**KEYNOTE-045: Randomized Phase 3 Trial of Pembrolizumab (MK-3475) Versus Paclitaxel, Docetaxel, or Vinflunine for Previously Treated Metastatic Urothelial Cancer**

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**INTRODUCTION**

- Urothelial cancer describes a range of tumors that arise from the urothelial endothelium, which includes the bladder, renal pelvis, ureter, and urethra
- Patients with metastatic urothelial cancer that has recurred or progressed following platinum-based chemotherapy present a challenge
- There are no approved therapies in the United States for recurrent/progressive urothelial cancer
- Paclitaxel, docetaxel, and vinflunine are commonly used as second-line therapy for advanced urothelial cancer, but median overall survival (OS) is only 7–8 months
- Pembrolizumab (MK-3475) is a humanized IgG4 kappa monoclonal antibody that directly blocks the interaction between the programmed death 1 (PD-1) receptor by its ligands resulting in inhibition of the active T-cell immune response to tumor rejection in vivo
- Preclinical data have demonstrated that blocking the interaction between PD-1 and its ligands promotes effector T-cell infiltration of the tumor and tumor rejection in vivo
- PD-L1 is widely expressed by tumor cells in urothelial cancer
- Preclinical data have demonstrated that blocking the interaction between PD-1 and its ligands promotes effector T-cell infiltration of the tumor and tumor rejection in vivo
- Pembrolizumab (MK-3475) is a humanized IgG4 kappa monoclonal antibody that directly blocks the interaction between the programmed death 1 (PD-1) receptor and its two ligands (PD-L1 and PD-L2)
- The PD-1 receptor is expressed on activated T cells, and activation of the PD-1 receptor by its ligands results in inhibition of the active T-cell immune surveillance of tumors
- Key inclusion criteria for patients with a total bilirubin ≤1.5 x ULN and an aspartate aminotransferase level ≤3 x ULN if alkaline phosphatase is also ≤2 x ULN
- The overall proportion of patients receiving vinflunine is capped at approximately 35% and will only be a comparator option in countries where vinflunine is approved for the treatment of metastatic urothelial cancer

**METHODS**

**Study Design**
- Multicenter, randomized, active-controlled, open-label, adaptively designed phase 3 KEYNOTE-045 clinical trial (ClinicalTrials.gov, NCT02256436)
- Pembrolizumab in patients with metastatic or locally advanced/unresectable urothelial cancer that has recurred or progressed following platinum-containing chemotherapy (Figures 2 and 3)
- Patients eligible for inclusion will be randomized centrally using an interactive voice/integrated Web response system in a 1:1 ratio to either the investigational treatment or an active comparator in an unblinded fashion using centrally randomized blocks
- Pembrolizumab will be given for up to 24 months or until confirmed disease progression, unacceptable toxicity, or investigator decision; treatment may be discontinued following complete response

**Patient Eligibility Criteria**
- Male/female patients aged ≥18 years
- Histologically or cytologically confirmed diagnosis of urothelial cancer of the renal pelvis, ureter, bladder, or urethra
- Provided written informed consent
- Prior platinum failure: disease progression or recurrence of urothelial cancer following receipt of first-line platinum-containing regimen (cisplatin or carboplatin)
- Received no more than 2 prior lines of systemic chemotherapy for urothelial cancer
- Tissue available for biomarker analysis from an archival tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated
- Measurable disease based on RECIST v1.1
- ECOG performance status: 0, 1, or 2
- Prior antinecancer monoblock antibody treatment within 4 weeks prior to study
- Prior chemotherapy, targeted small-molecule therapy, or radiation therapy within 2 weeks prior to study
- Active central nervous system metastases and/or carcinomatous meningitis
- Active cardiac disease, active noninfectious pneumonitis, or evidence of an interstitial lung disease
- Active infection requiring systemic therapy
- History of severe hypersensitivity reaction to study treatments

**Patient Assessments and Follow-Up**
- Assessments are to be performed prior to day 1 and prior to dosing for each treatment cycle
- Radiographic imaging assessment will be performed at 9 weeks after randomization and every 6 weeks for the first year (12 months) followed by every 12 weeks thereafter
- Adverse events (AEs) will be graded and recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0
- After the end of treatment, patients will be followed for a minimum of 30 days for AE monitoring
- Serious AEs will be collected for up to 90 days after end of treatment, or until 30 days after the start of a new anticancer treatment
- Once a patient stops receiving treatment, the patient may be contacted by telephone every 12 weeks to assess for survival status until death or the end of the study

**Planned Statistical Analyses**
- Analysis will be employed in the intent-to-treat population
- The all-patients-as-treated population will be employed for safety analyses

**REFERENCES**


**ACKNOWLEDGMENTS**

Editorial assistance was provided by the APO Group (Yardley, PA, USA) and was funded by Merck & Co., Inc.