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Bacillus Calmette-Guérin With or Without Pembrolizumab for High-Risk Non–Muscle-Invasive Bladder Cancer That Persists/Recurs After Bacillus Calmette-Guérin Induction: Cohort A of the Phase 3 KEYNOTE-676 Study

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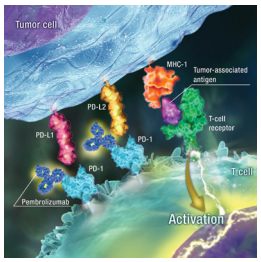
Background

- Intravesical instillation of bacillus Calmette-Guérin (BCG) is the standard of care for patients with high-risk non–muscle-invasive bladder cancer (HR NMIBC)[1]; however, many patients have persistent/recurrent HR NMIBC after BCG induction and are at a particularly increased risk for progression[2,3]
- PD-L1 expression is correlated with bladder cancer severity and outcome; PD-L1 expression in the tumor microenvironment can attenuate responses to BCG by repressing activated T cells[4,5]
- PD-1 is an immune checkpoint receptor known to play a role in tumor immune evasion[6]
- Pembrolizumab is a humanized monoclonal antibody that binds to PD-1, preventing interaction with its ligands, PD-L1 and PD-L2[7]; in the phase 2 KEYNOTE-057 trial, pembrolizumab monotherapy demonstrated efficacy in patients with BCG-unresponsive HR NMIBC and carcinoma in situ (CIS), with a safety profile consistent with that of other studies[8]
  - Centrally assessed complete response rate (CRR) was 41%
    - The combination of pembrolizumab and BCG has been shown to be safe and may increase the antitumor activity of BCG[9]
- KEYNOTE-676 (NCT03711032) is an open-label, comparator-controlled, phase 3 study designed to compare pembrolizumab + BCG with BCG monotherapy in patients with HR NMIBC
  - We report the study design of cohort A, which will enroll patients with persistent or recurrent HR NMIBC after BCG induction therapy

Pembrolizumab and the PD-1 pathway



MHC-1, major histocompatibility complex 1.

Objectives

Primary

- To compare the CRRs for the combination of pembrolizumab + BCG versus BCG monotherapy in patients with CIS
  - Complete response (CR) is defined as the absence of HR NMIBC, which is confirmed by cystoscopy, blinded independent central review (BICR) of urine cytology, biopsy (as applicable), and radiologic assessments

Secondary

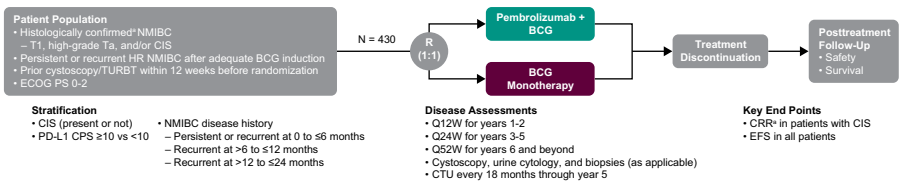
- To compare the following in patients treated with pembrolizumab + BCG versus BCG monotherapy:
  - Event-free survival (EFS)
  - Recurrence-free survival (RFS)
  - Overall survival (OS)
  - Disease-specific survival (DSS)
  - Time to cystectomy
- To assess the following in patients treated with pembrolizumab + BCG and BCG monotherapy:
  - 12-month EFS rate
  - Duration of response (DOR): responders only
  - 12-month DOR rate: responders only
- To evaluate and compare time to true deterioration in the EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) in patients treated with pembrolizumab + BCG versus BCG monotherapy
- To assess the safety and tolerability of pembrolizumab + BCG

Methods

Study design

- Approximately 430 patients with histologically confirmed HR NMIBC will be enrolled
- Patients will be randomly assigned 1:1 to receive pembrolizumab + BCG or BCG monotherapy
  - Pembrolizumab will be administered intravenously at the standard dose of 200 mg every 3 weeks
  - BCG (50 mg) will be administered via intravesical instillation first as induction therapy (once a week for 6 weeks) and then as maintenance therapy, with 12-week intervals (3 and 6 months) for the first and second maintenance cycles and then at 6-month intervals
- Treatment with pembrolizumab will continue until 35 doses have been given (approximately 2 years); treatment with BCG will continue for a total of 145 weeks (approximately 3 years)
- Treatment in either arm will be discontinued if the patient has persistent/recurrent high-risk disease, has progressive disease, experiences unacceptable toxicity, has intercurrent illness preventing further administration, or after investigator or patient decision to withdraw, after patient pregnancy, or for administrative reasons
- Patients will be stratified according to CIS (present or not), PD-L1 combined positive score (CPS; ≥10 or <10), and NMIBC disease history (persistent or recurrent NMIBC at 0 to ≤6 months, recurrent NMIBC at >6 to ≤12 months, or recurrent NMIBC at >12 to ≤24 months)

Study design



CTU, computed tomography urography; ECOG PS, Eastern Cooperative Oncology Group performance status; Q12W, every 12 weeks; Q24W, every 24 weeks; Q52W, every 52 weeks; R, randomization; TURBT, transurethral resection of bladder tumor.
[a]Assessed by local review and BICR.

Patient eligibility criteria

Key inclusion criteria	Key exclusion criteria
• Age ≥18 years • Histologically confirmed[a] diagnosis of NMIBC – T1, high-grade Ta, and/or CIS • Completed 1 adequate course of BCG induction therapy for the treatment of HR NMIBC • Persistent or recurrent HR NMIBC after adequate BCG induction therapy[b] • Underwent TURBT to remove all resectable disease within 12 weeks before randomization • Participants with T1 disease must have undergone restaging TURBT before randomization to confirm absence of muscle invasion • Tissue for biomarker analysis from most recent TURBT[c] • ECOG PS 0-2 • Adequate organ function	• Persistent T1 disease after BCG induction • Muscle-invasive, locally advanced nonresectable or metastatic UC • Concurrent extravesical NMIBC, concurrent locally advanced (T2, T3, or T4) metastatic UC, invasive UC of the prostatic urethra, or ductal invasion • Prior therapy with an anti–PD-1/L1/L2 agent or agent directed to another stimulatory or coinhibitory T-cell receptor • Prior systemic anticancer therapy ≤4 weeks from start of treatment or prior radiotherapy ≤2 weeks from start of treatment • Diagnosis of immunodeficiency or long-term systemic steroid therapy or immunosuppressive therapy ≤7 days from start of treatment • Active autoimmune disease necessitating systemic treatment in the preceding 2 years • ≥1 contraindications to BCG – Prior BCG sepsis or systemic infection – Total bladder incontinence – Adverse experience to previous BCG instillation that resulted in treatment discontinuation and precludes retreatment • Current pneumonitis or history of (noninfectious) pneumonitis that necessitated steroids • Known additional malignancy that is progressing or has necessitated active treatment in the past 3 years

UC, urothelial carcinoma.
[a]Confirmation by local review and BICR.
[b]Definitions: HR NMIBC: recurrent T1, high-grade Ta, and/or CIS
Persistent: remains present within 3-6 months after the start of BCG induction (persistent T1 will not be eligible for study)
Recurrent: reappearance of HR NMIBC after achieving CR or tumor-free state within 6 months after the start of BCG induction; recurrence must be within 24 months of the last exposure to BCG
[c]Patients will be assigned to the CPS <10 group if samples are not evaluable for PD-L1.

Assessments and follow-up

- Disease will be assessed based on integrated cystoscopy and BICR of urine cytology and biopsy (as applicable) Q12W for years 1-2, Q24W for years 3-5, and Q52W for years 6 and beyond, and by CTU every 72 weeks through year 4, then every 2 years; CTU might be performed more frequently, as clinically indicated
- Patients without malignant/suspicious lesions substantiated by cystoscopy and urine cytology will be considered disease free
  - Directed biopsy of the target malignant or suspicious lesions and CTU (as appropriate) will be performed in cases of abnormal cystoscopy findings
  - Patients with no malignant or suspicious lesions substantiated by cystoscopy but with urine cytology BICR–substantiated indicative/positive or suspicious malignant cells will undergo serial biopsies of the normal-looking mucosa and evaluation of extravesical disease by CTU
    - Protocol-defined treatment will be continued in these patients for up to 1 additional treatment cycle, pending biopsy findings
- Patients who discontinue treatment for reasons other than persistent, recurrent, or progressive high-risk disease will continue posttreatment follow-up disease assessments until an EFS event, initiation of a nonstudy cancer treatment, withdrawal of consent, death, or loss to follow-up
- Adverse events (AEs) will be monitored throughout the study and for 30 days during the follow-up period (90 days for serious AEs) and will be graded per the guidelines outlined in the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
- Patient-reported outcomes (PROs; EORTC QLQ-C30, Quality of Life Questionnaire for Non–Muscle-Invasive Bladder Cancer, and EuroQol 5-dimension, 5-level questionnaire [EuroQol 5Q-5D-5L]) will be measured at baseline (before notification of treatment assignment), before dosing at regular intervals throughout treatment, at treatment discontinuation, and at the safety follow-up visit (30 days after the final dose)

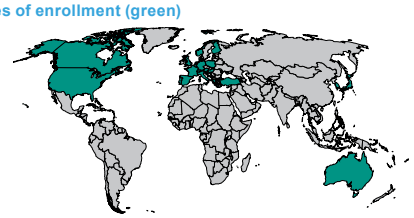
Analyses

- Efficacy
  - The efficacy population will include all randomly assigned patients (intention to treat [ITT]) and will be used for the analyses of EFS, RFS, OS, DSS, and time to cystectomy
    - CRR will be analyzed in the subset of the ITT population with CIS
    - DOR will be analyzed for responders with documented CR in the subset of patients with CIS
  - CRR will be analyzed using the stratified Miettinen and Nurminen method
  - Magnitude of treatment differences in EFS, RFS, OS, DSS, and time to cystectomy will be estimated using a stratified Cox proportional hazards model with the Efron method of handling ties
  - DOR and 12-month DOR and EFS rates will be summarized using the Kaplan-Meier method
- Safety
  - The safety analysis population will comprise all randomly assigned patients who receive ≥1 dose of the study treatment (all patients as treated)
  - Safety and tolerability will be analyzed using a tiered approach
- PROs
  - PRO analyses will be based on the PRO full analysis set population: patients who have received treatment and have ≥1 PRO assessment available
  - A constrained longitudinal data analysis model will be applied to assess treatment differences in PROs

Status

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

Sites of enrollment (green)



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