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

BACKGROUND

- The incidence of bladder cancer in the United States is increasing, with the majority of patients presenting with non–muscle-invasive bladder cancer (NMIBC)\(^2\).
- High-risk NMIBC (T1, high grade and/or carcinoma in situ (CIS)) is characterized by frequent recurrence and progression to muscle-invasive disease despite standard therapy with transurethral resection of bladder tumor (TURBT) and intravesical Bacillus Calmette-Guérin (BCG) administration\(^3\).
- The programmed death 1 (PD-1) pathway is a major pathway hijacked by tumors to evade immune surveillance (Figure 1).
- PD-1 is widely expressed in urothelial tumors, and studies have demonstrated markedly higher PD-1 expression in tumors that relapse after BCG treatment compared with BCG-naive tumors\(^4\).
- Pembrolizumab, a highly selective, humanized monoclonal anti-PD-1 antibody, is designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

- In the phase 1b KEYNOTE-012 (ClinicalTrials.gov, NCT01848834) study, pembrolizumab 10 mg/kg administered every 2 weeks demonstrated promising antitumor activity in patients with PD-L1–positive, recurrent/metastatic urothelial cancer\(^4\):
  - In these patients, overall response rate (ORR) was 25% (95% confidence interval (CI): 11%, 45%) with 3 complete responses (CRs) and 4 partial responses
  - Pembrolizumab was well tolerated in this patient population, with 15% experiencing grade 3/4 treatment-related adverse events (AEs)
- KEYNOTE-057 (ClinicalTrials.gov, NCT02625961) is a single-arm, open-label, phase 2 study to evaluate intravesical pembrolizumab in patients with high-risk NMIBC unresponsive to BCG who are ineligible for who have elected not to undergo radical cystectomy

OBJECTIVES

- Except where noted, each primary, secondary, and exploratory objective will be evaluated in the following populations:
  - Cohort A (patients with CIS at baseline [CIS only, Ta + CIS, T1 + CIS]):
    - All patients
    - PD-L1-positive patients
  - Cohort B (patients without CIS at baseline [high-grade Ta or any grade T1]):
    - All patients
    - PD-L1-positive patients
- Primary
  - Antitumor activity as evidenced by absence of high-risk NMIBC or progressive disease per cystoscopy, cystitis, biopsy (if applicable), and radiologic imaging by central pathology and radiology review
  - For cohort A, antitumor activity will be defined as the CR rate (i.e., the proportion of patients whose tumors are in response to treatment and who are free of high-risk NMIBC or worse)
  - For cohort B, antitumor activity will be defined as the disease-free survival (DFS) rate

Secondary

- CR rate of any disease (ie, the proportion of patients whose tumors are in response to treatment and who are free of any disease) (cohort A only)
- Duration of response (DOR) of high-risk NMIBC and any disease (cohort A only)
- Time to CR (cohort A only)
- Overall DFS and 3-month, 6-month, and 12-month DFS rates of high-risk NMIBC and any disease
- 12-month DFS of high-risk NMIBC is a secondary objective of cohort A only
- Progression-free survival (PFS) to worsening of grade or stage or death
- PFS to muscle invasive or metastatic disease or death
- Overall survival (OS)

Exploratory

- Association between candidate biomarkers and antitumor activity using pretreatment and on-treatment tumor biopsy and blood sampling
- Pharmacokinetic profile, including antitibodies
- Changes in health-related quality-of-life assessments from baseline using FACT-B1 and EuroQol EQ-SD
- Utilities using FACT-B1 and EuroQol EQ-SD
- Rates of lower urinary tract symptoms, including irritative and obstructive symptoms and gross hematuria, pelvic pain, and culture-positive urinary tract infections

DESIGN

- Approximately 260 patients will be enrolled in KEYNOTE-057 and placed into 1 of 2 cohorts based on tissue pathology at screening:
  - Cohort A: patients with CIS at baseline (CIS only, Ta + CIS, T1 + CIS)
  - Cohort B: patients without CIS at baseline (high-grade Ta or any grade T1)
- Patients in both cohorts will receive intravesical pembrolizumab 200 mg every 3 weeks for 24 months or until high-risk recurrence or disease progression, unacceptable toxicity, or investigator/patient decision (Figure 2)
  - Patients with pathology-confirmed persistent high-risk disease at the first disease assessment or recurrence or progression at any assessment time point will be discontinued
  - Patients with pathology-confirmed low-grade Ta will be permitted to undergo a repeat TURBT and remain on pembrolizumab; low-grade recurrence will not be considered treatment failure
  - At 18 months, patients without evidence of disease in at least 2 preceding evaluations may stop pembrolizumab

- All patients will be followed by telephone for survival until death or withdrawal of consent

Assessments and follow-up

- Tumors will be evaluated by cystoscopy and urine cytology every 12 weeks for the first 2 years, every 24 weeks for the next 2 years, and every 52 weeks thereafter
- The presence of extravesical disease will be evaluated using computed tomographic urography or magnetic resonance imaging every 24 weeks for the first 2 years and every 52 weeks thereafter
- Computed tomography or magnetic resonance imaging will be used to assess the presence of metastatic or nodal disease
- Patients with abnormal cystoscopy will undergo biopsy of the lesion
- AEs will be monitored throughout the study and for 30 days (90 days for serious AEs and events of clinical interest) after treatment end and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0
- The disease status of patients who discontinue pembrolizumab for reasons other than high-risk recurrence or disease progression will be continued until disease progression, initiation of a new anticancer therapy, withdrawal of consent, or death

Analyses

- Efficacy
  - All patients who receive ≥1 dose of pembrolizumab and who have a pre-enrollment cystoscopy and baseline computed tomographic/magnetic resonance image will serve as the primary population for efficacy analyses
  - Efficacy will be analyzed separately for the 2 cohorts
  - The point estimates and 95% CIs for CR rates will be provided using the binomial exact method
  - DFS, PFS, OR, and OS will be estimated using the Kaplan-Meier method
- Safety
  - All patients who received ≥1 dose of pembrolizumab will serve as the population for safety analyses
  - Descriptive summary statistics will be provided

STATUS

- Enrollment in KEYNOTE-057 is ongoing in 8 countries, with additional sites in up to 15 countries anticipated to open (Figure 3)

REFERENCES

3. Keyes S, Bapori D. The University of Texas MD Anderson Cancer Center (Houston, TX, USA), Dana-Farber Cancer Institute (Boston, MA, USA). 2016 Annual Meeting accepted poster.