KEYNOTE-B15/EV-304: A Phase 3, Randomized, Open-Label Study of Perioperative Enfortumab Vedotin Plus Pembrolizumab Versus Chemotherapy in Cisplatin-Eligible Patients With Muscle-Invasive Bladder Cancer

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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 plus 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 for patients with
  - Locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy and are PD-L1 positive (combined positive score [CPS] ≥10) or ineligible for any platinum-containing chemotherapy regardless of PD-L1 status[3,4]
  - Locally advanced or metastatic urothelial carcinoma who experience disease progression during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy[3,4]
  - Bacillus Calmette-Guerin–unresponsive, high-risk non–muscle-invasive bladder cancer (NMIBC) plus carcinoma in situ with or without papillary tumors and who are ineligible for or have elected not to undergo cystectomy[3]
- 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]
  - Received accelerated approval 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 for neoadjuvant/adjuvant locally advanced or metastatic disease
- EV + pembrolizumab showed 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 to evaluate perioperative EV + pembrolizumab versus neoadjuvant gemcitabine + cisplatin in cisplatin-eligible participants with MIBC

Objectives

Primary Objectives

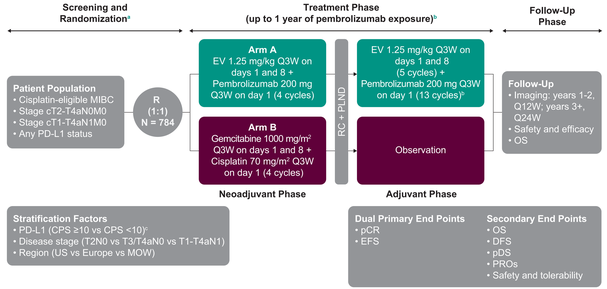
- To compare the following between perioperative EV + pembrolizumab and RC + PLND versus neoadjuvant gemcitabine + cisplatin and RC + PLND in cisplatin-eligible patients with MIBC
  - Pathologic complete response (pCR)
  - Event-free survival (EFS)

Secondary Objectives

- 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 (include 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 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	• Additional nonurothelial malignancy that is progressing or has necessitated active anticancer treatment ≤3 years before study randomization
• 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]	• Any prior systemic treatment, chemoradiation, or radiation therapy treatment for MIBC[c]; radiation therapy to the bladder; or partial cystectomy
• Clinically nonmetastatic bladder cancer (N≤1, M0)[b]	• ≥N2 disease or metastatic disease (M1)
• Eligibility for RC + PLND and must agree to undergo curative-intent standard RC + PLND	• Cisplatin ineligibility[d]
• TURBT (obtained ≤60 days [+14 days] before enrollment) submitted for central pathology assessment and adequate to determine urothelial histology and PD-L1 expression	• 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
• ECOG PS 0 or 1	• Prior systemic anticancer therapy that included investigational agents ≤3 years before randomization
• Adequate organ function	• Active autoimmune disease necessitating steroids
	• Current pneumonitis or history of (noninfectious) pneumonitis necessitating steroids
	• History of HIV infection or active HBV or 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. 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 one of the following: impaired renal function with measured CrCl <60 mL/min; ECOG PS ≥2; CTCAE v.5.0 grade ≥2 peripheral neuropathy; CTCAE v.5.0 grade ≥2 audiometric hearing loss; NYHA class III heart failure.

Assessment and Follow-Up

Assessments	Details
Tumor response	• Imaging of the chest, abdomen, and pelvis will be performed ≤5 weeks (35 days + 7 days) before cystectomy and 6 weeks (42 days ± 14 days) after cystectomy – To exclude disease progression that might preclude curative-intent surgery, patients who remain radiographically free of distant metastases will undergo RC + PLND ≤6 weeks before the last dose of neoadjuvant treatment • After postcystectomy imaging at 6 weeks (±14 days), 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 BICR 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 EQ-5D-5L questionnaires

EORTC, European Organisation for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire Core 30; BCI, bladder cancer index; EQ-5D-5L, EuroQol 5-dimension, 5-level questionnaire.

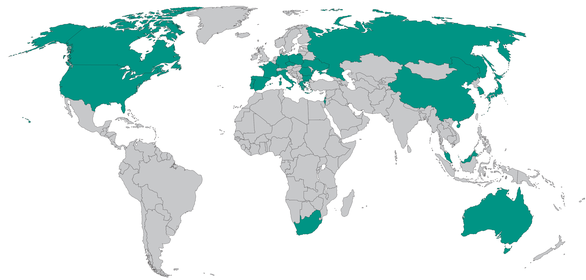
Analyses

Analyses	Details
Efficacy	• 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 Efron's 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	• 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

- KEYNOTE-B15/EV-304 is currently enrolling in Africa, Asia, Australia, Europe, and North America



References

1. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines): bladder cancer (Version 3.2021). April 22, 2021. Accessed May 2, 2021. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf
2. Stenzl A et al. *Eur Urol.* 2009;55:815-825.
3. KEYTRUDA® (pembrolizumab) injection, for intravenous use. 05/2021. Merck Sharp & Dohme Corp.: Whitehouse Station, NJ, USA; 2021.
4. Keytruda (pembrolizumab) 50 mg powder for concentrate for solution for infusion (summary of product characteristics). Hoddesdon, UK: Merck Sharp & Dohme Limited; March 2021.
5. Padcev (enfortumab vedotin) injection, for intravenous use. Northbrook, IL: Astellas Pharma US, Inc.; March 2021.
6. Rosenberg JE et al. *J Clin Oncol.* 2020;38(suppl 6). Abstract 441. Accessed May 2, 2021. https://ascopubs.org/doi/abs/10.1200/JCO.2020.38.6_suppl.441
7. Miettinen O, Nurminen M. *Stat Med.* 1985;4:213-226.

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