

FAST FACTS

A031803 - PHASE II TRIAL OF INTRAVESICAL GEMCITABINE AND MK-3475 (PEMBROLIZUMAB) IN THE TREATMENT OF PATIENTS WITH BCG-UNRESPONSIVE NON-MUSCLE INVASIVE BLADDER CANCER

Eligibility Criteria

1. Documentation of Disease
 - a. High grade Ta, T1 or CIS urothelial carcinoma. Accrual of patients with Ta or T1 disease may be closed to ensure adequate patients enrollment to meet the primary endpoint (See Section 4.6).
 - b. Persistent disease after completing therapy with at least induction BCG (≥ 5 doses) and the first round of maintenance or second induction course (≥ 2 doses).
 - i. Persistent high risk NMIBC (T1, high grade Ta and/or CIS) must be within 9 months of the last BCG instillation despite having received adequate BCG as defined above.
 - c. High grade T1 after completing therapy with at least induction BCG (≥ 5 doses) or after completing therapy with at least induction BCG (≥ 5 doses) and first round of maintenance or second induction course (≥ 2 doses).
 - i. Persistent high risk NMIBC (T1, high grade Ta and/or CIS) must be within 9 months of the last BCG instillation despite having received adequate BCG as defined above.
 - d. Mixed variant histology (adenocarcinoma, squamous cell carcinoma) is eligible, but pure variant histology is ineligible.
 - e. Patients who are disease free at 6 months after starting BCG but have high grade recurrence (T1, Ta, CIS) while on maintenance therapy would be eligible.
 - i. The recurrence must be within 6 months of the last BCG dose.
2. Patients must be deemed unfit for radical cystectomy by the treating physician or refuse radical cystectomy.
3. All visible tumor must be completely resected 60 days prior to registration (residual pure CIS is permitted).
 - a. All patients must have histologically confirmed urothelial cancer of the bladder within 60 days prior to registration. All patients must have had a cystoscopy without papillary tumor and negative urinary cytology within 21 days of registration. (positive cytology is allowed in patients with pure CIS)
4. All patients with T1 tumors must undergo a re-staging transurethral resection of bladder tumor (TURBT) within 60 days of registration. There must be uninvolved muscularis propria present in the re-staging TURBT. The initial TURBT prior to re-staging TURBT may be greater than 60 days prior to registration.
5. Patients must have had imaging with CT or MRI abdomen/pelvis within 90 days of registration demonstrating no evidence of metastasis.
6. Patients cannot have had a history of urothelial carcinoma in the ureters or prostatic urethra 24 months prior to registration.

7. Prior/Concurrent Clinical Study Experience
 - a. Patients must not be currently participating in or have participated in a study of an investigational agent or have used an investigational device within 4 weeks prior to study registration.
 - b. Note: Participants who have entered the follow-up phase of an investigational study may participate as long as it has been more than 4 weeks after the last dose of the previous investigational agent at time of registration.
8. **Prior/Concomitant Treatment**
 - a. Patients must not have prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137)
 - b. Patients must not have prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137)
 - c. Patients must not have received prior systemic anti-cancer therapy including investigational agents within 4 weeks prior to treatment.
 Note: Participants must have recovered from all AEs due to previous therapies to \leq Grade 1 or baseline. Participants with \leq Grade 2 neuropathy may be eligible.
 Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
 - d. Patients must not have received prior radiotherapy within 2 weeks of study registration. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
 - e. Patients must not have received radiation therapy to the lung that is >30 Gy within 6 months prior to trial registration.
9. Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.
 - a. Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Include as applicable: Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).
 - b. A WOCBP must not have a positive urine pregnancy test within 7 days prior to registration. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
 - c. Patients must not be pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study, starting with registration through the last dose of treatment.
10. Age \geq 18 years
11. ECOG Performance Status 0-2
12. Required Initial Laboratory Values:
 - a. Absolute Neutrophil Count (ANC) \geq 1,500/mm³
 - b. Platelet Count \geq 100,000/mm³
 - c. Hemoglobin \geq 9.0 g/dL
 - d. Creatinine \leq 1.5 x upper limit of normal (ULN)*
 - e. Total Bilirubin \leq 1.5 x ULN**
 - f. AST / ALT \leq 2.5 x ULN
 * In patients with creatinine $>$ 1.5 x ULN, if measured or calculated creatinine clearance $>$ 30 mL/min, then patient is eligible.

** In patients with a total bilirubin > 1.5 x ULN, if direct bilirubin < 1.0 X ULN, then patient is eligible.

13. Comorbid conditions

- a. Patients must not have had an active autoimmune disease requiring systemic treatment within 7 days prior to registration. Autoimmune diseases include, but not limited to, lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid syndrome, Wegener's granulomatosis, Sjogren's syndrome, Bell's palsy, Guillain-Barre syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.
- b. Patients must not have a 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 registration.
Note: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
- c. Patients must not have a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
- d. Patients must not have active tuberculosis
- e. Patients must not have been treated with antibiotics for an active infection within 14 days prior to registration. Prophylactic antibiotics are permitted. Treatment for a UTI is allowed but must be deemed adequately treated by the treating physician prior the start of C1 D1.
- f. Patients must not have a history of idiopathic pulmonary fibrosis or organizing pneumonia.
- g. Patients must not have a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
- h.
- i. Patients with HIV are eligible with the following:
 - i. Patients must not have a known psychiatric or substance abuse disorder that would interfere with the participant's ability to cooperate with the requirements of the study.
- j. HIV-infected participants must not have a history of Kaposi sarcoma and/or Multicentric Castleman Disease.
- k. Patients must not have a known additional malignancy that has had progression or has required active treatment in the last three years. Exceptions include basal or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer. A history of prostate cancer that was treated with definitive intent is allowed, provided that the prostate-specific antigen (PSA) is undetectable for at least 1 year while off androgen deprivation therapy.

14. Diagnostic assessments. Patients must not have known active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases may participate provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of study treatment.
- b. Patients must not have severe hypersensitivity (\geq Grade 3) to pembrolizumab and/or any of its excipients.
 - c. Patients must not have an active infection requiring systemic therapy.
 - d. Patients must not have a known history of Hepatitis B (defined as HBsAg reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection.
- Note: No testing for Hepatitis B and Hepatitis C is required unless mandated by a local health authority.

15. Patients must not have received live vaccines within 30 days of study drug administration. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

Schema

