5 STUDY POPULATION

As stated in the Code of Conduct for Interventional Clinical Trials (Appendix 10.1.1), this study includes participants of varying age, race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Refer to Appendix 7 for country-specific requirements.

5.1 Inclusion Criteria

An individual is eligible for inclusion in the study if the individual meets all of the following criteria:

Type of Participant and Disease Characteristics

1. The participant must have a diagnosis of MIBC (cT2-T4aN0-N1) per investigator assessment with TURBT performed within 120 days before randomization.
   Note: Individuals with mixed histology as assessed locally are eligible provided there is a urothelial component. Participants with any small cell or neuroendocrine component are not permitted.

   Note: Tissue from a diagnostic TURBT must be submitted for biomarker research. FFPE tissue blocks are preferred to slides (details pertaining to tumor tissue submission can be found in the Procedures Manual).

   Note: Confirmation of submission and adequacy of tumor tissue is not required prior to randomization.
2. Has clinically nonmetastatic bladder cancer (N0-N1M0) determined by imaging, assessed by the site and verified by BICR.
3. Is either ineligible for radical cystectomy or has opted for bladder preservation and is planned to receive CRT.

Demographics

4. Is an individual of any sex/gender, at least 18 years of age at the time of providing the informed consent or assent, as applicable. Follow local regulatory requirements if the legal age of consent for participation is >18 years of age.

Assigned Male Sex at Birth

5. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is:
   - Sac-TMT: 120 days following the last dose
   - MK-3475A: no male contraception measures are required
   - CRT: 90 days following the last dose of chemotherapy or radiation therapy, whichever is later

- Refrains from donating sperm
- Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant PLUS partner use of an additional contraceptive method (refer to Section 10.5.3), as a condom may break or leak
  If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.

  Note: If the participant is azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview), no contraception is required.

Assigned Female Sex at Birth

6. A participant assigned female sex at birth is eligible to participate if not breastfeeding during the study intervention period and for at least 10 days after the last dose of study intervention with sac-TMT, 120 days after the last dose of study intervention MK-3475A and CRT.
7. A WOCBP is eligible to participate if not pregnant and if a negative highly sensitive pregnancy test (urine or serum), as required by local regulations, has been obtained within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.

8. A WOCBP is eligible to participate if they use a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or if they adhere to penile-vaginal intercourse abstinence as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5, during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. In addition, the participant agrees not to donate eggs (ova, oocytes) to others or freeze/store eggs during this period for the purpose of reproduction. The length of time required to continue contraception for each study intervention is:
   - Sac-TMT: 210 days following the last dose
   - MK-3475A: 120 days following the last dose
   - CRT: 180 days following the last dose of chemotherapy or radiation therapy, whichever is later
     Note: It is recommended that the investigator or designee evaluate the potential for contraceptive method failure (ie, noncompliance, recent initiation) in relationship to the first dose of study intervention. If the local contraception requirements for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed. It is recommended that the investigator or designee review medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a WOCBP with an early undetected pregnancy.

Informed Consent

9. The participant (or legally acceptable representative) has provided documented informed consent for the study.

Additional Categories

10. HIV-infected participants must have well controlled HIV on ART, defined as:
    a. Participants on ART must have a CD4+ T-cell count ≥350 cells/mm^3 at the time of screening
    b. Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening
    c. Participants must not have had any AIDS-defining opportunistic infections within the past 12 months
    d. Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (Day 1) and agree to continue ART throughout the study
    e. The combination ART regimen must not contain any antiretroviral medications that interact with strong CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers).
11. An ECOG performance status of 0 to 2 assessed within 7 days before randomization.

12. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks, and have undetectable HBV viral load prior to randomization.
    Note: Participants are to remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.

    Hepatitis B screening tests are not required unless:

    - Known history of HBV infection
    - As mandated by local guidelines

13. Participants with history of HCV infection are eligible if HCV viral load is undetectable at screening.
    Note: Participants must have completed curative antiviral therapy at least 4 weeks prior to randomization.

    Hepatitis C screening tests are not required unless:

    - Known history of HCV infection
    - As mandated by local guidelines

14. Adequate organ function as defined in the following table (Table 8). Specimens must be collected within 14 days before randomization of study intervention.

Table 8 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/µL[a]
Platelets	≥100,000/µL[a]
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
eGFR per local institutional standard	≥30 mL/min/ 1.73 m^2
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as INR is within therapeutic range of intended use of anticoagulants.
Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as aPTT is within therapeutic range of intended use of anticoagulants.

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); eGFR=estimated glomerular filtration rate; ULN=upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

5.2 Exclusion Criteria

An individual must be excluded from the study if the individual meets any of the following criteria:

Medical Conditions

1. Has known presence of diffuse CIS (multiple foci [4 or greater] of CIS) throughout the bladder.
2. Has the presence of bilateral hydronephrosis during the Screening period.
   Note: Participants with unilateral hydronephrosis or with a temporary ureteral stent are eligible if their measured or calculated GFR per the institutional standard permits enrollment on the study.
3. Has presence of high-grade, muscle-invasive UC at any site outside of the urinary bladder in the previous 2 years. Prior or concomitant Ta/T1/CIS of the bladder or upper tract is permitted, provided there is no diffuse CIS (Exclusion #1) and the participant has undergone curative intervention and remains disease-free at the time of study entry.
4. Has history of documented severe dry eye syndrome, severe Meibomian gland disease and/or blepharitis, or severe corneal disease that prevents/delays corneal healing.
5. Has active inflammatory bowel disease requiring immunosuppressive medication or previous history of inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis, or chronic diarrhea).
6. Has uncontrolled, significant cardiovascular disease or cerebrovascular disease, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, uncontrolled symptomatic arrhythmia, prolongation of QTcF interval to >480 ms, and/or other serious cardiovascular and cerebrovascular diseases within the 6 months preceding study intervention.
7. HIV-infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.

Prior/Concomitant Therapy

8. Has received prior pelvic/local radiation therapy for any reason or any systemic antineoplastic treatment for MIBC.
   Note: Prior treatment for NMIBC with intravesical instillation therapy such as BCG or intravesical chemotherapy or other intravesical agents is permitted but must be completed ≥28 days before randomization.
9. Received prior treatment with a TROP2-targeted ADC.
10. Received prior treatment with a topoisomerase 1 inhibitor-containing ADC.
11. Is currently receiving a strong inducer/inhibitor of CYP3A4 that cannot be discontinued for the duration of the study. The required washout period before starting sac-TMT is 2 weeks.
    Note: A list of strong inhibitors or inducers of CYP3A4 can be found at the following website: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers.

12. Received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent, or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137) within 1 year before randomization.
13. Has not recovered to Grade ≤1 or baseline from AE associated with anticancer therapy before randomization.
14. Received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Administration of inactivated (non-live or non-live-attenuated) vaccines is allowed.

Prior/Concurrent Clinical Study Experience

15. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.

Diagnostic Assessments

16. Diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in dosing exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study intervention.
17. Known additional malignancy that is progressing or has required active treatment within the past 2 years.
    Note: Participants with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ that have undergone potentially curative therapy are not excluded. Participants with low-risk early-stage prostate cancer (T1-T2a, Gleason score ≤6, and PSA <10 ng/mL) either treated with definitive intent or untreated in active surveillance with stable disease are not excluded.
18. Active autoimmune disease that has required systemic treatment in the past 2 years. Hormonal supplementation (eg, thyroxine, insulin, or physiologic corticosteroid) is allowed.
19. Has a history of (noninfectious) pneumonitis/interstitial lung disease that required steroids, has current pneumonitis/interstitial lung disease, or has suspected ILD or pneumonitis that cannot be ruled out by standard diagnostic assessments at Screening.
20. Active infection requiring systemic therapy other than those permitted in Section 5.1.
21. History or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the participant's ability to cooperate with the requirements of the study, such that it is not in the best interest of the participant to participate, in the opinion of the investigator or designee.
22. Severe hypersensitivity (≥Grade 3) to study intervention(s) (as listed in Table 9), any of its/their excipients, and/or to another biologic therapy.
    Note: Hypersensitivity to one TPC and/or its excipients does not exclude an individual from the study if they are eligible to receive one of the other TPC options.

Other Exclusions

23. History of stem cell/solid organ transplant.
24. Participants who have not adequately recovered from major surgery or have ongoing surgical complications.

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

It is recommended that participants randomized to Arm A be advised to modify their diet to avoid foods that may cause damage to the mucosa (eg, pretzels and chips) and foods that are acidic.

5.3.2 Caffeine, Alcohol, and Tobacco Restrictions

It is recommended that participants randomized to Arm A be advised to avoid alcohol (ie, beverages and mouthwash) and tobacco [Brown, T. J. and Gupta, A. 2020] [Elad, S., et al 2020].

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study and are deemed ineligible or are not subsequently randomized in the study. A minimal set of screen-failure information is required to ensure transparent reporting of screen-failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen-failure details, eligibility criteria, and any AEs or SAEs meeting reporting requirements.

Retesting may be performed only within the screening/rescreening periods; see Section 8.10.1 for details. Participants who are retested will retain their original participant identification code.

Participants who fail screening may be rescreened for eligibility, see Section 8.10.1.2.

5.5 Participant Replacement Strategy

A participant who withdraws from the study will not be replaced.