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Bacillus Calmette-Guérin With Pembrolizumab in Patients With Bacillus Calmette-Guérin–Naive High-Risk Non–Muscle-Invasive Bladder Cancer: Cohort B of the Phase 3 KEYNOTE-676 Study

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Background

- Standard treatment for high-risk non–muscle-invasive bladder cancer (NMIBC) is transurethral resection of bladder tumor (TURBT) followed by intravesical bacillus Calmette-Guérin (BCG) induction and maintenance therapy[1,2]
  - Despite a high rate of complete response (CR), up to 50% of patients experience recurrence or become unresponsive to BCG and are at increased risk for progression to muscle-invasive disease[3,4]
- Pembrolizumab monotherapy provided effective antitumor activity and acceptable safety in a cohort of patients with BCG-unresponsive carcinoma in situ (CIS) of the bladder, with or without papillary tumors, in the KEYNOTE-057 study[5]
- Combining pembrolizumab and BCG earlier in the disease course of high-risk NMIBC might provide anticancer activity superior to that of BCG monotherapy
  - Results from a phase 1 study of pembrolizumab + BCG showed acceptable safety and a rate of 69% for no evidence of disease at 3 months after BCG treatment in patients with high-grade NMIBC who had persistent or recurrent disease after intravesical therapy with BCG[6]
- KEYNOTE-676 (NCT03711032) is an open-label, comparator-controlled, phase 3 study designed to compare pembrolizumab + BCG with BCG monotherapy in patients with high-risk NMIBC
  - The study design for patients with persistent or recurrent high-risk NMIBC after BCG induction enrolling in cohort A was previously reported[7]
- We report the study design of cohort B, a new, randomized cohort, in which patients will be enrolled who are BCG naive or have not received BCG treatment ≥2 years before enrollment

Objectives

Primary

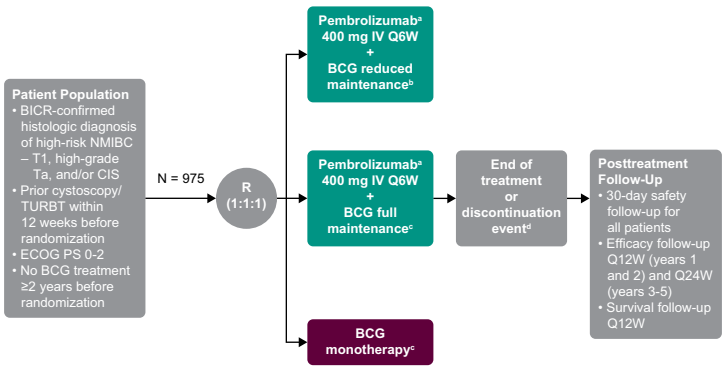
- To compare the event-free survival (EFS) between pembrolizumab + BCG (reduced maintenance) versus BCG alone and pembrolizumab + BCG (full maintenance) versus BCG alone in the treatment of patients with high-risk NMIBC
  - EFS is defined as the time from random assignment to the first occurrence of high-grade Ta or CIS, any T1 disease of the bladder, high-risk disease (high-grade Ta, CIS, or ≥T1) of the urethra or upper tract, locally advanced/metastatic disease as determined by blinded independent central review (BICR), or death from any cause

Secondary

- To compare the following end points for pembrolizumab + BCG (reduced maintenance) versus BCG alone and pembrolizumab + BCG (full maintenance) versus BCG alone in the treatment of patients with high-risk NMIBC:
  - Complete response rate (CRR) in patients with CIS, as determined by BICR of urine cytology, biopsy, and radiology assessments as applicable and evaluation of results of local cystoscopy
  - Recurrence-free survival (RFS), defined as the time from random assignment to the first occurrence of any event included in the definition of EFS or until any urothelial carcinoma recurrence, including low-grade Ta
  - Overall survival (OS), defined as time from random assignment to death from any cause
  - Disease-specific survival (DSS), defined as time from random assignment to death from bladder cancer
  - Time to cystectomy, defined as time from a patient's random assignment to a cohort to date of cystectomy
  - Changes from baseline and time to deterioration in health-related quality-of-life scores in all treatment groups, using 2 general instruments (EORTC Quality of Life Questionnaire Core 30 [QLQ-C30] and EuroQol 5-dimension, 5-level questionnaire [EuroQol 5Q-5D-5L]) and 1 disease-specific instrument (EORTC Quality of Life Questionnaire for NMIBC)
- To evaluate the following for pembrolizumab + BCG (reduced maintenance), pembrolizumab + BCG (full maintenance), and BCG alone for treatment of patients with high-risk NMIBC:
  - 24-month EFS rate
  - Duration of response (DOR) for patients with CIS who achieve CR
  - 12-month DOR rate
  - Safety and tolerability

Methods

Study design



Stratification
- NMIBC stage (CIS or non-CIS histology, as determined by the designated central laboratory)
- PD-L1 expression (CPS ≥10 vs CPS <10)[e]

Disease Assessments
- Q12W for years 1 and 2
- Q24W for years 3-5
- Q52W for years 6 and after
- With cystoscopy, urine cytology, and biopsy (as applicable)
- CTU Q72W through year 5 then Q104W

Primary End Point
- EFS in all patients

Secondary End Points
- CRR in patients with CIS
- 24-month EFS rate
- RFS
- OS
- DSS
- DOR
- 12-month DOR rate
- Time to cystectomy
- Safety and tolerability

CPS, combined positive score; CTU, computed tomography urography; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; Q6W, every 6 weeks; Q12W, every 12 weeks; Q24W, every 24 weeks; Q52W, every 52 weeks; Q72W, every 72 weeks; Q104W, every 104 weeks; R, randomization.

[a]Pembrolizumab treatment will be limited to 9 infusions (approximately 1 year).
[b]BCG 50-mg induction therapy administered via intravesical instillation weekly for 6 weeks followed by maintenance weekly for 3 weeks at week 13.
[c]BCG 50-mg induction therapy administered via intravesical instillation weekly for 6 weeks followed by maintenance weekly for 3 weeks at weeks 13, 25, 49, and 73.
[d]Treatment will continue until central pathology–confirmed high-grade Ta or any CIS at 24 weeks or thereafter, T1 or higher at any time point, disease progression to muscle-invasive or metastatic bladder cancer, unacceptable toxicity, or patient/physician decision to withdraw.
[e]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 • BICR-confirmed histologic diagnosis of high-risk NMIBC (T1, high-grade Ta, and/or CIS) • History of cystoscopy/TURBT ≤12 weeks before random assignment • ECOG PS 0-2 • Tissue for biomarker analysis	• History of or concurrent locally advanced (ie, T2, T3, T4) or metastatic urothelial carcinoma • Concurrent extravesical (ie, urethra, ureter, renal pelvis) non–muscle-invasive urothelial carcinoma or invasive prostatic urothelial carcinoma, including T1 or greater disease, or ductal invasion • Previous therapy with an anti–PD-1/L1/L2 agent or with an agent directed to another stimulatory or coinhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137) • Previous treatment with BCG for NMIBC ≤2 years before study entry • Previous systemic anticancer therapy, including investigational agents, ≤4 weeks before start of study treatment

CD137, tumor necrosis factor receptor superfamily, member 9; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; OX-40, tumor necrosis factor receptor superfamily, member 4.

Safety assessments and follow-up

Assessment	Details
AEs	• AEs will be monitored throughout the study and up to 30 days after cessation of study treatment (90 days for serious AEs or 30 days if the patient begins a new anticancer therapy regimen, whichever comes first), graded in severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
After treatment	• Safety follow-up visit will occur within 30 days after discontinuation of study drug

AE, adverse event.

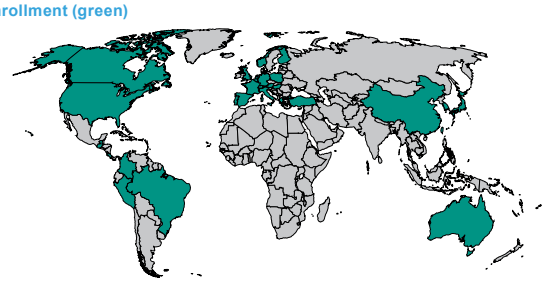
Analyses

Analysis	Details
Efficacy	• The efficacy analysis population will include all randomly assigned patients (intention to treat) • EFS, RFS, DSS, OS, and time to cystectomy will be evaluated using a stratified log-rank test – The hazard ratio will be estimated using a stratified Cox proportional hazards model with the Efron method of handling ties – Event rates over time will be estimated within each treatment group using the Kaplan-Meier method • CRR will be analyzed in patients with CIS using the stratified Miettinen and Nurminen method, with strata weighted by sample size • DOR will be summarized descriptively using the Kaplan-Meier method – Only the subset of patients with CIS who achieve CR will be included in this analysis
Safety	• The safety analysis population will comprise all randomly assigned patients who received ≥1 dose of study drug (all patients as treated) • Safety results will be analyzed following a tiered approach • The Miettinen and Nurminen method will be used to perform analysis in which 95% CIs will be provided for between-treatment differences in the percentages of patients who experience AEs

Status

- KEYNOTE-676 is enrolling or planning to enroll patients in cohort B at sites in Asia, Australia, Europe, North America, and South America

Sites of enrollment (green)



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