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Phase 2 Study of Pembrolizumab With Favezelimab or Vibostolimab for Patients With Bacillus Calmette-Guérin–Unresponsive High-Risk Non–Muscle-Invasive Bladder Cancer: Cohort C of KEYNOTE-057

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Background

- Pembrolizumab, a PD-1 inhibitor, was shown to have antitumor activity in cohort A of the open-label phase 2 KEYNOTE-057 study (NCT02625961), resulting in US Food and Drug Administration approval of pembrolizumab for the treatment of patients with bacillus Calmette-Guérin (BCG)–unresponsive high-risk (HR) non–muscle-invasive bladder cancer (NMIBC) with carcinoma in situ (CIS) ± papillary tumors who are ineligible for or have elected not to undergo radical cystectomy[1,2]
- Novel combinations that can further improve the efficacy of pembrolizumab are urgently needed
- The immune checkpoints T-cell immunoglobulin and ITIM domain (TIGIT) and lymphocyte activation gene 3 (LAG-3) have been shown to contribute to treatment resistance in many cancers and have been expressed in bladder cancer
  - Compared with healthy donors, increased peripheral blood total NK cells and higher TIGIT expression on NK, CD4+, and CD8+ T cells have been observed in patients with NMIBC[3]
  - Stromal expression of LAG-3 has been shown to correlate with poor prognosis in metastatic urothelial cancer, and expression in immune cell subsets has been found to correlate with PD-1 expression[4]
- Because inhibition of TIGIT and LAG-3 may enhance the efficacy of pembrolizumab, cohort C of KEYNOTE-057 will evaluate the efficacy and safety of coformulations (receiving both treatments as a single infusion) of pembrolizumab with the TIGIT inhibitor vibostolimab or with the LAG-3 inhibitor favezelimab in patients with HR BCG-unresponsive NMIBC with CIS ± papillary tumors

Objectives

Primary efficacy

- To evaluate antitumor activity of the coformulations of pembrolizumab with vibostolimab and pembrolizumab with favezelimab using the 12-month complete response (CR) rate of HR NMIBC as determined by cystoscopy, cytology, biopsy, and radiologic imaging by central pathology and radiology review

Secondary efficacy

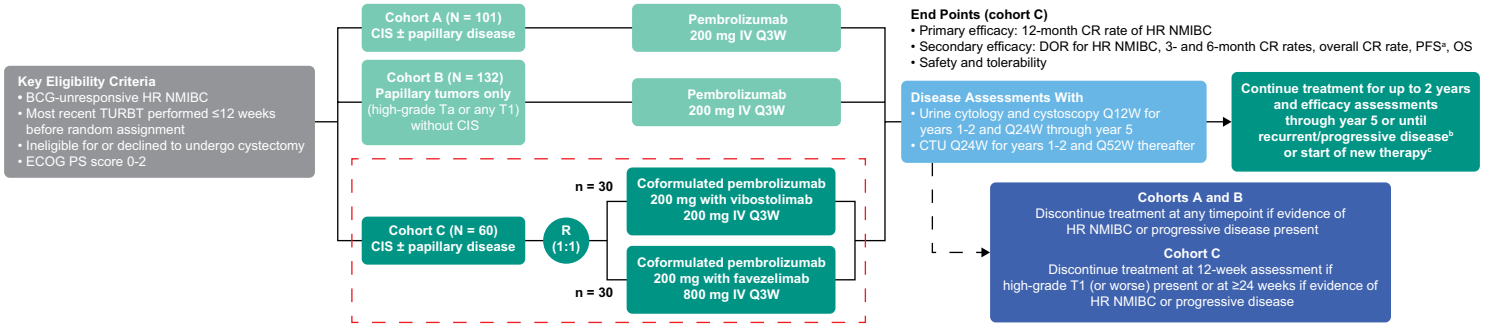
- To evaluate the following for the coformulations of pembrolizumab with vibostolimab and pembrolizumab with favezelimab
  - Duration of response (DOR) of HR NMIBC in responders
  - CR rates at 3 and 6 months
  - Overall CR rate
  - Progression-free survival (PFS) to worsening of grade or stage or death
  - PFS to muscle-invasive or metastatic disease or death
  - Overall survival (OS)

Safety

- To characterize safety and tolerability of the coformulations of pembrolizumab with vibostolimab and pembrolizumab with favezelimab in patients with NMIBC

Methods

Study design



CTU, computed tomography urography; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; Q3W, every 3 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks; Q52W, every 52 weeks; R, randomization; TURBT, transurethral resection of bladder tumor.

[a]PFS to worsening of grade or stage or death and PFS to muscle-invasive or metastatic disease or death.
[b]Persistent HR disease at the 12-week disease assessment for cohorts A and B or thereafter and central pathology–confirmed ≥T1 at any time point or persistent or recurrent CIS or high-grade ≥Ta at the 24-week efficacy review for cohort C or thereafter.
[c]In the absence of disease persistence/recurrence or progression, treatment will continue until unacceptable toxicity, decision to withdraw, or for administrative reasons. Patients with central pathology–confirmed low-grade Ta recurrence at any time point may continue treatment after resection of visible tumors.

Patient eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Histologically confirmed diagnosis of HR non–muscle-invasive (CIS with/without papillary disease [T1, high-grade Ta]) transitional cell carcinoma of the bladder[a] • For patients with papillary tumors (Ta and T1), a complete TURBT ≤12 weeks before random assignment must have been performed, as characterized by attainment of a visually complete resection of all papillary tumors (Ta and T1)[b] – Patients with T1 disease should undergo a restaging TURBT within 12 weeks before randomization to confirm complete resection • Treated with adequate BCG therapy[c] and developed HR NMIBC unresponsive to BCG therapy defined as persistent or recurrent CIS alone or with Ta/T1 within 12 months of completion of treatment • Elected not to undergo or considered ineligible for radical cystectomy • ECOG PS 0-2 • Adequate organ function	• Centrally assessed muscle-invasive (ie, T2, T3, T4) locally advanced nonresectable or metastatic urothelial carcinoma • Centrally assessed concurrent extravesical (ie, urethra, ureter, or renal pelvis) non–muscle-invasive transitional cell carcinoma of the urothelium • Undergone any intervening intravesical chemotherapy or immunotherapy from the time of most recent cystoscopy/TURBT to starting trial treatment • Prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to starting trial treatment • Active autoimmune disease that necessitated systemic treatment in past 2 years • Received prior therapy with an anti–PD-1/L1/L2 agent, TIGIT inhibitor, LAG-3 inhibitor, or any other agent directed to another coinhibitory T-cell receptor • Active infection that necessitates systemic therapy • History of HIV, hepatitis B virus, or active hepatitis C virus infection

[a]Patients with tumors of mixed transitional/nontransitional cell histology are eligible, but transitional cell carcinoma must be the predominant histology. Patients with predominant or exclusively nontransitional cell histology are not eligible.
[b]Residual CIS not amenable to complete resection is permitted.
[c]Adequate BCG therapy is defined as an induction course with ≥5 instillations of BCG (adequate induction) and ≥7 instillations of BCG within 9 months of the first instillation of adequate induction course.

Assessments and follow-up

Assessment	Details
Tumor response	• Tumor evaluation using cystoscopy and urine cytology will be performed Q12W (±2 weeks) from the start of trial treatment (cycle 1, day 1) for the first 2 years, then Q24W (±2 weeks) thereafter for up to 5 years • Patients will also be evaluated with cross-sectional imaging CTU of the abdomen and pelvis Q24W (±2 weeks) for the first 2 years and yearly (52 ± 4 weeks) thereafter • Random biopsies will be performed at week 48
Adverse events	• Will be monitored and assessed by investigators throughout the study and for 30 days (90 days for serious adverse events) after the last dose of study treatment • Severity will be graded per NCI CTCAE v4.0 guidelines

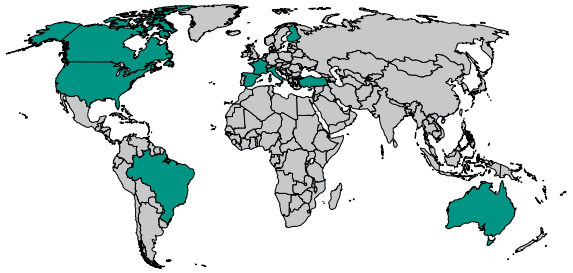
CTCAE v4.0, Common Terminology Criteria for Adverse Events, version 4.0; NCI, National Cancer Institute.

Analyses

Analysis	Details
Efficacy	• Efficacy analyses will be conducted in the full analysis set, which consists of all enrolled patients who receive ≥1 dose of trial treatment and have a baseline evaluation consisting of pre-enrollment cystoscopy, TURBT/biopsy, urine cytology, and baseline CTU imaging • CR rates will be evaluated using point estimates, and CIs will be evaluated using the binomial exact method • DOR, PFS, and OS will be summarized using the Kaplan-Meier method
Safety	• Safety analyses will be conducted in the all-patients-as-treated population, defined as all enrolled patients who received at ≥1 dose of trial treatment • Safety will be summarized descriptively

Status

Sites of enrollment for KEYNOTE-057 cohort C (green)



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