Cancer Research Consortium of West Michigan
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FAST FACTS

ALLIANCE A031501
PHASE III RANDOMIZED ADJUVANT STUDY OF MK-3475 (PEMBROLIZUMAB) IN MUSCLE INVASIVE AND LOCALLY ADVANCED UROTHELIAL CARCINOMA (AMBASSADOR) VERSUS OBSERVATION

On-Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ or incidental organ-confined prostate cancer found on cystoprostatectomy (provided that the following criteria are met: Stage T2N0M0 or lower;
- Gleason score ≤ 3+4, PSA undetectable). Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years and currently do not require systemic therapy.
- Has received systemic chemotherapy in the adjuvant setting following cystectomy, nephrectomy, or ureterectomy.

In addition:

- 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.
- Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

Pre-Registration Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility for pre-registration by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

1. **Documentation of Disease:**
   Histologically confirmed muscle-invasive urothelial carcinoma of the bladder, urethra, upper tract, or LN+ disease. Variant histology allowed as long as urothelial carcinoma is predominant (any amount of squamous differentiation is allowed). Any component of neuroendocrine carcinoma is excluded.

2. Tissue available for Central PD-L1 Testing

- Paraffin tissue samples obtained by transurethral resection of muscle-invasive bladder tumor, upper tract resection, or radical cystectomy/nephrectomy/ureterectomy/ nephroureterectomy/cystoprostatectomy or urethrectomy must be available.
- This specimen submission is mandatory prior to registration as results will be used for stratification.
- Specimens from radical/definitive surgery (radical cystectomy/nephrectomy/ureterectomy /nephroureterectomy/cystoprostatectomy and LN dissection) are preferred over transuretheral resection, if available. See Section 6.2 for details on specimen submission.

3. Disease Status

- Patient must fit into one of the following three categories:
  - Patients who received neoadjuvant chemotherapy and pathologic stage at surgical resection is ≥ pT2 and/or N+
    OR
  - Patients who are not cisplatin-eligible (according to ≥ 1 of the following criteria: ECOG performance status of 2, creatinine clearance < 60 mL/min, grade ≥ 2 hearing loss, grade ≥ 2 neuropathy, or New York Heart Association Class III heart failure [38]) and pathologic stage at surgical resection is ≥ pT3 or pN+)
    OR
  - Patients that decline adjuvant cisplatin-based or other systemic chemotherapy based on an informed discussion with the physician and pathologic stage at surgical resection is ≥ pT3 or pN+

4. Surgical History

- The 7th edition of AJCC staging will be utilized.
- Patient must have had radical cystectomy (cystoprostatectomy for men) and lymph node dissection (for bladder primary), or nephrectomy, nephroureterectomy or ureterectomy (for uppertract tumors) or urethrectomy (in addition to a radical cystectomy-either simultaneously or in the past) ≥4 weeks but ≤ 16 weeks prior to pre-registration. Patients who have had a partial cystectomy as definitive therapy are not eligible.
- No gross cancer at the surgical margins. Microscopic invasive urothelial carcinoma positive margins are allowed. CIS at margins is considered negative margins.
- No evidence of residual cancer or metastasis after surgery. Patients with uppertract urothelial carcinoma must have a negative cystoscopy within 3 months prior to pre-registration. If the bladder has been removed a cystoscopy is not required.

5. No metastatic disease (or radiologic findings "concerning" for metastatic disease) on cross-sectional imaging (according to RECIST v1.1 criteria).

6. Patient History

- No active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome because of the risk of recurrence or exacerbation of disease. HIV infected patients on effective anti -retroviral therapy with undetectable viral load within 6 months are eligible.

- No current pneumonitis or prior history of non-infectious pneumonitis that required steroids within the previous 5 years.
- Patients with vitiligo, endocrine deficiencies including type I diabetes mellitus, thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible.
- Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.
- No known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected)
- No live vaccine within 30 days prior to the first dose of study drug. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster (chicken pox), yellow fever, rabies, Bacillus Calmette-Guerin (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.

7. Prior Treatment

- No postoperative/adjuvant systemic therapy.
- No prior treatment with any therapy on the PD-1/PD-L1 axis.
- No treatment with any other type of investigational agent ≤ 4 weeks before pre-registration
- No major surgery ≤ 4 weeks before pre-registration
- No radiation therapy ≤ 4 weeks before pre-registration
- No neoadjuvant chemotherapy ≤ 4 weeks before pre-registration
- Not currently requiring hemodialysis

8. Age ≥ 18 years

9. Not pregnant and not nursing, because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown.

10. ECOG Performance Status ≤ 2

11. Required Pre-registration laboratory values:

Absolute Neutrophil Count (ANC)	$\geq 1{,}200/mm^3$
Leukocytes	$\geq 3{,}000/ mm^3$
Platelet Count	$\geq 75{,}000/mm^3$
Hemoglobin	≥ 9 g/dL or ≥ 5.6 mmol/L
Total Bilirubin Bilirubin for patients with Gilbert's	≤ 1.5 x upper limit of normal (ULN) ≤ 3.0 x ULN
Calc. Creatinine Clearance	≥ 30 mL/min (using either CKD-EPI equation or Cockroft-Gault formula)
AST / ALT	≤ 3.0 x ULN
Serum Albumin	≥ 2.8 g/dL
For women of childbearing potential only: a negative urine or serum pregnancy test done ≤ 7 days prior to pre-registration is required.	

Registration Eligibility Criteria

1. Results of central PD-L1 testing available.

- Q2 Solutions will forward the PD-L1 results to the statistical center and the statistical center will notify the site that the result is available.
- Since the results will be blinded to the site the notification from the Alliance registration/randomization office will serve as a confirmation of this eligibility criteria; after sites receive the confirmation e-mail from Alliance they can register the patient.

Schema
1 Cycle = 21 Days