TPS4601

KEYNOTE-905/EV-303: A Phase 3 Study to Evaluate the Efficacy and Safety of Perioperative Pembrolizumab or Pembrolizumab Plus Enfortumab Vedotin for Muscle-Invasive Bladder Cancer

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Background

- Standard of care for patients with cisplatin-ineligible muscle-invasive bladder cancer (MIBC) is radical cystectomy + pelvic lymph node dissection (RC + PLND) alone, but rates of recurrence are high (up to 50%)[1-3]
- The PD-1 inhibitor pembrolizumab is approved for patients who are cisplatin ineligible with locally advanced or metastatic urothelial carcinoma who have tumors expressing PD-L1 and for patients unable to receive platinum-based chemotherapy regardless of PD-L1 status[4,5]
  - Pembrolizumab is also approved for locally advanced or metastatic urothelial carcinoma that progressed during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy
- Enfortumab vedotin is an antibody-drug conjugate comprising a fully human monoclonal antibody directed to Nectin-4 conjugated to the clinically validated microtubule-disrupting agent monomethyl auristatin E via a protease-cleavable linker[6]
  - Enfortumab vedotin is approved for the treatment of adults with locally advanced or metastatic urothelial cancer who have previously received a PD-1 or PD-L1 inhibitor and platinum-containing chemotherapy, or adults who are ineligible for cisplatin-containing chemotherapy and have previously received ≥1 prior lines of therapy[6]
- In a phase 1b/2 study, pembrolizumab + enfortumab vedotin demonstrated promising activity and durability as with a manageable safety profile as a first-line therapy in patients with cisplatin-ineligible locally advanced/metastatic urothelial cancer[7,8]
  - In the dose-escalation cohort and expansion cohort A, the confirmed investigator-assessed objective response rate (ORR) was 73.3% (complete response [CR], 15.6%)[7]
  - In the randomized cohort K, pembrolizumab + enfortumab vedotin demonstrated a higher confirmed ORR by blinded independent central review (BICR) (64.5% vs 45.2%), 12-month progression-free survival rate (55.1% vs 35.8%), and 12-month overall survival (OS) rate (80.7% vs 70.7%) than enfortumab vedotin alone[8]
- KEYNOTE-905/EV-303 (NCT03924895) is a randomized, controlled, parallel-group, multicenter, open-label, phase 3 study of perioperative pembrolizumab and RC + PLND or perioperative pembrolizumab + enfortumab vedotin and RC + PLND versus RC + PLND alone in patients with MIBC who are cisplatin ineligible or who are cisplatin eligible but decline cisplatin-based chemotherapy

Objectives

Primary

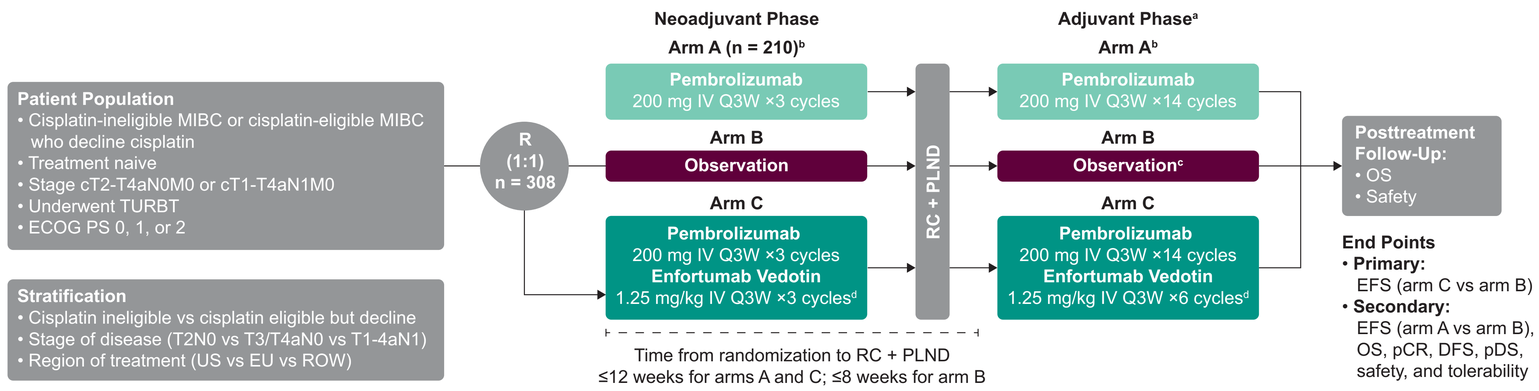
- To compare event-free survival (EFS) for patients treated with perioperative pembrolizumab + enfortumab vedotin and RC + PLND versus those treated by RC + PLND alone

Secondary

- To compare EFS for patients treated with perioperative pembrolizumab and RC + PLND versus those treated by RC + PLND alone
- To compare the following for patients treated with perioperative pembrolizumab or perioperative pembrolizumab + enfortumab vedotin and RC + PLND versus those treated by RC + PLND alone
  - OS
  - Pathological complete response (pCR) rates (based on central pathology review)
- To evaluate the following for patients treated with perioperative pembrolizumab and RC + PLND, perioperative pembrolizumab + enfortumab vedotin and RC + PLND, and those treated by RC + PLND alone
  - Disease-free survival (DFS)
  - Rates of pathological downstaging (pDS)
- To evaluate the safety and tolerability of perioperative pembrolizumab with RC + PLND and perioperative pembrolizumab + enfortumab vedotin with RC + PLND

Methods

Study design



ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; IV, intravenously; Q3W, every 3 weeks; R, randomization; ROW, rest of world; TURBT, transurethral resection of the bladder tumor.
[a]Until disease progression, unacceptable adverse events (AEs), intercurrent illness preventing further treatment administration, or investigator's or patient's decision to withdraw.
[b]Prior to the protocol amendment 8, patients were enrolled in arm A. Enrollment for that arm will be stopped once the current protocol amendment is initiated, and further randomization will focus on arms B and C.
[c]Patients at high risk of recurrence after RC + PLND may receive treatment with adjuvant nivolumab per the approved product label.
[d]Administered on days 1 and 8 of every 3-week cycle.

Patient eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Histologically confirmed MIBC with predominant (≥50%) urothelial histology[a] • Clinically nonmetastatic bladder cancer (N ≤1M0)[b] • Eligible for and agrees to undergo curative-intent standard RC + PLND per EAU/AUA/ASTRO/ASCO/SUO guidelines • Ineligible for treatment with cisplatin,[c] or cisplatin eligible but declined cisplatin-based chemotherapy • TURBT sample submitted ≤60 days before enrollment that is adequate for evaluation of histology, muscle invasion, and PD-L1 status • Adequate organ function • ECOG PS 0, 1, or 2	• Additional malignancy that is progressing or necessitated active treatment ≤3 years before randomization • Participants with ≥N2 or M1 disease • Previous systemic antineoplastic treatment for MIBC[d] • Pelvic lymph node ≥15 mm in the short axis • Prior therapy with anti–PD-1/L1/L2 agent or agent directed to another stimulatory or coinhibitory T-cell receptor • Prior systemic anticancer therapy, including investigational agents, ≤3 years before randomization • Prior radiotherapy to the bladder • Diagnosis of immunodeficiency or receiving long-term systemic steroid therapy • Active autoimmune disease necessitating systemic treatment in the preceding 2 years • Pneumonitis or history of (noninfectious) pneumonitis necessitating steroids • Active infection necessitating systemic therapy • History of HIV infection or active hepatitis B or C virus infection • Ongoing sensory or motor neuropathy grade ≥2 • History of uncontrolled diabetes • Allogeneic tissue/solid organ transplant

ASCO, American Society of Clinical Oncology; ASTRO, American Society for Radiation Oncology; AUA, American Urological Association; CrCl, creatinine clearance; CTCAE v4.0, Common Terminology Criteria for Adverse Events, version 4.0; EAU, European Association of Urology; NMIBC, non–muscle-invasive bladder cancer; NYHA, New York Heart Association; SUO, Society of Urologic Oncology.
[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 with N1 disease (confirmed by BICR).
[b]Determined by imaging (computed tomography [CT] of the chest and CT or magnetic resonance imaging of the abdomen/pelvis), confirmed by BICR.
[c]Cisplatin ineligibility defined as meeting ≥1 of the following criteria: impaired renal function with calculated CrCl 30-59 mL/min; ECOG PS 2; grade ≥2 audiometric hearing loss per CTCAE v4.0; or NYHA class III heart failure.
[d]Prior treatment for NMIBC with intravesical instillation therapy permitted.

Assessments and follow-up

- On-study tumor imaging assessments to evaluate disease status will be conducted with contrast until an EFS event or discontinuation occurs or at withdrawal of consent
- All surgical specimens obtained during RC + PLND will be assessed centrally to determine pathologic response
- Patients with new recurrent/metastatic disease at the 6-week (±14 days) postcystectomy imaging will have met the primary EFS end point and will not receive additional trial therapy but will transition to survival follow-up stage until death, withdrawal of consent, or the end of the study
  - Patients who discontinue for reasons other than an EFS event will be followed up for posttreatment 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
- AEs will be monitored and assessed by the investigator per CTCAE v4.0 from randomization for up to 30 days after the last dose of study treatment (90 days for serious AEs)

Analyses

Efficacy

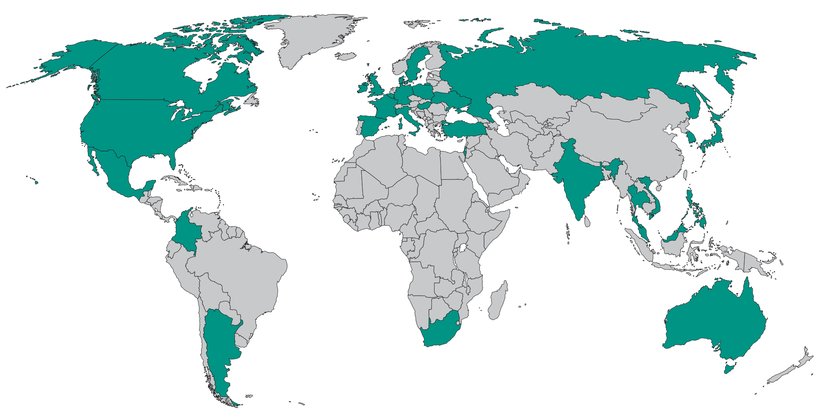
- The intention-to-treat population (all randomly assigned patients regardless of whether they received treatment) will serve as the analysis population for EFS and OS
- The nonparametric Kaplan-Meier method will be used to estimate EFS and OS curves in each treatment group; treatment differences in EFS and OS will be assessed using the stratified log-rank test and will be estimated using the stratified Cox model with the Efron method of handling ties
  - The hazard ratio and its 95% CI from the Cox model with the Efron method of handling ties and a single treatment covariate will be reported
- The DFS analysis population will consist of patients who are disease free at postsurgical baseline imaging; data will be summarized descriptively using the Kaplan-Meier method
- The full analysis set will consist of all randomly assigned patients regardless of whether they received treatment, with the exception of the analysis rules applied to patients who decline to undergo surgery, and will serve as the analysis population for the pCR and pDS rates; patients with no disease who decline to undergo surgery will have achieved clinical CR and will be excluded from the primary analysis of pCR rate
- pCR and pDS rates will be analyzed using the stratified Miettinen and Nurminen method with strata weighting by sample size

Safety

- Safety and tolerability analyses (clinical review of all relevant parameters, including AEs, laboratory tests, vital signs, and electrocardiographic measurements) will be conducted on data from all randomly assigned patients who received at least 1 dose of study treatment

Status

Sites of enrollment for KEYNOTE-905/EV-303 (green)



Presented at the 2023 ASCO Annual Meeting; Chicago, Illinois, and online; June 2-6, 2023

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Acknowledgments

The authors thank the patients and their families and caregivers for participating in this trial and all investigators and site personnel. Medical writing and/or editorial assistance was provided by Matthew Grzywacz, PhD, of ApotheCom (Yardley, PA, USA). This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Funding for this research was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Astellas and Seagen are collaborative partners for this study.

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