Clinical trial summary (S2427)

Combining immunotherapy and radiation therapy to help patients avoid bladder removal after treatment shrinks muscle invasive bladder cancer

What is the purpose of this clinical trial?

People in this trial have muscle invasive bladder cancer — and the cancer has shrunk or can't be found after treatment with chemotherapy, immunotherapy, targeted drugs, or a combination of these. The study asks if these patients can avoid having their bladder removed if they receive an immunotherapy drug called pembrolizumab along with radiation therapy.

Immunotherapy is a type of treatment that helps the immune system fight cancer. Radiation therapy uses energy from X-rays to kill cancer cells.

This trial is set up to find out:

- If combining pembrolizumab and radiation therapy can help keep the cancer from coming back or getting worse
- If this combination can prevent the need for bladder removal surgery

Why is this trial important?

Many people with muscle invasive bladder cancer have their bladder removed as part of their treatment. Bladder removal surgery can have a big impact on quality of life — for example, it changes the way people pee and can affect sexual health.

This trial will help researchers find out if it's possible to prevent the need for bladder removal surgery so patients can have better quality of life.

Who can be in this trial?

This trial is for adults age 18 or older who were treated for muscle invasive bladder cancer.

This trial is for people who:

- Received chemotherapy, immunotherapy, targeted drugs, or a combination of these and then had a surgery called transurethral resection of bladder tumor (TURBT)
- Had a tumor that shrunk or can't be found after earlier treatment and TURBT

This trial is not for people who:

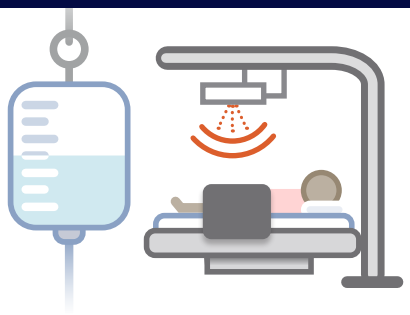
- Already received radiation therapy
- Received certain immunotherapy or targeted drugs
- Need to take steroids (like prednisone) to control the body's immune system responses
- Are pregnant or breastfeeding

Talk with your doctor to learn more about who can join the study.

What treatments will I get?

You'll get pembrolizumab once every 3 weeks for a year. You'll get the drug through an IV (a needle placed into a vein in your arm). Pembrolizumab (Keytruda) is approved by the Food and Drug Administration (FDA) to treat bladder cancer.

You'll also get radiation therapy treatment once a day, Monday through Friday (except on holidays) for about 1 month. You'll get a total of 20 radiation therapy treatments.



How long will I be in the trial?

You'll be in the study for **5 years** total. You'll receive treatment during the first year. After that, you'll continue to have visits with your study doctor so they can see how you're feeling and if the cancer comes back or gets worse.

Are there costs? Will I get paid?

You won't need to pay for the pembrolizumab you get during the study. To learn more about what costs will and won't be covered, talk to your health care provider and insurance provider.

You won't be paid for joining the study.

Where can I find more information about this trial?

- Talk with your health care provider
- Call the National Cancer Institute at **1-800-4-CANCER**
- Go to **www.ClinicalTrials.gov** and search the national clinical trial number: **NCT07061964**
- For a list of trial locations, visit **swog.org/NCI-S2427**

Key information

Protocol number: S2427

NCT number: NCT07061964

Trial sponsor: SWOG Cancer Research Network

Publishing date: July 25, 2025

Full trial title: Single Arm Phase II Study of Bladder Preservation with Immunoradiotherapy after a Clinically Meaningful Response to Neoadjuvant Therapy in Patients with Muscle Invasive Bladder Cancer (BRIGHT)

Thank you!

When you join a clinical trial,
you're moving cancer medicine and patient care forward.

BRIGHT S2427

Single Arm Phase II Study of Bladder Preservation with Immunoradiotherapy After a Clinically Meaningful Response to NAT in Patients with MIBC

OVERVIEW

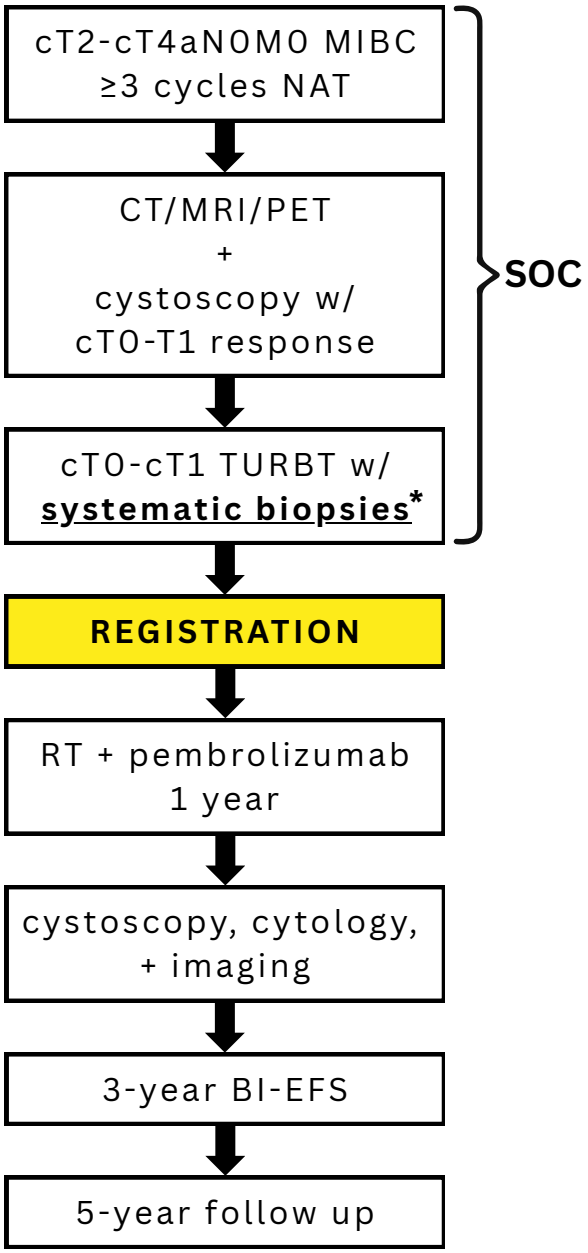
- Response adapted bladder preservation based on response to NAT.
- Post-registration, patients receive RT+IO if ≤cT1 disease after NAT.

KEY ELIGIBILITY

- Age ≥18
- Zubrod PS 0-2
- Histologically confirmed cT2-T4aN0M0 MIBC ≤180 days before starting NAT
  - Mixed histology allowed if >50% of tumor is urothelial cell carcinoma
- 3-6 cycles of NCCN approved NAT
  - No evidence of ≥T2, N1-3 or M1 disease after NAT
- *** TURBT with biopsies of left and right lateral, dome, posterior wall and trigone biopsies and radiologic staging showing T0-T1 disease ≤60 days after last dose of NAT**
- Blue light cystoscopy allowed
- No prior pelvic RT

SEE PROTOCOL SECTION 5 FOR FULL ELIGIBILITY CRITERIA

SCHEMA



ENROLLING
111 PARTICIPANTS

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NCI National Clinical Trials Network
SWOG CANCER RESEARCH NETWORK
NCI Community Oncology Research Program

S2427

Single Arm Phase II Study of Bladder Preservation with Immunoradiotherapy After a Clinically Meaningful Response to Neoadjuvant Therapy in Patients with Muscle Invasive Bladder Cancer (BRIGHT)

Study Chair:
Leslie Ballas, MD

Medical Oncology Co-Chair:
Abhishek Tripathi, MD

Radiation Oncology Co-Chairs:
Daniel Hamstra, MD
James Yu, MD, MHS

Urology Co-Chair:
Siamak Daneshmand, MD

PRO-CTCAE Chair:
Mark Tyson, MD

Translational Medicine Chairs:
Kent Mouw, MD, PhD
Josh Meeks, MD, PhD
David McConkey, PhD

Champions:
Sean Sachdev, MD – NRG
Kriti Mittal, MD – ECOG-ACRIN
Karine Tawagi, MD – Alliance

Community Engagement Chair:
Kyle Rose, MD

Patient Advocate:
Darrell Nakagawa

Statisticians:
Sam Callis, MS
Cathy Tangen, DrPH

PRO-CTCAE Statistician:
Joseph Unger, PhD

Data Coordinator:
Tonya Johnson

Protocol Project Manager:
Megan Keim

Clinical and Pragmatic Need: Risk adapted bladder preservation

- With increased use of neoadjuvant therapy (NAT) and new NATs, what is the role of radiotherapy (RT) in those with a clinically meaningful response
- Many patients who receive NAT will ask if they still need a cystectomy after NAT shows a clinically significant response
- Clinical question in group of patients highly motivated to save their bladder
  - Patients who change their mind after starting definitive therapy or decide they want bladder preservation later
  - Patients who weren't offered trimodal therapy (TMT) upfront
- We don't know optimal thing to do

Background

	RETAIN (N=26;37%)	HCRN (N=33; 45%)
Median F/U	41 months	30 months
Any recurrence	N=18 (69%)	N=10 (30%)
Met disease at any point	N=10 (38%)	N=2 (6%)
Death	N=3 (12%)	N=1 (3%)
Cystectomy	N=8 (31%)	N=9 (27%)
Bladder Intact + Alive + No M1	*N=12 (46%)*	*N=23 (70%)*

RETAIN

Major Inclusion Criteria:
- **cT2-T3 N0M0**
- **ECOG 0-1**
- **Urothelial Predominant Histology**

Not a randomized trial

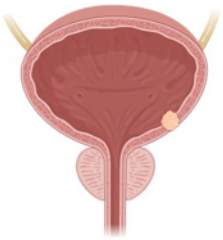
TURBT #1 → AMVAC x 3 → TURBT #2

Sequencing (Caris)
Mutation positive defined as any alterations in:
- *ATM*
- *RB1*
- *FANCC*
- *ERCC2*

- No residual tumor/cT0 AND Mutation Pos (+) → Active Surveillance
- cTa or cTis or cT1 or Pos (+) cytology OR cT0 mutation Neg (-) → Patient & Physician Choose → Intravesical Tx OR Chemo-RT OR Cystectomy
- cT2 → Patient & Physician Choose → Chemo-RT OR Cystectomy
- ≥cT3 → Cystectomy

HCRN

cT2-T4aN0M0
Cisplatin-eligible



Gemcitabine + Cisplatin + Nivolumab x 4 cycles

Clinical Restaging
Cystoscopy
Biopsies
Urine cytology
MRI

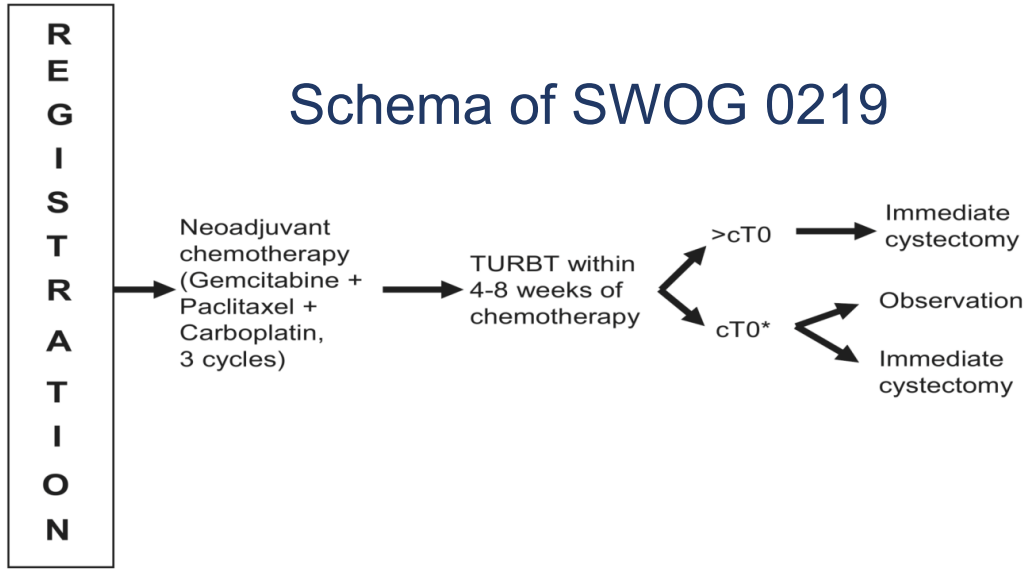
- Clinical CR → * → No cystectomy → Nivolumab x 8 cycles
- Clinical CR → * → Cystectomy
- No Clinical CR → Cystectomy

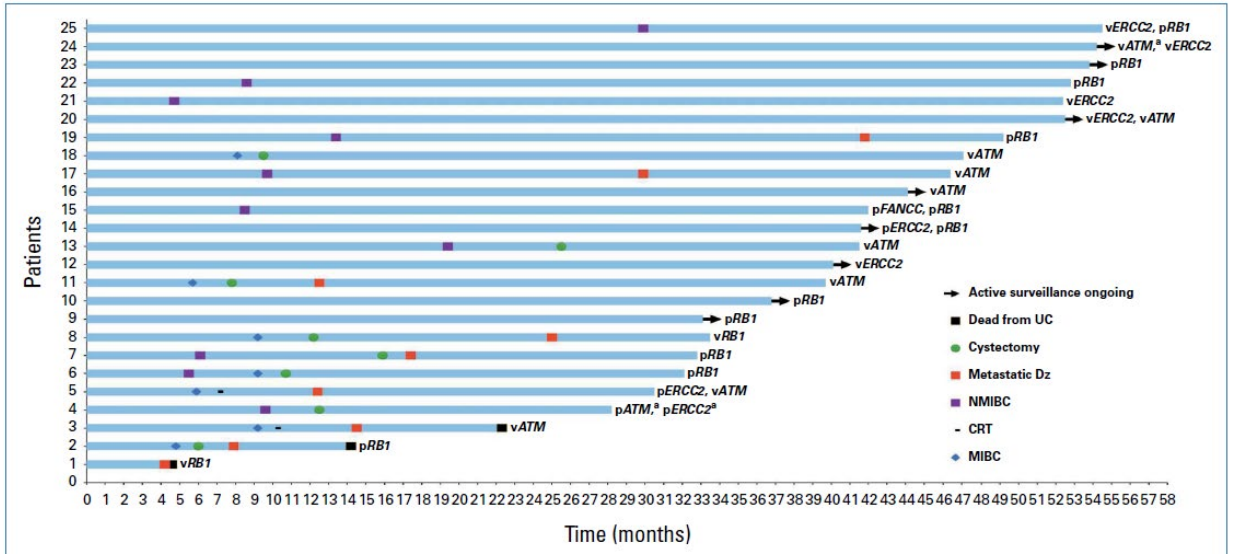
*patient choice

Background/Overview

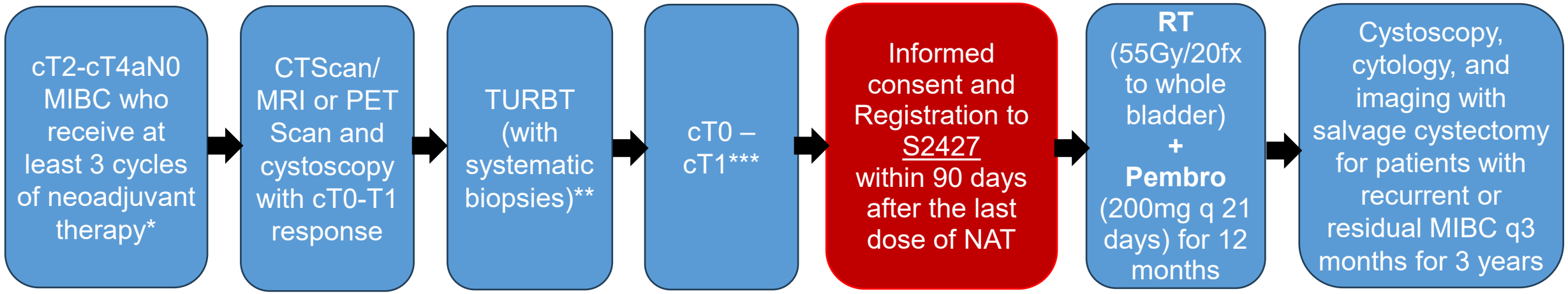
- Remember that cT0 is not pT0 – SWOG 0219 found that of the cT0 patients after NAC, only 40% were pT0…local therapy is still important
- On RETAIN, 9/17 patients who recurred developed metastatic disease, of whom eight recurred with localized disease first

Schema of SWOG 0219





S2427 Schema



* Patients who receive NAC as the NAT must have at least 3 cycles of cis-based regimen

** Patients found to have >T1 disease on TURBT will proceed to SOC cystectomy

*** Diffuse CIS patients will be excluded (>3 cm area of contiguous CIS or >3 separate locations of CIS on TURBT (dome/posterior/left/right/trigone)

Statistical Design and Enrollment Goals

Sam Callis

Primary Objective

- **3-year bladder intact event-free survival (BI-EFS):** To evaluate whether 3-year BI-EFS is at least 70% in participants with clinically T0-clinically T1 without multifocal CIS following neoadjuvant therapy (NAT) for muscle-invasive bladder cancer (MIBC)

    - Event components: Histologically proven presence of muscle-invasive bladder cancer, clinical evidence of nodal or metastatic disease, radical cystectomy, or death due to any cause.

Secondary Objectives

- Bladder intact event-free survival (BI-EFS)
- Muscle invasive recurrence-free survival (RFS)
- Metastasis-free survival (MFS)
- Overall survival (OS)
- Rate of salvage cystectomy
- To evaluate the frequency and severity of toxicities

PRO-CTCAE and Banking

- **PRO-CTCAE Objective**
  - To evaluate participant-reported symptoms using selected items from gastrointestinal, genitourinary and sexual function domains of the PRO-CTCAE, with the goal of characterizing the frequency, severity, and interference of treatment-related symptoms.

- **Banking Objective**
  - To bank specimens for future correlative studies.

Statistical Considerations

- **Sample size**
  - We are targeting **90 eligible participants**.
    - Assuming 10% of participants will be ineligible and 10% of eligible patients will be censored prior to reaching year 3, 111 total participants will be accrued to the study. Only participants who receive some protocol treatment will be evaluable.
  - We anticipate enrollment to last two years, assuming 4 participants per month are registered.
- **Interim analyses**
  - One interim futility analysis will be conducted after the first 45 eligible participants have been followed for sufficient time to allow estimation of 3-year BI-EFS using the Kaplan-Meier method.

Primary Analysis

- The final 3-year BI-EFS analysis will be conducted when all 90 eligible patients have been evaluated for the primary endpoint
- A single-arm, one-sided test of proportions will be utilized to test the hypothesis:
  - H_0: 3-year BI-EFS = 55%
  - H_A: 3-year BI-EFS = 70%
  - Alpha = 4.4%, Power = 89%

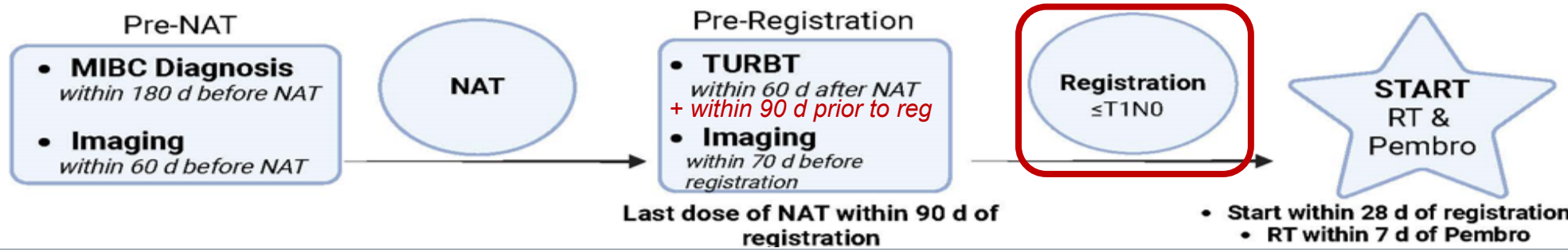
Key Eligibility and Timing/Workflow Considerations

Siamak Daneshmand, MD

Key Eligibility – Disease Criteria

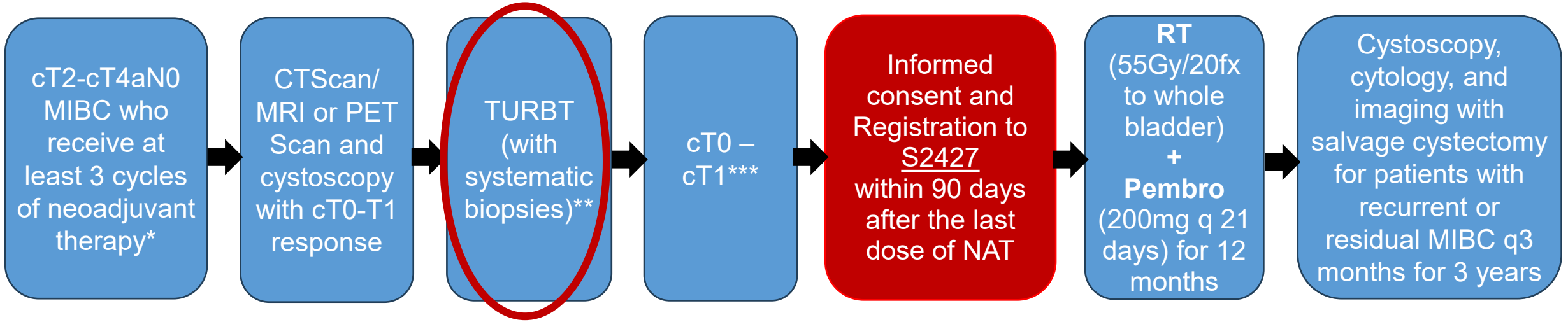
- Participants must have histologic evidence of cT2-T4aN0M0 muscle invasive urothelial carcinoma of the bladder within 180 days prior to starting neoadjuvant therapy (NAT).
- Participants must have cT0-cT1 on TURBT after NAT (This requires systematic biopsies and biopsy of tumor bed)
  - Blue light cystoscopy can be used
- No evidence of ≥T2, N1-3 or metastatic disease after NAT.
  - Pts. with lymph nodes ≥ 1.0 cm on imaging (CT or MRI of abdomen and pelvis) after completion of NAT must have a PET-CT within 70 days prior to registration. Pts. with a positive PET are deemed ineligible unless a biopsy is performed and shows no evidence of tumor involvement.
- No presence of small cell, neuroendocrine carcinoma, plasmacytoid variants on any pathology.
- No urothelial carcinoma or histological variant at any site outside of the urinary bladder within 24 months prior to registration except Ta/T1/CIS of the upper urinary tract, including renal pelvis or ureter if the Pt. underwent complete nephroureterectomy.
  - Pts. with mixed variant histology are eligible if the majority (>50%) of the tumor is urothelial cell carcinoma.

Timing Requirements for Eligibility



Key Eligibility – Disease Criteria

Please note that patients must have **systematic biopsies** as part of **pre-registration** TURBT



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Key Eligibility – Prior/Concurrent Therapy Criteria

- Participants must have received at least 3 and no more than 6 cycles of NCCN guideline concordant NAT for MIBC.
  - **NOTE:** Prior intravesical immunotherapy or chemotherapy for non-muscle invasive disease is allowed.
- Participants must not have had prior pelvic radiotherapy.
- Participants must not have had anti-PD-1, anti PD-L1, anti PD-L2 or anti-CTLA4 antibody, any other antibody or drug targeting T-cell co-stimulation, enfortumab vedotin, or any other drug targeting Nectin-4.
  - THIS REFERS TO PRIOR TO THEIR BLADDER CANCER DIAGNOSIS
  - PATIENTS CAN GET GC-D or EV-P FOR THEIR MIBC AS NAT PRIOR TO REGISTRATION ON TRIAL
- Participants with conditions requiring immunosuppressive doses of steroids (>10 mg / day of prednisone or equivalent) or other immunosuppressive medications must not be taking steroids at time of trial registration.

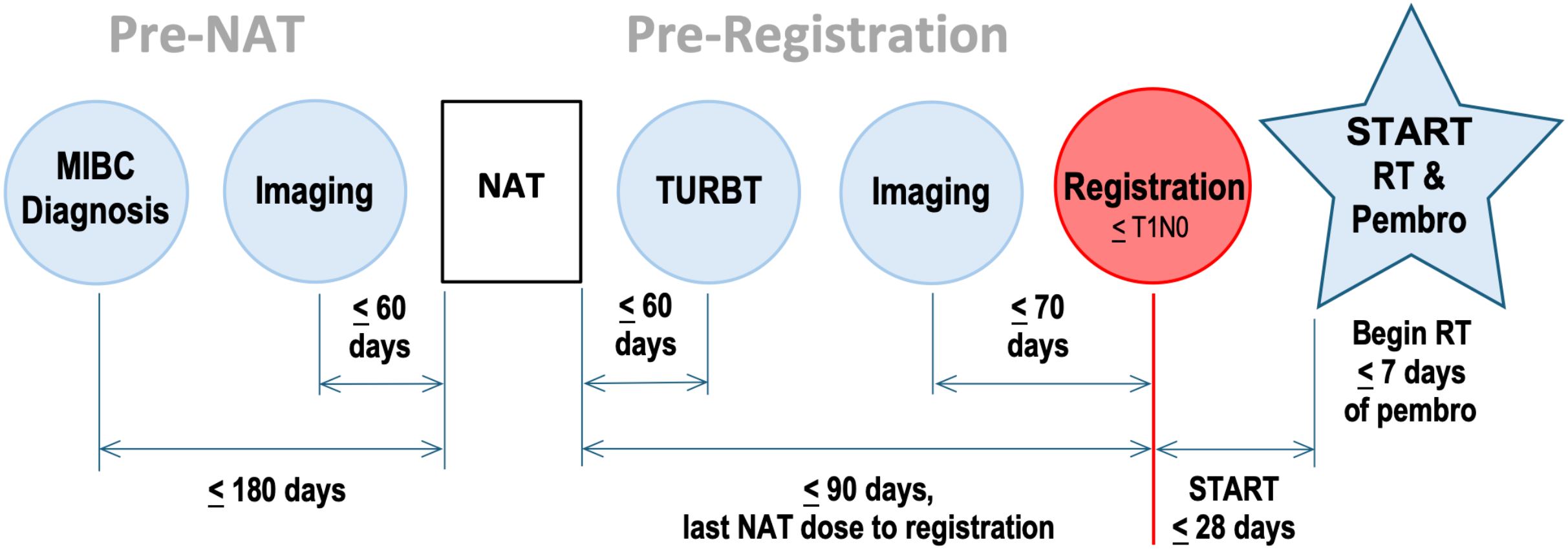
Key Eligibility – Clinical Laboratory Criteria

- Participants must be ≥ 18 years old at the time of registration.
- Participants must have Zubrod Performance Status of 0-2.
- Participants must have a creatinine ≤ IULN OR measured OR calculated creatinine clearance ≥ 40 mL/min using the Cockcroft-Gault Formula (see Protocol Section 5.3e). The specimen must have been drawn and processed **within 3 days prior to registration**.
- **Within 28 days prior to registration**, participants must have a complete history and physical exam and adequate organ and marrow function, defined as:
  - Leukocytes ≥3 x 10^3/uL.
  - Absolute neutrophil count ≥1.5 x 10^3/uL.
  - Platelets ≥100 x 10^3/uL.
  - Total bilirubin ≤ IULN unless history of Gilbert's disease. Pts. with history of Gilbert's disease must have total bilirubin ≤ 5 x IULN.
  - AST/ALT ≤ 3 × IULN.

No one on the study team may grant waivers to any of the eligibility criteria.

- **Refer to: https://dctd.cancer.gov/research/ctep-trials/memos/protocol-deviations.pdf**

Protocol Steps



Required Central Radiotherapy Review

- Pre-treatment review is required for the first case registered *for each modality* (3DCRT/IMRT) from each institution PRIOR TO DELIVERY of radiotherapy.
  - The pre-treatment review requires **3 business days** from the receipt of complete data.
  - For all other participants: Radiotherapy plan review must be submitted within 7 days after completion of radiotherapy.
- After an institution has passed pre-treatment review of the first case for each modality, for each subsequent case, radiotherapy data must be submitted within 1 week after the completion of radiotherapy treatment.

Overview of Treatment, Disease Assessment, Anticipated Adverse Events and Dose Modifications, Criteria for Removal from Protocol Treatment and Follow-up

Abhishek Tripathi, MD
and
Leslie Ballas, MD

Overview of Treatment: RT

Target Standard Name	Dose (Gy)	Fraction Size (Gy)	# of Fractions	Frequency	Dose Specification Technique
PTVwb	55 Gy	2.75 Gy	20	Daily	Covering ≥ 95% of PTVwb

- RT will be administered in a single phase of treatment to the whole bladder, without inclusion of pelvic nodes, and without a cone down bladder tumor boost.
- Total dose will be 2.75 Gy per day to a total of 55 Gy to the whole bladder.
- 20 total radiotherapy treatments will be delivered once daily (M-F), with exception of holidays and linear accelerator breakdowns, continuously without a planned break for tumor assessment during treatment.
    - Elapsed treatment should be no more than 28-35 days.
  - During RT, Zubrod PS must be taken once a week at the beginning of the week (M-F)
  - Dose reduction may be required to meet normal tissue (i.e. small bowel) constraints as per Protocol Section 7.2k.

Treatment Administration: Pre-Medication

- Pre-medication associated with standard drug administration and supportive care (including anti-diarrheals, antibiotics, diuretics, growth factors, or other medications) may be given as indicated by the current American Society of Clinical Oncology (ASCO) guidelines.

Pembrolizumab (MK-3475) Treatment Administration - Prohibited Concomitant Vaccination and Medications:

- Participants must not have had any infectious disease vaccination (e.g., standard influenza, H1N1 influenza, pneumococcal, meningococcal, tetanus toxoid) 1 week before or after any dose of pembrolizumab (MK-3475).
- Participants with conditions requiring immunosuppressive doses of steroids (> 10 mg / day of prednisone or equivalent) or other immunosuppressive medications must not be taking steroids at time of trial registration.

Pembrolizumab (MK-3475) Treatment Administration - Concomitant and Supportive Care:

- Inhaled or topical steroids are permitted in the absence of active autoimmune disease.
- Physiologic replacement doses of corticosteroids are permitted for participants with adrenal insufficiency.
- Refer to Section 8.3a (Table 1) for toxicity management guidelines and allowable supportive care, including administration of corticosteroids, prophylactic antibiotics, insulin, nonselective beta-blockers, thyroid replacement therapy, and/or other therapies to manage immune-related adverse events (irAEs).

Treatment: Pembrolizumab (MK-3475)

AGENT [a]	DOSE	ROUTE [b]	DAY [c]	SCHEDULE [d]
Pembrolizumab (MK-3475)	200 mg	IV (over 30 minutes) [b]	Day 1 of every cycle (± 3 days)	up to 18 doses for a total of 12 months OR until progression or unacceptable toxicity

a. Monitoring / Precautions:
   - **The first 2 cycles will require a 1-hr observation period after pembrolizumab (MK-3475) infusion.**
   - For all cycles thereafter, no observation period will be required, unless clinically indicated.

b. Pembrolizumab (MK-3475) 200 mg (fixed dose) will be administered over a 30-minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window between -5 minutes and +10 minutes is permitted (that is, allowable infusion time is between 25 and 40 minutes).

c. One cycle = 21 days.

d. Pembrolizumab (MK-3475) treatment must begin within 28 days after registration to the trial.

Disease Assessment

- Disease assessment timing is based on calendar timing counted as weeks after registration, not based on cycles or drug administration.
- Prior to First BI-EFS Event: Participants will undergo CT, MRI, or PET of the chest/abdomen/pelvis, cystoscopy, and urine cytology:
  - Every 12 weeks starting at 21 weeks after registration until 2 years after registration or first BI-EFS event.
  - Then, every 26 weeks until 3 years after registration.

Additional Laboratory Assessments

- Chemistry panel (as defined below) and CBC with differential and platelets must be performed at the following timepoints:
  - Within 28 days prior to registration,
  - Prior to initiation of treatment on Cycle 1, Day 1, and
  - Prior to pembrolizumab (MK-3475) infusion on Day 1 of Cycles 2-18 (Allowable window for labs: Within 3 days prior to each D1 infusion).

  Notes:
  - Chemistry panel must include: Total bilirubin, SGOT (AST) or SGPT (ALT), and creatinine clearance. TSH (Reflex to Free T4, Free T3 for abnormal TSH result) is only required at timepoints listed after pre-registration, beginning with Cycle 1, Day 1.
  - Chemistry panel or CBC with differential and platelets tests performed within 28 days prior to initiation of treatment do not need to be repeated on Cycle 1, Day 1.
  - During radiation therapy: CBC timepoints should follow institutional practices.
- EKG is recommended to be done within 28 days prior to registration, if clinically indicated.

Study Procedures Schedule

REQUIRED STUDIES	Pre-Registration (within 28 days prior to reg, unless otherwise noted)	Cycle (1 Cycle=21 Days)		21 weeks after registration until first BI-EFS event or 5 years from registration	At time of first BI-EFS event (See Protocol Section 10.1a)	After first BI-EFS event (q 26 wks until Wk 104, then q 52 wks until Wk 260)
		C1	C2-C18			
PHYSICAL						
History & PE (incl. Height, Weight, Vitals)	X	X[3]	X	X		X
Performance Status		X				
Toxicity Notation		X	X	X		X
Baseline Abnormalities	X					
LABORATORY						
Chemistry panel	X	X	X			
CBC with differential and platelet counts	X	X	X			
Cystoscopy			X	X	X	
Urine cytology				X	X	
EKG (if clinically indicated)	X (within 28 days prior to reg)					
PROCEDURES						
TURBT (see Protocol Section 5.1c)	X					
X-RAYS AND SCANS						
CT, MRI or PET	X[6]			X	X	

Anticipated Adverse Events

- POTENTIAL common RT side effects:

Short-term side effects *	Long-term side effects
Fatigue	Scar tissue in bladder or rectum
Urinary urgency/frequency/dysuria	
More frequent and/or loose bowel movements	

* Short-term side effects of RT usually resolve within 1-2 months after completion of treatment

- POTENTIAL common Pembrolizumab (MK-3475) side effects:

Short-term side effects	Long-term side effects *
Fatigue	Thyroid disorders
Rash/itching,	Inflammation of liver/bowel
Arthralgia/myalgia	Inflammation/scarring of lungs

* Pembrolizumab (MK-3475) side effects are usually treated with immunosuppression and are usually reversible

Serious Adverse Event Reporting

- This study requires that expedited adverse events be reported using CTEP-AERS. (http://ctep.cancer.gov)
- **Initially report on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave.**
  - Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting.
- For AEs that meet expedited (SAE) reporting requirements, **the CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave**. Do not initiate the CTEP-AERS report via the CTEP-AERS website.
  - The investigational agent used in this study is Pembrolizumab (MK-3475). Refer to the expedited reporting requirements table in Protocol Section 8.7e
- If there is any question about the reportability of an adverse event the SAE Program at the SWOG Network Operations Center – San Antonio via email to: adr@swog.org, before preparing the report.

Dose Modifications/Interruptions - Pembrolizumab

- **No dose reductions are allowed** for pembrolizumab (MK-3475).
- Dose interruptions and discontinuations are allowed to manage toxicity.
  - The maximum delay in dosing for pembrolizumab (MK-3475) for any reason is **84 days**.
  - Missed doses will not be made up after the maximum delay in dosing has been reached.
- If pembrolizumab (MK-3475) must be permanently discontinued, the participant must be removed from protocol therapy.
- Refer to Protocol Section 8.3 for toxicity-specific guidelines.

Criteria for Removal from Treatment

- Completion of protocol treatment.
- If participant has MIBC or N+ or M+ disease at any disease assessment time point.
- Radical cystectomy.
- Unacceptable toxicity.
- Permanent discontinuation of Pembrolizumab (MK-3475).
- Pembrolizumab (MK-3475) delay > 84 days.
- Radiotherapy delay > 21 days.
- Participants may withdraw from the protocol treatment at any time for any reason.

Discontinuation of Treatment: All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

Follow-up

- All participants will be followed until death or 5 years after registration, whichever occurs first.
- Follow-up assessments start after the patient comes off-treatment:
  - History and physical exam to be performed every 26 weeks until Year 2, then every 52 weeks until max follow-up (5 years).

IROC Credentialing Requirements and Drug Ordering

Leslie Ballas, MD
and
James Yu, MD, MHS

Site Initiation Protocol-Specific Requirement for Radiation and/or Imaging (RTI)

- S2427 includes a RTI component.
- Enrolling sites must be aligned to an RTI provider.
- To manage provider associations: Access the Provider Association page from the Regulatory section on the CTSU members' website.

Site Initiation Protocol-Specific Requirement: IROC Houston Credentialing (IMRT and 3DCRT)

- S2427 involves central RTI review and use the Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application to transmit images.
- S2427 includes an IMRT and 3DCRT credentialling requirement (via IROC Houston). Sites must follow the instructions below to verify credentialing status for S2427 or to begin a new modality credentialing process.

RT Credentialing Requirements	**Web Link for Procedures and Instructions: http://irochouston.mdanderson.org**	
	Treatment Modality	
	Photon	Key Information
Facility Questionnaire	X	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email irochouston@mdanderson.org to receive your FQ link.
Credentialing Status Inquiry Form	X	To determine whether your institution needs to complete any further credentialing requirements, please complete the "Credentialing Status Inquiry Form" found under credentialing on the IROC Houston QA Center website http://irochouston.mdanderson.org
Phantom Irradiation	X	An IMRT phantom study provided by the IROC QA Center Houston must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (http://irochouston.mdanderson.org). Tomotherapy treatment delivery modality must be credentialed individually. CyberKnife is not allowed.
Credentialing Notification Issued to:		
Institution	X	IROC Houston QA Center will notify the institution and SWOG Headquarters that all desired credentialing requirements have been met.

Site Initiation Protocol-Specific Requirement: IROC Credentialing Approval

- Upon the IROC QA center approving the RTI provider for the study modality, IROC will automatically send the approval to the Regulatory and Roster Maintenance applications to comply with the protocol-specific requirement, unless otherwise noted at the bottom of the IROC Credentialing Approval notification. IROC will continue to copy the provider and/or enrolling site on modality approvals.
- After site registration approval in the Regulatory application, the enrolling site may access Oncology Patient Enrollment Network (OPEN) to complete enrollments. If the study is using the IROC integration suite, the enrolling site will select their credentialed provider treating the subject in the OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

Drug Ordering: Pembrolizumab (MK-34-75)

Pembrolizumab (MK-34-75) is investigational and is being provided under an IND held by the National Cancer Institute (NCI). NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution.

- Submit agent requests through the PMB AURORA application: https://ctepcore.nci.nih.gov/aurora/login.
  - Access to AURORA requires the establishment of credentials necessary to access secure NCI Clinical Oncology Research Enterprise (CORE) systems, maintenance of an “active” account status, a “current” password, and active person registration status.
  - The CTEP assigned protocol number S2427 must be used for ordering all CTEP-supplied investigational agents.
  - PMB AURORA application and AURORA Document Access (including IBs) training courses are located in the CTSU CLASS learning management system.
- No starter supplies may be ordered.
  - Participants must be enrolled to a treatment arm prior to order submission via AURORA.

Drug Ordering: Pembrolizumab (MK-34-75): Additional Resources

- Refer to the Agent Management webpage for policies and guidelines related to agent management.
  - All unused drug supplies must be returned to the PMB.
- Direct questions pertaining to drug orders, transfers, returns, or accountability to:
  - Email: PMB email: PMBAfterHours@mail.nih.gov | Ph: (240) 276-6575, M-F 8:30 am-4:30 pm ET, or
  - Use the dialog function in AURORA to communicate with PMB staff.
  - Direct questions about IB access to the PMB IB Coordinator: IBCoordinator@mail.nih.gov.

Timing of Participant Registration and Data Submission

Sam Callis

Participant Registration

- It is highly recommended that a radiation oncology consult occurs before study registration.
- Central Radiotherapy Pre-treatment Review is required for the first case registered for each modality (3DCRT/IMRT) from each institution PRIOR TO DELIVERY of radiotherapy.
  - For the first case registered (for each modality): Sites must allow 3 business days (after receipt of all required documents) for pre-treatment radiotherapy review.
- Initiation of pembrolizumab (MK-3475) (C1D1) should be planned to start no more than 28 calendar days after registration.
- Initiation of radiotherapy must start within 35 days after registration and within 7 calendar days before or after the start of pembrolizumab (MK-3475).

Data Submission

- The Medidata Rave® clinical data management system is to be used for all data submission. Access to the S2427 in Rave is controlled through the CTEP-IAM system and role assignments.
  - For questions pertaining to CTEP-IAM role assignments (including Rave), contact CTSU.
- Data must be submitted according to the protocol requirements for ALL participants registered, whether or not assigned treatment is administered, including participants deemed to be ineligible.
  - Participants for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.
- See Protocol Section 14.0 for complete Data Submission Requirements, Procedures and Timepoints.
  - Cystoscopic assessment form detailing systematic biopsies for eligibility is required at baseline.
  - Radiographic reporting form required if CT/MRI criteria are met on the disease assessment form.
- A printable (.PDF) version of the Master Forms Set is accessible from the S2427 protocol abstract page on CTSU.org.

Central Radiotherapy Review (IROC Rhode Island)

- **Pre-treatment review is required for the first case registered for each modality (3DCRT/IMRT) from each institution PRIOR TO DELIVERY of radiotherapy.**
  - Submission of treatment plans in digital format as DICOM RT is required.
  - Digital data must include planning CT scan, structures, plan, and dose files.
- Submission of data should be via TRIAD.
  - If necessary, sites may use sFTP. Instructions for data submission via sFTP are on the IROC Rhode Island web site at http://irocri.qarc.org under "Digital Data."
  - Any items on the list below (next slide) that are not part of the digital submission may be included with the transmission of the digital RT data via TRIAD or sFTP or submitted separately.
- To submit via TRIAD, the individual holding the TRIAD Site User role must install the TRIAD application on their workstation.
  - Refer to TRIAD Installation Documentation at: https://triadinstall.acr.org/triadclient/.
  - For TRIAD Access Requirements: Refer to Protocol Section 12.2a.
  - Direct questions pertaining to TRIAD to the TRIAD Technical Support staff: Email TRIAD-Support@acr.org or Ph: 1-703-390-9858.

Central Radiotherapy Review: Procedure for the First Case Registered for Each Modality

- **The following radiotherapy data must be submitted 3 business days prior to the initiation of radiotherapy treatment for pre-treatment review:**
  - DICOM RT treatment plans including CT, structures, dose, and plan files.
  - Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
  - RT-1 Dosimetry Summary Form
  - Copies (in DICOM format) and reports of all imaging studies used to define the target volume.
- Then, the following radiotherapy data must be submitted within 1 week of the completion of radiotherapy treatment:
  - The treatment chart including prescription, daily, and cumulative doses to all required areas and organs at risk.
  - RT-2 Radiotherapy Total Dose Record

Central Radiotherapy Review: Subsequent Cases

- **After the institution has passed the pre-treatment review of the first case *for each modality***, all subsequent case reviews will be performed after IROC Rhode Island has received the following complete final data.
- Submit the following within 1 week after completion of radiotherapy treatment:
  - DICOM RT treatment plans including CT, structures, dose, and plan files.
  - Treatment planning system summary report that includes the monitor unit calculations, beam parameters, calculation algorithm, and volume of interest dose statistics.
  - RT-1 Dosimetry Summary Form
  - Copies (in DICOM format) and reports of all imaging studies used to define the target volume.
  - The treatment chart including prescription, daily, and cumulative doses to all required areas and organs at risk.
  - RT-2 Radiotherapy Total Dose Record

Specimen Submission

- **With participant consent**, specimens must be submitted to the SWOG Biospecimen Bank– Solid Tissue, Myeloma and Lymphoma Division, Lab #201 (Email: bpcbank@nationwidechildrens.org) at the following timepoints.

Specimen Type	Amount / Description	Timepoints	Allowable Window	Kit Provided?	Additional Instructions
FFPE tissue	Submit: • Minimum of 10 unstained, charged, unbaked (4-6 micron) FFPE slides OR • 1 FFPE block from specimen with tumor	Baseline sample (ideally with tumor identified) collected prior to C1, D1 from either: • Diagnostic TURBT in which MIBC was diagnosed OR • reTUR, whichever is available.	Submit within 30 days after registration	No	Follow the Specimen Collection and Handling Guidelines for FFPE Tissue.
Peripheral whole blood	• 20 mL collected in two 10 ml Streck Tubes	• Cycle1, Day 1 • Cycle 3, Day 1 • End of pembrolizumab (MK-3475) treatment IMPORTANT: After collection: • **Do not refrigerate.** • Do not process.	Within 3 days prior to Cycle 1, Day 1. ± 3 days for Cycle 3, Day 1 and EOT.	Yes; Order kits online. Allow 7 days after order for receipt of shipment.	• Follow the Specimen Collection and Handling Guidelines for Whole Blood. • Ship ambient the same day as collected, if possible or the next working day.
Peripheral whole blood	• 10 mL peripheral blood in 1 EDTA tube for PBMC isolation (one time only - can occur at any point)	• Collection at 1 timepoint only. • Collection may occur at any time.	N/A	No	• Follow the Specimen Collection and Handling Guidelines for Whole Blood.
Urine	• 20 mL of urine	• Cycle1, Day 1 • Cycle 3, Day 1 • End of pembrolizumab (MK-3475) treatment	Within 3 days prior to C1/D1. ± 3 days for C3/D1 & EOT.		• Aliquot (2 x 10mL) and freeze without processing and store at -80°C until shipment.

Specimen Tracking and Documentation

- **Prior to EACH Shipment: All specimen submissions for this study must be entered and tracked using the SWOG online Specimen Tracking System** (STS) (https://spectrack.crab.org).
  - If a specimen was not collected at any timepoint, this must be documented in the Specimen Tracking System by using the "Notify that Specimen Cannot be Submitted" link.
  - If limited tissue is available or fewer than the required number of tubes of blood were collected, document the reason for incomplete specimen submission in the SWOG Specimen Tracking System under "Comments" on the "Verify Shipment" page.
- **Specimen labels must contain all information specified (per each specimen type) in Protocol Section 15.2** and the information contained on the specimen label must match the information entered into the SWOG STS (exactly). **Differences between the label and tracking system will generate a query.**
  - Participant initials format (in both places) should be L,FM (Last, First Middle).
    Any difference in spacing or punctuation of Participant initials will create a query.
  - Specimen labelling templates are available from the SWOG website at:
    https://www.swog.org/SpecimenLabelingInstructions
- The Specimen Tracking System Packing List (produced by the STS) **must be included with each shipment**.
  - Print the Packing List and place in the pocket of the specimen bag (if it has one), or in a separate resealable bag.
- **FFPE submissions**: The corresponding partially redacted **pathology report(s) must be included**. (LABEL each page with the SWOG Participant ID. REMOVE: Identifiers such as name, date of birth, medical record #, and insurance information. KEEP: Date of procedure, Surgical pathology ID (SPID), block #, and diagnosis.)

Patient Reported Outcomes

Instrument Name	Planned Assessment Times [1]	Number of questions	Estimated Time for completion
PRO-CTCAE (paper only) *Available in English and Spanish*	• Cycle 1, Day 1 (prior to starting pembrolizumab) • Cycle 2, Day 1 (to correspond with mid-to-late RT and specimen collection) • Cycle 5, Day 1 (roughly 11 weeks after completion of RT, to assess early post-RT toxicity) • End of pembrolizumab treatment (to capture end-of treatment symptoms and match biospecimen collection) [1] *Calculate target date from date of study registration.* *The recall period for the PRO-CTCAE measures is 7 days.*	15	15 minutes

- **PRO-CTCAE forms are collected in conjunction with Investigator adverse event assessments.**
- The PRO assessments must be administered according to the protocol-defined assessment schedule regardless of eligibility, treatment status or delay, or if pt. goes off protocol for any reason.
- If a participant misses an appointment or is too sick to complete the questionnaires on the scheduled date, the questionnaire can be mailed to the patient or sent home with him/her.
- If the participant appointment is conducted via a telehealth visit within 7 days of the originally scheduled timepoint, and the toxicity assessment is also conducted via the telehealth visit, then, the PRO-CTCAE questionnaire may also be administered via telephone (or videoconference) at the same timepoint. Refer to Protocol Section 15.4b.8 for detailed instructions.

Patient Reported Outcomes – Administration

- PRO-CTCAE questionnaires will be administered to participants by paper-and-pencil.
- The PRO-CTCAE assessment should take participants ~15 mins to complete at each time point.
- The S2427 Cover Sheet for Participant-Completed Questionnaires must be completed by site staff and submitted at each patient reported outcome timepoint.
  - If a pt. refuses or cannot complete the questionnaire for some reason, then this must be documented in the S2427 Cover Sheet for Participant-Completed Questionnaires.
  - If pt. refuses or cannot complete the questionnaires at one time point, they should be asked to do so at the next scheduled administration time.
- Anyone involved in the collection of patient-reported outcomes/quality of life data in SWOG trials should review the Patient Reported Outcome Questionnaires training program, which is accessible via the CTSU CLASS learning management system at: https://classlms.org/#/online-courses/03e094d1-3b95-408e-a698-b8b9b9cf73c7 (login with credentials to access NCI systems required).
- Refer to Protocol Section 15.4b for detailed administration instructions.

Questions:

- For questions pertaining to PRO Assessments, contact the SWOG Statistics and Data Management Center at: Phone: 206-652-2267 or Email Dr. Mark Tyson: Tyson.Mark@mayo.edu.

Patient Advocate Perspective

Darrell S. Nakagawa

Patient Advocate Perspective

- This is possibly a new chance to keep your bladder
- Key Patient Points
  - What am I committing to?
  - Are there any significant points I should consider?
  - What are the logistics for this treatment?

Quality Assurance, Funding, Additional Resources, Acknowledgements and Who to Contact

Mark Tyson, MD

Study Monitoring and Quality Assurance

- There is no formal Data and Safety Monitoring Committee for this study.
  - Accrual reports are generated weekly and study-specific accrual is monitored by the Study Chair, Study Statistician and the Disease Committee Chair.
  - Reports summarizing adverse events, serious adverse events (SAEs), and treatment administration are provided monthly to the Study Chair and Study Statistician for monitoring.
  - All SAEs are reviewed and processed by the Adverse Event Coordinator at the SWOG Network Operations Center and a physician reviewer based on data provided via the NCI CTEP-AERS system. Cumulative study-specific SAE reports are provided to the Study Chair and Study Statistician upon occurrence of an event.
  - Formal reports summarizing the study are prepared for all SWOG members every 6 months.
- Audits will be conducted at frequency of 3 years.

Funding

Accessing the Funding Memo	CTSU.org website >> **S2427** protocol abstract page >> **Funding Information >> S2427 Funding Sheet**
General Reminders	• Specimen submission dates must be entered in OPEN. • See Protocol Section 15.0 for submission information.
CTSU OPEN Funding Screen Guide	https://www.ctsu.org/open/Site_Resources/Training/Users_Manual/FundingScreenSiteUserGuide.pdf

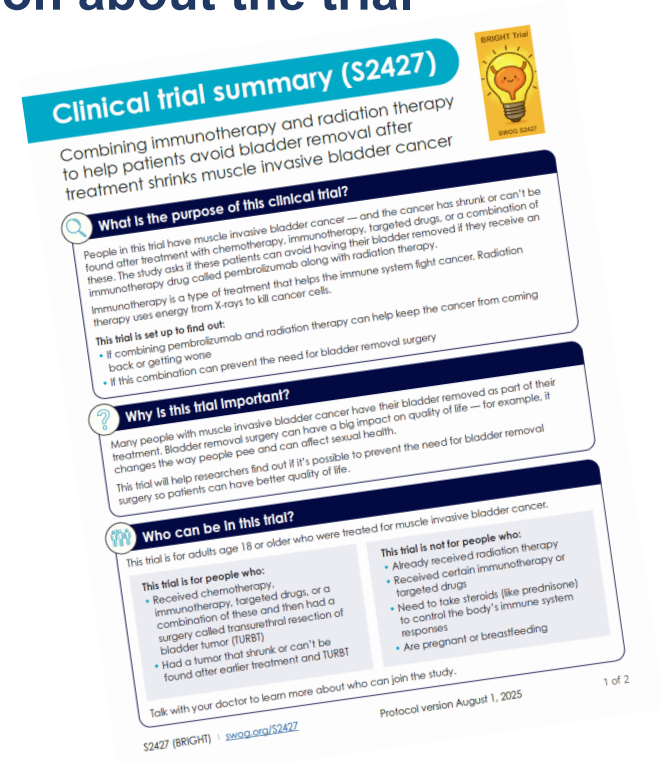
Funding Source and Study Component		Collect Type	Study Specific Notes	Enter Date in Open?	NCTN Funding per Patient Std/HP LAPS	NCORP Funding per Patient Std/HP
Federal	Base Intervention – Standard / High Performance LAPS & NCORP	Mandatory		No	$3,600/$5,200	$3,600/$5,200
Federal	Biospecimen – Multiple Blood, urine, and tissue submissions required if participant consents.	Mandatory Request	1	Yes	$500	$500
Total Potential Federal Funds					**$4,100/$5,700**	**$4,100/$5,700**
Total Potential Funds					**$4,100/$5,700**	**$4,100/$5,700**

Study specific Notes: 1. See Protocol Section 15 for detailed biospecimen collection information. Payments will be triggered by submission of information for the first time point into the OPEN system.

Resources and Materials — Patient-Friendly Clinical Trial Summary

The Patient-Friendly Summary is an educational tool to share key information about the trial

- Easy to understand, written in plain language
- Explains why the study is important, study treatments, who is eligible, length of trial involvement, costs, and how to learn more
- May include graphics to illustrate study design or treatments
- Translated into Spanish


Clinical trial summary (S2427)

Combining immunotherapy and radiation therapy to help patients avoid bladder removal after treatment shrinks muscle invasive bladder cancer

What is the purpose of this clinical trial?

People in this trial have muscle invasive bladder cancer — and the cancer has shrunk or can't be found after treatment with chemotherapy, immunotherapy, targeted drugs, or a combination of these. The study asks if these patients can avoid having their bladder removed if they receive an immunotherapy drug called pembrolizumab along with radiation therapy.

Immunotherapy is a type of treatment that helps the immune system fight cancer. Radiation therapy uses energy from X-rays to kill cancer cells.

This trial is set up to find out:
- If combining pembrolizumab and radiation therapy can help keep the cancer from coming back or getting worse
- If this combination can prevent the need for bladder removal surgery

Why is this trial important?

Many people with muscle invasive bladder cancer have their bladder removed as part of their treatment. Bladder removal surgery can have a big impact on quality of life — for example, it changes the way people pee and can affect sexual health.

This trial will help researchers find out if it's possible to prevent the need for bladder removal surgery so patients can have better quality of life.

Who can be in this trial?

This trial is for adults age 18 or older who were treated for muscle invasive bladder cancer.

This trial is for people who:
- Received chemotherapy, immunotherapy, targeted drugs, or a combination of these and then had a surgery called transurethral resection of bladder tumor (TURBT)
- Had a tumor that shrunk or can't be found after earlier treatment and TURBT

This trial is not for people who:
- Already received radiation therapy
- Received certain immunotherapy or targeted drugs
- Need to take steroids (like prednisone) to control the body's immune system responses
- Are pregnant or breastfeeding

Talk with your doctor to learn more about who can join the study.

Protocol version August 1, 2025

1 of 2

S2427 (BRIGHT) | swog.org/S2427

We recommend a study team member review the summary with the patient as an introduction to the trial, or alongside the consent

- Also available as a PDF to be printed or shared electronically

The summary is accessible from:

- **swog.org/S2427** (publicly accessible link, with printable PDF)
- Also via the S2427 protocol abstract page on CTSU.org under Documents >> CIRB Approved Documents tab >> Support Documents filter, listed as “Clinical Trial Summary” (login required)

Additional Resources and Materials

- S2427 Social Media Toolkit (text and graphics) is available via the S2427 protocol abstract page on CTSU.org under
  - Documents>>CIRB Approved Documents tab>> Support Documents filter
  - **or** via swog.org/clinical-trials/S2427 under “Other Study Materials” (no login)
- EMR Template will be accessible from the Documents>>Protocol Related Documents>>Education and Promotion filter on the S2427 protocol abstract page.

Acknowledgements

- Imaging and Radiation Oncology Core (IROC)
- SWOG Imaging Committee
- SWOG Drug Information Subcommittee (DISC)
- David McFadden, MS, RPh and Merck & Co., Inc.

Contact Information

Eligibility, RAVE, Data Submission	SWOG Statistics and Data Management Center E-mail: guquestion@crab.org or Phone: 206/652-2267
Regulatory, Protocol, Informed Consent	SWOG Network Operations Center E-mail: protocols@swog.org or Phone: 210/614-8808
Medical Queries (treatment or toxicity related questions)	E-mail: S2427chairs@swog.org or by phone: Dr. Leslie Ballas at: 323/423-1496
Radiotherapy Requirements	See Protocol Section 7.2 or Email: IROCRI@qarc.org | Ph: 401/753-7600
PRO-CTCAE questions	Dr. Mark Tyson: Ph: 480/342-3868 or Email: Tyson.mark@mayo.edu
Specimen collection/submission questions	E-mail: guquestion@crab.org
Investigational Drug questions	See Protocol Section 3.0 or Email: PMBAfterHours@mail.nih.gov
Requests for Investigator's Brochures	See Protocol Section 3.0 or CTEP Agent Management or Email: ibcoordinator@mail.nih.gov
PMB Online Agent Management System (AURORA) questions (https://ctepcore.nci.nih.gov/aurora/login)	Refer to: AURORA FAQs or Email: PMBAfterhours@mail.nih.gov
Specimen Tracking System Amendments, Errors, Connectivity Issues and Technical issues with the SWOG CRA Workbench	Email: technicalquestion@crab.org
Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) (new account requests, reset password)	Refer to: CTEP Registration and Access Management
Access to iMedidata Rave or Delegation of Task Log (DTL), Oncology Patient Enrollment Network (OPEN) questions	See Protocol Sections 14.3 or 13.5 or contact the CTSU Help Desk at: Phone: 1-888-823-5923 or Email: ctsucontact@westat.com
Participant Transfers	patienttransfer@crab.org
Serious Adverse Event Reporting questions	See Protocol Section 8.7 or Email: adr@swog.org
Patient Advocate	Darrell Nakagawa: E-mail: dnakagawa@comcast.net

Thank you