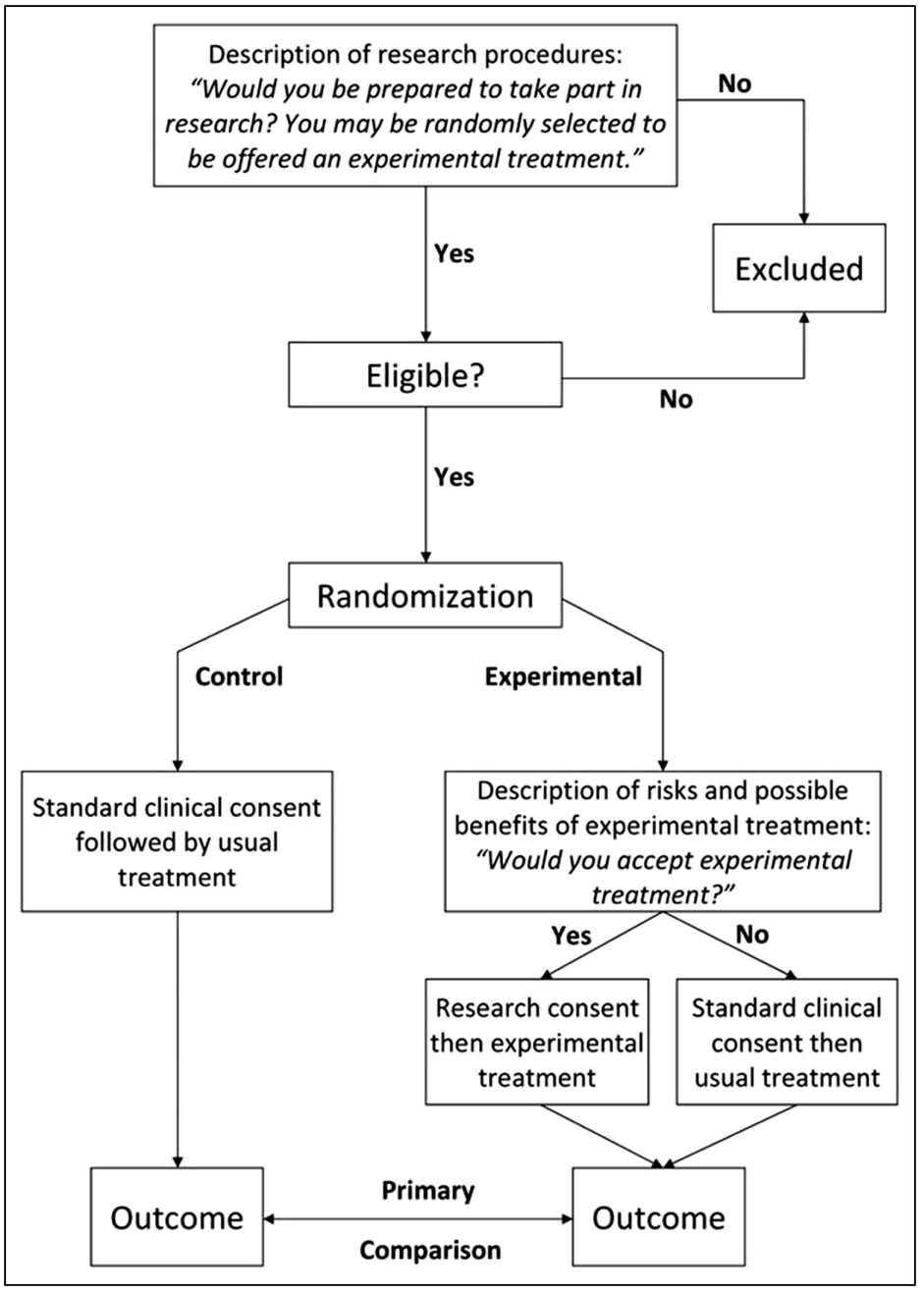


Figure 2. Schema of 2-stage consent process.

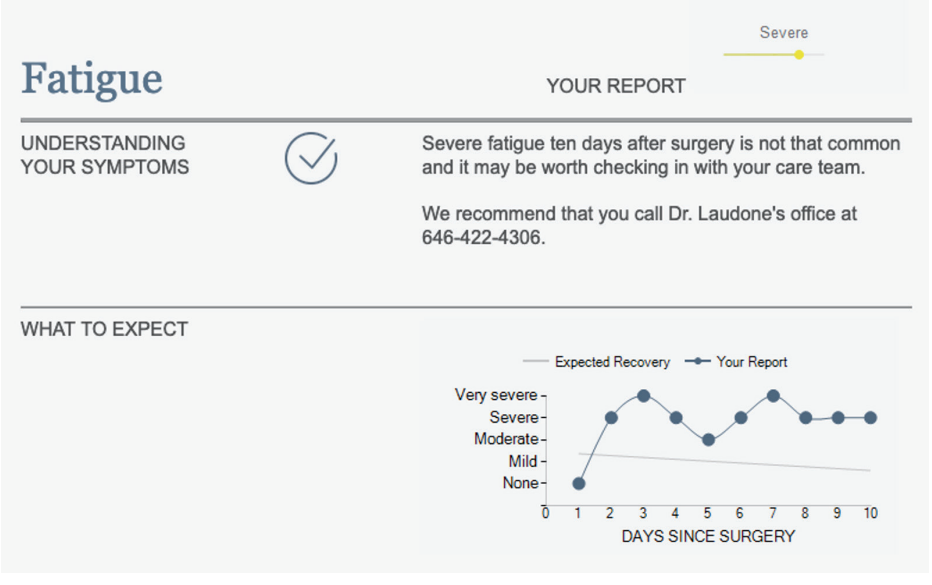


Figure 3. Sample Symptom Tracking and Reporting system screenshot showing a red-flag symptom after surgery.

rates that would offset moderate functional improvements.

We applied 2 novel approaches to facilitating this large RCT

Table. Overview of the 24-Month Study Calendar

Study calendar							
	Day -365 to 0	Day 0[e]	Day 7[e]	Day 30[e]	Day 180[e]	Day 360[e]	Day 720[e]
Eligibility	X[a]						
Informed consent	X						
Demographics	X						
Medical history[b, e]	X						
Physical exam[c, e]	X						
Randomization	X						
Radical prostatectomy		X					
HRQoL[e]	X			X	X	X	X
Decision regret							X
Assessment of adverse events[d, e]		X	X	X	X	X	X
PSA[e]	X				X	X	X

Abbreviations: HRQoL, health-related quality of life; MRI, magnetic resonance imaging; PSA, prostate-specific antigen.
[a]To be performed prior to informed consent.
[b]Medical comorbidities, MRI features (prostate volume and clinical stage), PSA, biopsy characteristics (grade group and tumor volume).
[c]Height and weight, evidence of unilateral or bilateral inguinal hernia(s), captured as part of routine medical practice.
[d]Assessed by operative note and study participant questionnaires. Events are graded using CTCAE v5.0.
[e]Are not research requirements; are part of standard of care. May vary postoperatively by clinical judgment or by months.

to increase accrual and decrease costs. First, we are using a 2-stage consent process, which aims to reduce information overload and patient decisional burden (Figure 2). This also reduces investigator time burden, as the second consent is only obtained for patients randomized to the intervention arm. Prior studies have demonstrated that this facilitates RCT rapid accrual and maintains patient understanding of trial consent.[10] Indeed, a RCT using the 2-stage consent by Vickers et al is ongoing at Memorial Sloan Kettering and New York Presbyterian Weill Cornell on prostate biopsy and radical prostatectomy approaches with >95% enrollment rate and few patients refusing the second consent. Quality of Informed Consent scores have been almost identical to normative data in the literature at 76.0 (95% CI 74.4, 77.5), and consenting professionals report motivation to approach patients for consent has remained high as the process is easier with less anxiety for the patient.

Second, we are incentivizing patient self-reporting through a web portal, Symptom Tracking and Reporting system (STAR), which increases compliance with questionnaire completion and dramatically reduces costs of data collection. This web portal is used by patients as part of routine care and offers individualized clinical and prognostic information based on their responses, for example showing their progress over time and alerting "red flag" symptoms, thereby providing incentive to complete the surveys (Figure 3). By using STAR in routine care, research patients can be confident that their trial participation will not involve additional tests, clinic visits, questionnaires, or appointments. This system is already in use, with over 10,000 RP patients completing outcome questionnaires with a compliance rate at 1-year HRQoL of 75% (without incentives or followup from research staff).

The PARTIAL trial (Clinical Trials.gov, NCT05155501) is applying these innovative methodical advances in a multi-institutional surgical RCT evaluating the functional

→ Continued on page 12

PARTIAL, A RANDOMIZED CONTROLLED TRIAL COMPARING PELVIC FASCIA-SPARING

→ Continued from page 11

and oncologic outcomes of PFS-RP. The target enrollment for the PARTIAL trial is 600 patients over 3 years to achieve 85% power. Men aged 40-85 without a history of previous major pelvic surgery, radiotherapy, or prior focal therapy for prostate cancer are included, and the study duration is 24 months (see Table). The primary outcome is cancer control, and secondary outcomes are HRQoL (sexual and urinary function), decision regret, and adverse events.

Recruitment is ongoing at Northwestern, Johns Hopkins, Georgetown, and Weill Cornell, and we hypothesize that PFS-RP will have similar cancer control and sexual function outcomes with significantly improved urinary function, lower risk of penile shortening/deformity, and lower rates of inguinal hernia compared to conventional RP. In summary, the 2-stage consent and STAR system overcome traditional barriers and expenses to conducting RCTs and have been critical to early enrollment for PARTIAL and other surgical trials. ■

1. Chen J, Oromendia C, Halpern J, Ballman K. National trends in management of localized prostate cancer: a population based analysis 2004-2013. *Prostate.* 2018;78(7):512-520.
2. Lim SK, Kim KH, Shin TY, et al. Retzius-sparing robot-assisted laparoscopic radical prostatectomy: combining the best of retropubic and perineal approaches. *BJU Int.* 2014;114(2):236-244.
3. Huri E. Novel anatomical identification of nerve-sparing radical prostatectomy: fascial-sparing radical prostatectomy. *Prostate Int.* 2014;2(1):1-7.
4. Wagaskar VG, Mittal A, Sobotka S, et al. Hood technique for robotic radical prostatectomy–preserving periurethral anatomical structures in the space of Retzius and sparing the pouch of Douglas, enabling early return of continence without compromising surgical margins. *Eur Urol.* 2021;80(2):213-221.
5. Sundi D, Kryvenko O, Carter H, Ross A, Epstein J Schaeffer E. Pathological examination of radical prostatectomy specimens in men with very low risk disease at biopsy reveals distinct zonal distribution of cancer in black American men. *J Urol.* 2014;191(1):60-67.
6. Egan J, Marhamati S, Carvalho FL, et al. Retzius-sparing robot-assisted prostatectomy leads to durable improvement in urinary function and quality of life versus standard robot-assisted radical prostatectomy without compromise on oncologic efficacy: single-surgeon series and step-by-step guide. *Eur Urol.* 2021;79(6):839-857.
7. Kowalczyk KJ. Accessed August 17, 2023. https://twitter.com/KeithKow/status/1237406461686435842?s=20
8. Ahmed HU, Berge V, Bottomley D, et al. Can we deliver randomized trials of focal therapy in prostate cancer?. *Nat Rev Clin Oncol.* 2014;11(8):482-491.
9. McCulloch P, Taylor I, Sasako M, Lovett B, Griffin D. Randomised trials in surgery: problems and possible solutions. *BMJ.* 2002;324(7351):1448-1451.
10. Vickers A, Vertosick E, Carlsson S, Ehdaie B, Kim S. Patient accrual and understanding of informed consent in a two-stage consent design. *Clin Trials.* 2021;18(3):377-382.

CLINICAL TRIALS

Leveraging Quality Improvement Networks for Clinical Trials: Making BLUES and SOUL MUSIC

Russell E.N. Becker, MD, PhD
University of Michigan, Ann Arbor

Stephanie Daignault-Newton, MS
University of Michigan, Ann Arbor

Elaina Shoemaker, MS
University of Michigan, Ann Arbor

Mahmoud Hijazi, BA
William Beaumont School of Medicine, Oakland University, Rochester, Michigan

Andrew M. Higgins, MD
University of Michigan, Ann Arbor

Golena Fernandez Moncaleano, MD
University of Michigan, Ann Arbor

Todd Morgan, MD
University of Michigan, Ann Arbor

Anna Johnson, MS
University of Michigan, Ann Arbor

Susan Linsell, MHSA
University of Michigan, Ann Arbor

Cathie Spino, ScD
University of Michigan, Ann Arbor

Noelle Carlozzi, PhD
University of Michigan, Ann Arbor

William J. Meurer, MD, MS
University of Michigan, Ann Arbor

Anne Sales, PhD, RN
Sinclair School of Nursing, University of Missouri, Columbia

Casey A. Dauw, MD
University of Michigan, Ann Arbor

Khurshid R. Ghani, MBChB, MS, FRCS
University of Michigan, Ann Arbor

Ureteroscopy is the most common procedure for the surgical management of nephrolithiasis in the United States.[1] At the conclusion of ureteroscopic stone treatment, the urologist must decide whether or not to place a ureteral stent. AUA guidelines recommend stent omission for uncomplicated cases (ie, no ureteric injury, no ureteral stricture, normal contralateral kidney, normal renal function, and no planned secondary ureteroscopy procedure).[2] Despite this, studies reveal urologists continue to place stents in approximately 80% of all patients after ureteroscopy.[3-5] There is also tremendous variation in this practice. In an analysis of 140 urologists in Michigan, while the average stenting rate was 74%, it ranged from 10% to 100%.[4]

A stent ensures ureteral patency and drainage of the renal unit and can offer security for the surgeon and patient. However, the decision on whether to place a stent can have health-related quality of life consequences for patients. Ureteral stents lead to postoperative pain and urinary symptoms in the majority of patients.[6] Some will seek additional care for these symptoms, which can drive unplanned health care utilization, such as electronic medical record messages, telephone encounters, and clinic or emergency department visits.[4,7] Thus, the urologist must strike the appropriate balance in each case between the promise of safety offered by stenting, and the improved patient experience offered by stent omission.[8]

> "Ureteral stents lead to postoperative pain and urinary symptoms in the majority of patients."

Unfortunately, we have poor evidence on which to base these decisions. A recent Cochrane review of the comparative effectiveness of stent placement vs omission after uncomplicated ureteroscopy (16 trials consisting of 1,970 participants), found a trend for stenting to reduce the number of unplanned visits.[9] However, studies were limited by low confidence of evidence, performance bias, inconsistency, and imprecision, prohibiting clear interpretation of these results. The review concluded that higher-quality and sufficiently large trials are needed to better inform decision-making. Toward that end, the Michigan Urological Surgery Improvement Collaborative (MUSIC) recently launched the Stent Omission after Ureteroscopy and Lithotripsy (SOUL) trial, which is funded by the Patient-Centered Outcomes Research Institute.

Established in 2011, MUSIC is a collaborative quality improvement initiative funded by Blue Cross Blue Shield of Michigan consisting of 46 urology practices in Michigan, representing urologists, advanced practice providers, patient advocates, and other stakeholders. Additional practices outside Michigan have now joined MUSIC, and include the University of North Carolina, the Montefiore Medical Center, New York, and the University of Florida. Members regularly engage with each other through periodic workshops, webinars, ongoing quality improvement initiatives, quality metric-based payer reimbursement incentives, and triannual collaborative-wide symposia. Recently, this unique framework has shown advantages in conducting

→ Continued on page 13

LEVERAGING QUALITY IMPROVEMENT NETWORKS FOR CLINICAL TRIALS

→ Continued from page 12

several randomized clinical trials (RCTs) within MUSIC.

The first RCT in MUSIC was the Genomics in Michigan Impacting Observation or Radiation (G-MINOR) trial (funded by GenomeDx; NCT02783950), using the Decipher classifier to help predict which patients undergoing radical prostatectomy may benefit from postoperative radiotherapy. The second was the Genomics in Michigan to AdJust Outcomes in Prostate canceR (G-MAJOR) trial (NIH funded; NCT04396808), which seeks to determine the clinical impact of gene expression classifier testing in patients with newly diagnosed favorable risk prostate cancer.

Key advantages for conducting RCTs in MUSIC include the preexisting infrastructure, data registry, and community engagement to promote sustained participation. Importantly, the broad variety of participating practices and urologists provides a more accurate representation of the diversity of urologic care across our health care system. MUSIC is able to bring trials to large and small centers, academic or private practices, and urban and rural communities, which is important for generalization. Although this can make the logistics of implementation challenging, it also holds tremendous potential to capture the real-world forces that shape practice. We have found this be helpful in the conduct of our third RCT, assessing silicone vs polyurethane ureteral stents for ureteroscopy on patient-reported outcomes, the Better Lithotripsy and Ureteroscopy Evaluation of Stenting (BLUES) trial (funded by Coloplast; NCT05026710).

Our most recent trial, SOUL MUSIC (NCT05866081) is a clinical trial of stent omission vs stent placement following uncomplicated ureteroscopy and lithotripsy that aims to address shortcomings of prior trials by assessing patient-reported outcomes, collecting standardized health care–related outcomes, and assessing provider and patient attitudes regarding stenting to inform implementation strategies. Because the trial was designed with the input of

→ Continued on page 14

> “MUSIC is able to bring trials to large and small centers, academic or private practices, and urban and rural communities, which is important for generalization. Although this can make the logistics of implementation challenging, it also holds tremendous potential to capture the real-world forces that shape practice.”

LEVERAGING QUALITY IMPROVEMENT NETWORKS FOR CLINICAL TRIALS

→ Continued from page 13

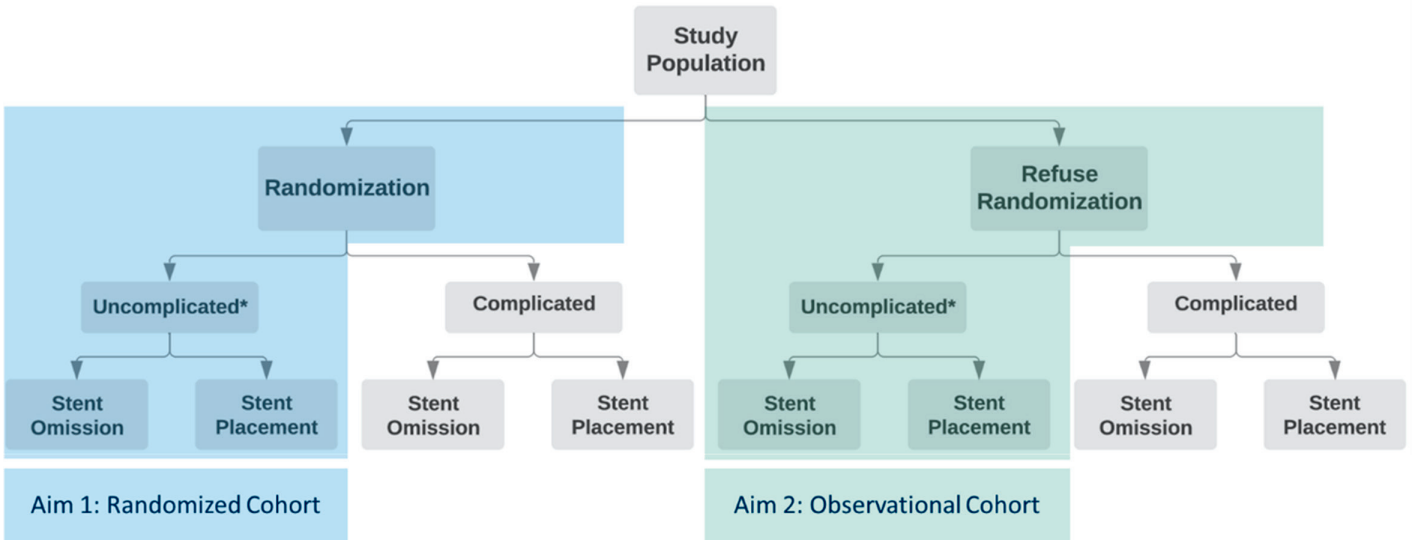


Figure. Schematic of the SOUL MUSIC trial, assessing outcomes between stent placement vs omission after uncomplicated ureteroscopy, demonstrating the combined randomized and observational study design.

> "Because the trial was designed with the input of patients, it has a unique combined randomized and observational design, the latter for patients who decline randomization."

patients, it has a unique combined randomized and observational design, the latter for patients who decline randomization (see Figure). The 2 coprimary outcomes are Patient Reported Outcomes Measurement Information System Pain Interference at postoperative day 7-10, and unplanned health care utilization within 30 days. Adult patients with stones ≤1 cm in size in either the ureter or kidney, who are not prestented, are eligible. We plan to recruit approximately 800 patients over 2 years, with one-third being randomized, across 14 centers in the MUSIC network (see Table). The study also includes a qualitative arm, consisting of semistructured interviews with both patients and urologists. These conversations will assess existing opinions and preferences around stenting and stent omission and characterize the barriers and facilitators to stent omission.

SOUL leverages the existing interpersonal and professional networks within MUSIC to strengthen and support the trial's success. As a multicenter prospective trial, the success of the SOUL study will depend on sustained engagement and participation by investigators and site champions across a broad spectrum of urologic practices throughout Michigan and beyond. This will be achieved in part by utilizing the existing sense of community and regular cadence of both in-person and virtual meetings between members of MUSIC. Investigators and other key personnel from multiple trial performance sites can be refreshed about key aspects of the study, provided with progress updates, and recognized for their contributions at collaborative-organized functions. Similarly, issues that may arise at individual performance sites can be efficiently resolved and solutions quickly disseminated to the broader group through existing networks.

In summary, quality improvement networks are uniquely positioned to support clinical trials that address relevant and impactful knowledge gaps, through their existing infrastructure and community, as well as inherent practice variation. These aspects can strengthen engagement by different centers, and make the trials conducted pragmatic and applicable to diverse real-world practice, with the goal to benefit patients and our field. ■

Table. Participating Sites and Clinical Champions for SOUL MUSIC Trial

SOUL Trial participating center	Clinical champion
St Joseph Mercy, Chelsea Hospital, MI	Dr Andre C. King
Integrated Health Associates (IHA), Ypsilanti, MI	Dr Eduardo Kleer
Ascension Providence (Comprehensive Urology), Novi, MI	Dr David Wenzler
Corewell Health (Comprehensive Urology and Michigan Institute of Urology), Royal Oak, MI	Dr Mohammad Jafri Dr Brian Seifman
Henry Ford Vattikuti Institute of Urology, Detroit, MI	Dr David Leavitt
Michigan Medicine, Ann Arbor	Dr Khurshid Ghani
Sparrow Medical Group, Lansing, MI	Dr Richard Sarle
MyMichigan Health, Midland	Dr Karla Witzke
Michigan State Urology, Lansing	Dr Arya Khatiwoda
Cadillac Urology, Munson Healthcare, Cadillac, MI	Dr Laris Galejs
Montefiore Medical Center, Bronx, NY	Dr Dima Raskolnikov
University of North Carolina, Chapel Hill	Dr Ray Tan, Dr David Friedlander
Mount Sinai Medical Center, New York, NY	Dr Mantu Gupta
University of Florida, Gainsville	Dr John Michael DiBianco

1. Oberlin DT, Flum AS, Bachrach L, Matulewicz RS, Flury SC. Contemporary surgical trends in the management of upper tract calculi. *J Urol.* 2015;193(3):880-884.
2. Assimos D, Krambeck A, Miller NL, et al. Surgical management of stones: American Urological Association/endourological society guideline, part II. *J Urol.* 2016;196(4):1161-1169.
3. Mittakanti HR, Conti SL, Pao AC, et al. Unplanned emergency department visits and hospital admissions following ureteroscopy: do ureteral stents make a difference?. *Urology.* 2018;117:44-49.
4. Hiller SC, Daignault-Newton S, Pimentel H, et al. Ureteral stent placement following ureteroscopy increases emergency department visits in a statewide surgical collaborative. *J Urol.* 2021;205(6):1710-1717.
5. de la Rosette J, Denstedt J, Geavlete P, et al. The clinical research office of the endourological society ureteroscopy global study: indications, complications, and outcomes in 11,885 patients. *J Endourol.* 2014;28(2):131-139.
6. Joshi HB, Stainthorpe A, MacDonagh RP, Keeley FX Jr, Timoney AG, Barry MJ. Indwelling ureteral stents: evaluation of symptoms, quality of life and utility. *J Urol.* 2003;169(3):1065-1069.
7. DiBianco JM, Daignault-Newton S, Dupati A, et al. Stent omission in pre-stented patients undergoing ureteroscopy decreases unplanned health care utilization. *Urol Pract.* 2023;10(2):163-169.
8. Becker REN, Daignault-Newton S, Higgins AM, et al. MP19-01 Stone location and stenting influence patient-reported pain and quality of life after ureteroscopy. *J Urol.* 2023;209(Suppl 4):e264.
9. Ordonez M, Hwang EC, Borofsky M, Bakker CJ, Gandhi S, Dahm P. Ureteral stent versus no ureteral stent for ureteroscopy in the management of renal and ureteral calculi. *Cochrane Database Syst Rev.* 2019;2(2):CD012703.

Merck Oncology
Clinical Trials

Consider Investigational Trials for Patients With

Bladder Cancer

Clinical trials for **patients with bladder cancer**

KEYNOTE MK-3475-676

- Evaluating MK-3475, an investigational immunotherapy, plus BCG in high-risk, non-metastatic, non-muscle invasive bladder cancer (NMIBC) that has progressed after TURBT

KEYNOTE MK-3475-905

- Evaluating MK-3475, an investigational immunotherapy, plus cystectomy in non-metastatic muscle invasive bladder cancer (MIBC) for patients who are cisplatin ineligible or who decline cisplatin therapy

KEYNOTE MK-3475-992

- Evaluating MK-3475, an investigational immunotherapy, plus chemoradiotherapy (CRT) in non-metastatic MIBC

KEYNOTE MK-3475-B15

- Evaluating MK-3475, an investigational immunotherapy, for patients with newly diagnosed MIBC that are eligible for neoadjuvant chemotherapy prior to cystectomy

For more information and to see if your patients may qualify, visit:

www.merckclinicaltrials.com/oncology/bladder

MERCK

Xtandi®
(enzalutamide)
40 mg tablets | 80 mg tablets

IT'S TIME FOR XTANDI

Scan the QR code to see the latest data at
XtandiHCP.com

astellas ONCOLOGY

Pfizer Oncology