TPS588

Perioperative Enfortumab Vedotin Plus Pembrolizumab Versus Chemotherapy in Cisplatin-Eligible Patients With Muscle-Invasive Bladder Cancer: Phase 3 KEYNOTE-B15/EV-304

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Background

- Standard of care for cisplatin-eligible patients with muscle-invasive bladder cancer (MIBC) is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy + pelvic lymph node dissection (RC + PLND); however, up to 50% of patients experience disease recurrence or progression[1,2]
- Pembrolizumab, a PD-1 inhibitor, is approved in the United States for patients with[3]
  - Locally advanced or metastatic urothelial carcinoma who are ineligible for any platinum-containing chemotherapy
  - Locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or within 12 months before neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
  - Bacillus Calmette-Guérin–unresponsive, high-risk non–muscle-invasive bladder cancer (NMIBC) + carcinoma in situ with or without papillary tumors and who are ineligible for or have elected not to undergo cystectomy
- In the European Union, pembrolizumab is approved for patients with[4]
  - Locally advanced or metastatic urothelial carcinoma who received prior platinum-containing chemotherapy
  - Locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy and whose tumors express PD-L1 with a combined positive score (CPS) of ≥10
- Enfortumab vedotin (EV) is a Nectin-4–directed antibody-drug conjugate composed of a fully human anti–Nectin-4 immunoglobulin G1 kappa monoclonal antibody conjugated to the small molecule microtubule-disrupting agent monomethyl auristatin E via a protease-cleavable maleimidocaproyl valine-citrulline linker[5]
  - Approved in the United States for the treatment of adults with locally advanced or metastatic urothelial cancer who:
    - Previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy
    - Are ineligible for cisplatin-containing chemotherapy and have previously received ≥1 prior lines of therapy
- EV + pembrolizumab was shown to have encouraging antitumor activity and acceptable safety as first-line treatment for cisplatin-ineligible patients with metastatic urothelial cancer in the EV-103/KEYNOTE-869 phase 1/2 study[6]
- KEYNOTE-B15/EV-304 (NCT04700124) is a randomized, open-label, phase 3 study designed to evaluate perioperative EV + pembrolizumab versus neoadjuvant gemcitabine + cisplatin in cisplatin-eligible participants with MIBC

Objectives

Primary

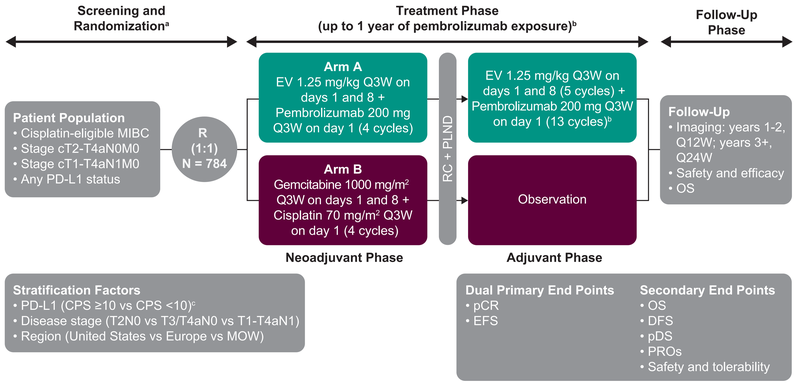
- To compare the following between perioperative EV + pembrolizumab and RC + PLND versus neoadjuvant gemcitabine + cisplatin and RC + PLND in cisplatin-eligible patients with MIBC:
  - Pathologic complete response (pCR)
  - Event-free survival (EFS)

Secondary

- To compare the following between perioperative EV + pembrolizumab and RC + PLND versus neoadjuvant gemcitabine + cisplatin and RC + PLND in cisplatin-eligible patients with MIBC:
  - Overall survival (OS)
  - Disease-free survival (DFS)
  - Pathologic downstaging (pDS)
    - Defined as any stage lower than pT2 (includes pT0, pTis, pTa, and pT1) and N0 in tissue obtained by RC + PLND
  - Patient-reported outcomes (PROs)
  - Safety and tolerability

Methods

Study design



AE, adverse event; BICR, blinded independent central review; CT, computed tomography; MOW, most of world; MRI, magnetic resonance imaging; Q3W, every 3 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks; R, randomization.

[a]All patients will undergo baseline imaging studies (CT or MRI) for clinical staging (evaluated by BICR before randomization) and central pathology confirmation for pathologic stage pT2-T4a or pT1 (only if N1), urothelial histology, and PD-L1 expression.

[b]Until unacceptable AEs, intercurrent illness preventing further treatment administration, or investigator or patient decision to withdraw.

[c]CPS is defined as the number of PD-L1–staining cells (tumor cells, lymphocytes, macrophages) divided by the total number of viable tumor cells, multiplied by 100.

Patient eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Histologically confirmed urothelial carcinoma (clinical stage T2-T4aN0M0 or T1-T4aN1M0) with predominant (≥50%) urothelial histology and any level of PD-L1 expression (CPS ≥10 or CPS <10)[a] • Clinically nonmetastatic bladder cancer (N≤1, M0)[b] • Eligibility for RC + PLND and must agree to undergo curative-intent standard RC + PLND • TURBT (obtained ≤60 days [+14 days] before enrollment) submitted for central pathology assessment and adequate to determine urothelial histology and PD-L1 expression • ECOG PS 0 or 1 • Adequate organ function	• Additional nonurothelial malignancy that is progressing or necessitated active anticancer treatment ≤3 years before study randomization • Any prior systemic treatment, chemoradiation, or radiation therapy treatment for MIBC[c]; radiation therapy to the bladder; or partial cystectomy • ≥N2 disease or metastatic disease (M1) • Cisplatin ineligibility[d] • Prior therapy with an anti–PD-1, anti–PD-L1, or anti–PD-L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor • Prior systemic anticancer therapy that included investigational agents ≤3 years before randomization • Active autoimmune disease necessitating steroids • Current pneumonitis or history of (noninfectious) pneumonitis necessitating steroids • History of HIV infection, active HBV infection, or active HCV infection • Ongoing sensory or motor neuropathy grade ≥2 • History of uncontrolled diabetes

CrCl, creatinine clearance; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; NYHA, New York Heart Association; TURBT, transurethral resection of bladder tumor.

[a]cT2-T4aN0M0 or cT1-T4aN1M0; histology and presence of muscle invasion to be confirmed by BICR (central pathology and/or central imaging assessment). Participants whose tumors are pT1 are eligible only if the participants have N1 disease (confirmed by BICR).

[b]Determined by imaging (CT of the chest and CT or MRI of the abdomen/pelvis), confirmed by BICR.

[c]Prior treatment for NMIBC with intravesical instillation therapy permitted.

[d]Determined by any 1 of the following: impaired renal function with measured CrCl <60 mL/min; ECOG PS ≥2; CTCAE v5.0 grade ≥2 peripheral neuropathy; CTCAE v5.0 grade ≥2 audiometric hearing loss; or NYHA class III heart failure.

Assessment and follow-up

Assessments	Details
Tumor response	• Imaging of the chest, abdomen, and pelvis will be performed 6 weeks before cystectomy to exclude disease progression that might preclude curative-intent surgery; patients who remain radiographically free of distant metastases will undergo RC + PLND within 6 weeks of the last dose of neoadjuvant treatment • Postoperative imaging will be conducted 6 weeks (42 days ± 14 days) after cystectomy • After postcystectomy imaging at 6 weeks, imaging will be performed Q12W (84 days ± 7 days) up to the end of year 2 (96 weeks), at discontinuation, and then Q24W (168 days ± 14 days) thereafter • All RC + PLND surgical specimens will be assessed by blinded independent central pathology to determine pathologic response • Patients with new recurrent/metastatic disease will have met the primary EFS end point and will not undergo further therapy but will transition into survival follow-up phase – Patients who discontinue for reasons other than an EFS event will be followed up for posttreatment efficacy and disease status until an EFS event occurs • All patients will be followed up for OS status until death, withdrawal of consent, or end of study, whichever occurs first
Safety	• AEs will be monitored and assessed by the investigator per CTCAE v5.0 from randomization for up to 30 days after the last dose of study treatment
PROs	• PROs will be assessed using the EORTC QLQ-C30, BCI, and EuroQol EQ-5D-5L questionnaires

BCI, Bladder Cancer Index; EORTC QLQ-C30, EORTC Quality of Life Questionnaire Core 30; EuroQol EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire.

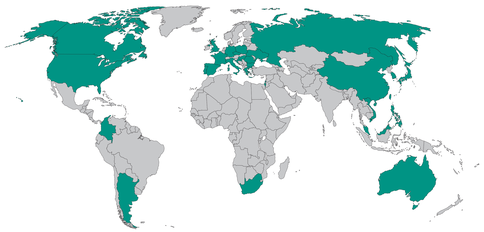
Analyses

Analyses	Details
Efficacy	• The full analysis set will serve as the analysis population for pCR and pDS and consists of all randomly assigned patients regardless of whether they received treatment – pCR and pDS will be analyzed using the stratified Miettinen and Nurminen method,[7] with strata weighting by sample size • The intention-to-treat population (all randomly assigned patients) will serve as the analysis population for EFS and OS – EFS and OS will be evaluated using the nonparametric Kaplan-Meier method; treatment differences (ie, HR) will be assessed using the stratified log-rank test and will be estimated using the stratified Cox proportional hazards model with the Efron method for handling ties (HR and 95% CI) • The DFS analysis population will consist of patients who are disease free at initial postsurgery imaging; data will be summarized descriptively using the Kaplan-Meier method
Safety	• Safety will be assessed by clinical review of all relevant parameters, including AEs, serious AEs, fatal AEs, laboratory test results, vital signs, ECG, and surgical complications

ECG, electrocardiography; HR, hazard ratio.

Status

Sites of enrollment for KEYNOTE B-15 (in green)



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