TITLE PAGE

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Protocol Title: A Phase 2 Open-label Randomized Study of V940 in Combination With BCG Versus BCG Monotherapy in Participants With High-risk Non-muscle Invasive Bladder Cancer (INTerpath-011)

Study Number: 011-00

Compound Code(s): V940

Sponsor Name: Merck Sharp & Dohme LLC (hereafter called the Sponsor or MSD)

Legal Registered Address:

126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Regulatory Agency Identifying Number(s):

NCT	Enter NCT Number
EU CT	Enter EU CT Number
jRCT	Enter jRCT Number
WHO/UTN	Enter WHO Identifier/UTN
IND	Enter IND Number
Enter Other Regulatory Agency Name	Enter Other Regulatory Agency Identifying Number

Approval Date: CLICK OR TAP TO ENTER A DATE.

5 STUDY POPULATION

As stated in the Code of Conduct for Clinical Trials (Appendix 1.1), this study includes participants of varying age (as applicable), 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.

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. **Cohort A:** Is an individual with a BICR-confirmed histological diagnosis of high-risk non-muscle invasive (HG Ta, T1, and/or CIS) UC of the bladder.
   Note: Individuals with unifocal high-grade Ta <3 cm alone are not eligible.

   Cohort B: Is an individual with a BICR-confirmed histological diagnosis of CIS +/- papillary non-muscle invasive UC of the bladder and is ineligible for, or refusing, any IVES therapy.
   Note: Individuals who have HG Ta or T1 without CIS are not eligible.

   Cohorts A and B:
   - Confirmation of T1 stage tumor requires the presence of detrusor muscle.
   - Individuals with tumors of mixed urothelial/non-urothelial histology are eligible, but UC must be the predominant histology. Individuals with predominant or exclusively non-urothelial histology are not eligible.
   - Individuals whose tumors contain *any* neuroendocrine or small cell component are not eligible.

2. For individuals with papillary tumors (Ta and T1), a complete TURBT must have been performed, as characterized by attainment of a visually complete resection of all papillary tumors (Ta and T1).
   Note: Individuals with residual CIS not amenable to complete resection are eligible.
   Note: The most recent cystoscopy/TURBT must have been performed within 12 weeks before randomization/allocation.
   Note: Individuals with T1 disease must have undergone a restaging TURBT procedure within 12 weeks before randomization/allocation to confirm complete resection and that the individual continues to meet eligibility criteria. If restaging TURBT is performed within 12 weeks before randomization/allocation and the absence of muscle invasive tumor (≥T2) is confirmed by central pathology review, individuals are still eligible even if the previous TURBT was performed >12 weeks before randomization/allocation. Tumor samples from the most recent TURBT/biopsy available before randomization, which includes the diagnostic and restaging TURBT/biopsy, as applicable, must be sent to the central pathology laboratory for tumor histology evaluation with results confirming eligibility before randomization/allocation.
3. Individuals who have never received BCG or who have received BCG as defined as:

   Cohort A: Individuals who have received BCG more than 2 years before HR NMIBC recurrence.
   Note: Recurrence must be at least 24 months from the last exposure to BCG with evidence of complete response during the 2-year period post BCG.

   Cohort B: Individuals who did *not* receive adequate dosing of BCG within the past 2 years before HR NMIBC recurrence. Adequate dosing is defined as at least:

   - 5 of 6 doses of induction, *and*
   - 2 additional doses of maintenance

Demographics

4. Is an individual of any sex/gender who is at least 18 years of age at the time of providing documented informed consent.

Assigned Male Sex at Birth

Note: There are no contraceptive requirements for individuals assigned male sex at birth.

Assigned Female Sex at Birth

5. A POCBP is eligible to participate if not pregnant and a negative highly sensitive pregnancy test (urine or serum), as required by local regulations, within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention has been obtained. 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.
   Note: Since the first dose of study intervention in Cohort B will not be received within the time periods specified in this criterion, eligibility for individuals in Cohort B can be confirmed at the time of screening but must be re-verified before the first dose of V940 is received.
6. A POCBP is eligible to participate if not breastfeeding during the study intervention period and for at least 15 days after study intervention with V940 and 7 days after study intervention with BCG.
7. A POCBP is eligible to participate if using an acceptable contraceptive method, or penile-vaginal intercourse abstinence, as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), is adhered to as described in Appendix 5 during the intervention period and for at least 15 days after the last dose of study intervention with V940 and 7 days after the last dose of study intervention with BCG.

- Note: The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. 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. Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

8. The individual has provided documented informed consent for the study.
   Note: Individuals who are legally blind, unable to read, or have a mild developmental or intellectual disability and can indicate a wish to participate in this study may enroll if eligibility criteria are met, a legally acceptable representative provides consent on their behalf, and an impartial witness participates in the consent process. If eligible, these individuals may be enrolled in this study to allow the possibility of benefit from the planned treatment(s).

Additional Categories

9. Individuals must provide an FFPE tumor tissue sample that is suitable for the NGS required for this study.
   Note: Tissue from the diagnostic TURBT is mandatory to ensure QC for NGS is successful, but tissue from screening/repeat TURBT, if needed, is allowed as long as tissue requirements are met.
   The tumor tissue sample must meet the following criteria:
   - The minimum standards for tissue quantity and quality as defined in the laboratory manual.
   - Pass the required QC checks for NGS by the Sponsor's NGS vendor.
10. Individuals must provide blood samples as specified in the protocol to enable V940 production.
11. Is an individual with a performance status of 0, 1, or 2 on the ECOG Performance Scale within 14 days before randomization/allocation.
12. Is an individual with adequate organ function as defined in Table 5. Specimens must be collected within 14 days before randomization/allocation.

Table 5 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
ANC	≥1500/μL
Platelets	≥100,000/μL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Measured or calculated CrCl[b]	≥30 mL/min
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	
INR or PT aPTT	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); CrCl=creatinine clearance; GFR=glomerular filtration rate; INR=international normalized ratio; pRBC=packed red blood cell; PT=prothrombin time; ULN=upper limit of normal.
a Criteria must be met without erythropoietin dependency and without pRBC transfusion with the last 2 weeks.
b Creatinine clearance should be calculated per institutional standards. GFR can also be used in place of CrCl.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific therapies.

13. HIV-infected individuals must have well controlled HIV on ART, defined as:
    a. Having a CD4+ T-cell count ≥350 cells/mm^3 at the time of screening
    b. Having achieved and maintained virologic suppression, defined as confirmed HIV RNA level below 50 or the LLOQ using the locally-available assay, at the time of screening and for at least 12 weeks before screening

c. Absence of any AIDS-defining opportunistic infections within the past 12 months
d. Being on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before randomization/allocation and agreeing to continue ART throughout the study

HIV testing at screening is not required unless:

- There is a known history of HIV infection
- Mandated by local health authority

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

    Hepatitis B testing at screening is not required unless:

    - There is a known history of HBV infection
    - Mandated by the local health authority

15. Individuals with a history of HCV infection are eligible if their HCV viral load is undetectable at screening.
    Note: Individuals must have completed curative antiviral therapy at least 4 weeks before randomization/allocation.

    Hepatitis C testing at screening is not required unless:

    - There is a known history of HCV infection
    - Mandated by the local health authority

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 a history of or concurrent locally-advanced (ie, T2, T3, T4) or metastatic UC.
2. Has concurrent extravesical (ie, urethra, ureter, renal pelvis) non-muscle invasive UC or a history of extravesical non-muscle invasive UC that recurred within the past 2 years.
    - Individuals with concurrent low-grade Ta of the prostatic urethra are eligible.
    - Individuals with ductal invasion regardless of histology are not eligible.

3. Has a known additional malignancy that is progressing or has required active treatment within the past 3 years.
   Note: Individuals with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder, who have undergone potentially curative therapy are eligible.
   Note: Individuals with a history of prostate cancer (T2N0M0 or lower with a Gleason score ≤7) that was treated with definitive intent (surgically or through radiation therapy) at least 1 year before study entry are eligible, provided they are considered prostate cancer disease free and the following criteria are met: i) individuals who underwent radical prostatectomy must have an undetectable PSA for >1 year and at screening; and ii) individuals treated with radiation must have a PSA doubling time >1 year (based on at least 3 values taken more than one month apart) and a total PSA that does not meet Phoenix criteria for biochemical recurrence (ie, PSA must be <2.0 above nadir level). Individuals with untreated low-risk (Gleason 6 or less) prostate cancer on active surveillance with a PSA doubling time of >1 year (based on at least 3 values taken more than one month apart) are also eligible.
4. Has had a myocardial infarction within 6 months of randomization/allocation.
5. HIV-infected individuals with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease.
6. Has concurrent active hepatitis B (defined as HBsAg positive and/or detectable HBV DNA) and hepatitis C virus (defined as anti-HCV Ab positive and detectable HCV RNA) infection.
   Note: Hepatitis B and C testing at screening is not required unless there is a known history of HBV and HCV infection or unless mandated by local health authority.

Prior/Concomitant Therapy

7. Has received any systemic anticancer therapy including investigational agents within 4 weeks before randomization/allocation.
   Note: Intravesical chemotherapy treatment given as part of the most recent cystoscopy/TURBT as per local/regional practices is acceptable.
   Note: All AEs due to previous therapies must have recovered to Grade ≤1 or baseline.
   Note: Individuals must have recovered adequately from the toxicity and/or complications of major surgery before randomization/allocation.

8. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention.
   Note: Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
   Note: Any licensed COVID-19 vaccine (including for Emergency Use) in a particular country is allowed in the study as long as it is an mRNA vaccine, replication-incompetent adenoviral vaccine, or inactivated vaccine. These vaccines will be treated just as any other concomitant therapy.
   Note: No vaccine should be administered within 10 days before the first dose of V940.
   Note: Since the first dose of study intervention in Cohort B may not be received within the time periods specified in this criterion, eligibility for individuals in Cohort B can be confirmed at the time of screening but must be re-verified before the first dose of V940 is received.
9. Has received prior treatment with a cancer vaccine.

Prior/Concurrent Clinical Study Experience

10. Is currently participating in or has participated in a study of an investigational agent or has used an investigational agent or device within 4 weeks before randomization/allocation.
    Note: Individuals who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent or device.

Diagnostic Assessments

11. 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 before randomization/allocation.
12. Active autoimmune disease that has required systemic treatment in the past 2 years. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid) is allowed.
13. Active infection and/or diagnosis requiring systemic therapy.
    Note: For Cohort A, treatment of latent tuberculosis is not allowed during screening.

Other Exclusions

14. Has severe hypersensitivity (Grade ≥3) to V940 and/or BCG and/or any of their excipients.
15. Has any contraindication to IV contrast *and* gadolinium or is otherwise unable to have imaging with either CTU or MRU.
16. Has a history of allogeneic tissue/solid organ transplant.
17. Has not adequately recovered from major surgery or has ongoing surgical complications.

18. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study, interfere with the individual's ability to cooperate with the requirements of the study, or interfere with the individual's participation for the full duration of the study, such that it is not in the best interest of the individual to participate, in the opinion of the treating investigator.
19. Individuals who are incapacitated are not eligible for this study.
20. **Cohort A only:** Has one or more of the following contraindications to BCG: prior BCG sepsis or systemic infection, total bladder incontinence, or an adverse experience to a previous BCG instillation that resulted in treatment discontinuation and precludes retreating with BCG.
21. **Cohort A only:** Has current active tuberculosis. Assessment method(s) per local standard of care and institutional guidelines.

5.3 Lifestyle Considerations

There are no lifestyle restrictions.

5.3.1 Meals and Dietary Restrictions

Participants should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea, or vomiting.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study, but are not subsequently randomized/allocated 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 as outlined in the data entry guidelines.

Participants who fail screening may be rescreened for eligibility after consultation between the investigator and the Sponsor and written documentation of the collaborative decision on participant management.

5.5 Participant Replacement Strategy

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