KEYNOTE-045 entry criteria

Subject Inclusion criteria

In order to be eligible for participation in this trial, the subject must:

1. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be ≥ 18 years of age on the day of signing informed consent.
3. Have histologically or cytologically-confirmed diagnosis of urothelial cancer of the renal pelvis, ureter, bladder, or urethra. Both transitional cell and mixed transitional/non-transitional cell histologies are allowed, but transitional cell carcinoma must be the predominant histology. Subjects with non-urothelial cancer of the urinary tract are not allowed.
4. ~~Have had progression or recurrence of urothelial cancer following receipt of a first-line platinum-containing regimen (cisplatin or carboplatin):~~
    - ~~Received a first-line platinum-containing regimen in the metastatic setting or for inoperable locally advanced disease;~~
    - ~~Received adjuvant platinum-containing therapy following cystectomy for localized muscle-invasive urothelial cancer, with recurrence/progression ≤ 12 months following completion of therapy.~~
    - ~~Received neoadjuvant platinum-containing therapy prior to cystectomy for localized muscle-invasive urothelial cancer, with recurrence ≤ 12 months following completion of therapy.~~
5. Have received no more than two prior lines of systemic chemotherapy for urothelial cancer. Subjects for whom the most recent therapy has been a non -platinum-based regimen following progression/recurrence on platinum-based therapy (i.e. third-line patients) are eligible if they have progressed/recurred on their most recent therapy.
6. Have provided tissue for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. A newly-obtained biopsy is strongly preferred but not required if archival tissue is adequate for analysis. Adequacy of the archived or freshly-obtained biopsy specimen for PD-L1 biomarker analysis must be confirmed by the central laboratory during the screening period prior to enrollment.
7. Have measurable disease based on RECIST 1.1 as assessed by the investigator/site radiologist. Tumor lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
8. Have a performance status of 0, 1, or 2 on the ECOG Performance Scale, as assessed within 10 days prior to treatment initiation. Subjects with an ECOG performance status of 2 must have a hemoglobin ≥10g/dL, must not have liver metastases, and must have received the last dose of their last prior chemotherapy regimen ≥ 3 months (90 days) prior to enrollment.
9. Demonstrate adequate organ function as defined in Table 1, all screening labs should be performed within 10 days of treatment initiation.

Table 1

System	Laboratory value
Hematological	
Absolute neutrophil count	≥1,500 /mcL
Platelets	≥100,000 /mcL
Hemoglobin	≥9.0 g/dL or ≥5.6 mol/L
Renal	
Creatinine OR measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5x ULN OR ≥30 mL/min for subjects with creatinine levels >1.5x institutional ULN.
Hepatic	
Total bilirubin	≤1.5x ULN OR Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5x ULN
AST and ALT	≤2.5x ULN OR ≤5x ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio or Prothrombin Time, activated Partial Thromboplastin Time	≤1.5x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants. ≤1.5x ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants.

10. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Female subjects of childbearing potential must be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.
12. Male subjects must agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Has disease that is suitable for local therapy administered with curative intent.
2. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks prior to the first dose of trial treatment.
3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
4. Has had a prior anti-cancer monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Subjects with ≤ Grade 2 neuropathy or ≤ Grade 2 alopecia are an exception to this criterion and may qualify for the study.

   Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
6. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer. A history of prostate cancer that was identified incidentally following cystoprostatectomy for bladder cancer is acceptable, provided that the following criteria are met: _Stage T2N0M0 or lower; Gleason score ≤ 6, PSA undetectable.
7. Has known active central nervous system metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.
8. Has an active autoimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic or immunosuppressive agents. Subjects with vitiligo, diabetes Type I, or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study. Subjects with hypothyroidism stable on hormone replacement or Sjøgren's syndrome will not be excluded from the study.
9. Has active cardiac disease, defined as:
    - Myocardial infarction or unstable angina pectoris within 6 months of the first date of study therapy.
    - History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation), high-grade atrioventricular block, or other cardiac arrhythmias requiring anti-arrhythmic medications (except for atrial fibrillation that is well controlled with antiarrhythmic medication); history of QT interval prolongation.
    - New York Heart Association Class III or greater congestive heart failure, or left ventricular ejection

fraction of < 40%.

10. Has evidence of interstitial lung disease or active non-infectious pneumonitis.
11. Has an active infection requiring systemic therapy.
12. Has a history of severe hypersensitivity reaction (e.g. generalized rash/erythema, hypotension, bronchospasm, angioedema, or anaphylaxis) to paclitaxel or to other drugs formulated with polyoxyethylated castor oil, or to vinflunine or other vinca alkaloids.
13. Requires ongoing therapy with a medication that is a strong inhibitor of the CYP3A4 enzymes.
14. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
16. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
17. Has received prior therapy with an anti-PD-1 or anti-PD-L1 agent, or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137).
18. Has received paclitaxel as chemotherapy for urothelial cancer (for subjects in regions where vinflunine is not an approved therapy), OR has received both prior paclitaxel and vinflunine as chemotherapy for urothelial cancer (in regions where vinflunine is an approved therapy).
19. Has a known history of Human Immunodeficiency Virus (HIV) (HIV-1/2 antibodies).
20. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
21. Has received a live virus vaccine within 30 days of planned start of trial treatment.
22. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling, or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.