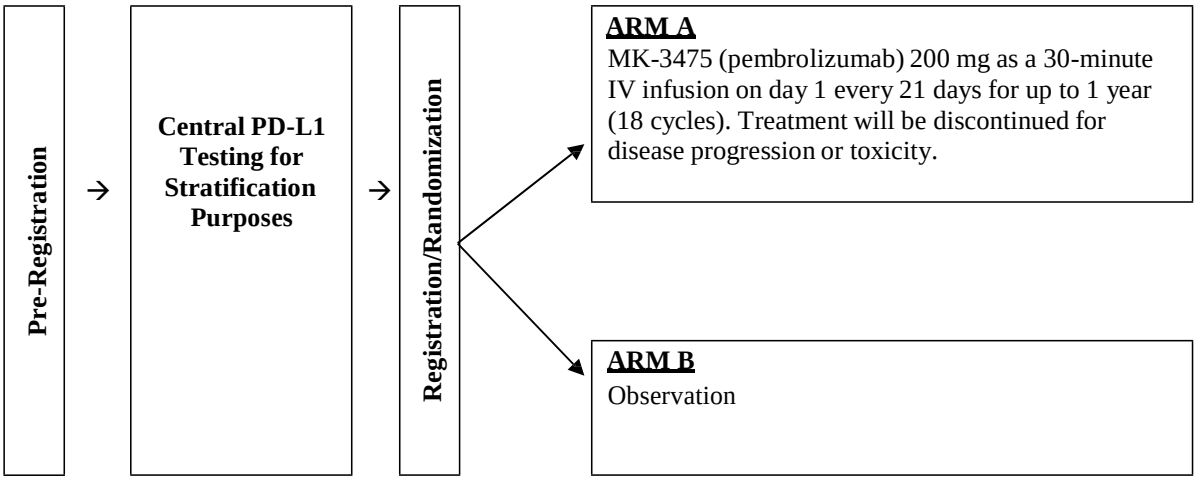
Phase III randomized "Adjuvant study of MK-3475 (pembrolizumab) in muScle invaSive and locAlly aDvanced urOthelial caRcinoma" (AMBASSADOR) versus observation

Pre-registration Eligibility Criteria	**Required Pre-registration Lab Values**	
Histologically confirmed muscle-invasive urothelial carcinoma of the bladder or upper tract	Absolute Neutrophil Count (ANC)	≥ 1,200/mm^3
Paraffin tissue available for PD-L1 analysis	Leukocytes	≥ 3,000/ mm^3
Disease status per Section 3.2.3	Platelet Count	≥ 75,000/mm^3
Radical resection of bladder cancer ≤16 weeks prior to pre-registration No invasive cancer at the surgical margins	Hemoglobin Creatinine	≥ 9 g/dL or ≥5.6 mmol/L ≤ 2.0 x ULN
No evidence of residual cancer or mets after surgery	**OR**	
No measurable disease on cross-sectional imaging	Calc. Creatinine	> 30 ml/min
No active autoimmune disease or history of autoimmune disease	Clearance	
that may recur No current or history of pneumonitis	Total Bilirubin AST/ALT	≤ 1.5 x ULN ≤ 3.0 x ULN
No known active Hepatitis B or C	Serum Albumin	≥ 2.8 g/dL
No postoperative/adjuvant systemic therapy		
No prior treatment with any therapy on the PD-1 Or PD-L1 axis		
No, treatment with an investigational agent, major surgery, radiation therapy or neoadjuvant chemotherapy ≤4 weeks prior to pre-registration		
Age ≥18 years; Non-pregnant and non-nursing; ECOG PS 0-2		
Registration Eligibility Criteria		
Central PD-L1 results available		

Schema
1 Cycle = 21 Days



Treatment is to continue until metastatic recurrence or unacceptable toxicity for up to one year. Metastatic recurrence is defined by a new lesion on CT scan. Patients will be followed for a total of 5 years from the date of registration or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 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 $\leq$ 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 $\geq$ 3 years.
- Has received systemic chemotherapy in the adjuvant setting following cystectomy/nephrectomy/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).

3.2 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).

3.2.1 Documentation of Disease:

___ Histologically confirmed muscle-invasive urothelial carcinoma of the bladder or upper tract. Variant histology allowed as long as urothelial carcinoma is predominant (>50%). Pure small-cell carcinoma is excluded.

3.2.2 Tissue available for Central PD-L1 Testing

Paraffin tissue samples obtained by transurethral resection of muscle-invasive bladder tumor, upper tract resection, cystectomy/nephrectomy/ureterectomy, or nephroureterectomy must be available. This specimen submission is mandatory prior to registration as results will be used for stratification. See Section 6.2 for details on specimen submission.

3.2.3 Disease Status

___ Patient must fit into <u>one</u> 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+

3.2.4 Surgical History

___ Patient must have had radical surgical resection of their bladder cancer ≥4 weeks but ≤ 16 weeks prior to pre-registration.

___ No invasive cancer at the surgical margins

___ No evidence of residual cancer or metastasis after surgery

3.2.5 No metastatic disease on cross-sectional imaging (according to RECIST v1.1 criteria).

3.2.6 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 (+) patients are eligible as long as they have: cd4 >200, undetectable viral load and on HAART therapy.

___ 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)

3.2.7 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

3.2.8 Age ≥ 18 years

3.2.9 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.

3.2.10 ECOG Performance Status ≤ 2