

FOOD AND DRUG ADMINISTRATION (FDA)
Center for Drug Evaluation and Research (CDER)

Oncologic Drugs Advisory Committee (ODAC) Meeting
FDA White Oak Campus, Building 31 Conference Center, the Great Room (Rm. 1503)
10903 New Hampshire Avenue, Silver Spring, Maryland
December 17, 2019

QUESTION

sBLA 125514/066
Keytruda (pembrolizumab) for injection
Applicant: Merck Sharp & Dohme Corp.

PROPOSED INDICATION: Treatment of patients with Bacillus Calmette-Guerin (BCG)-unresponsive, high-risk, non-muscle invasive bladder cancer (NMIBC) with carcinoma in-situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

BACKGROUND

High-risk BCG-unresponsive NMIBC carries a poor prognosis with a high incidence (>20%) of progression to muscle-invasive bladder cancer and cancer-related mortality. Cystectomy is the standard of care, however cystectomy is associated with morbidity and a 90-day mortality rate that may be as high as 10-15% in patients ≥ 70 years in the SEER population. Per FDA guidance, due to the lack of acceptable non-cystectomy treatment options, a single-arm trial may be sufficient to demonstrate efficacy in patients with BCG-unresponsive NMIBC containing CIS with complete response (CR) rate, with associated durability of response, as the primary endpoint.

EFFICACY

KEYNOTE-057 is a single-arm trial conducted in patients with high-risk BCG-unresponsive NMIBC who were medically ineligible for or refused cystectomy. Patients with CIS were enrolled into Cohort A, while patients with papillary-only disease were enrolled into Cohort B. Patients were treated with pembrolizumab 200 mg every 3 weeks and were discontinued for persistent or recurrent disease at any subsequent disease assessment. The primary efficacy outcome for Cohort A, which the FDA considers the primary efficacy population, was CR rate. Duration of response, calculated as the time from demonstration of response, was a secondary endpoint. CR was determined at the first efficacy evaluation (Month 3) and was defined as cystoscopy negative for malignancy and negative cytology. Patients in CR were subsequently followed with cystoscopy and cytology every 12 weeks, with directed biopsy mandated for patients with suspicious lesions on cystoscopy and random biopsies for patients with negative cystoscopy and positive cytology. Imaging for extravesical disease with CT or MRI was performed every 24 weeks.

A total of 102 patients were treated in Cohort A of KEYNOTE-057, of whom 97 were considered to have had adequate prior BCG therapy to be considered BCG-unresponsive per FDA guidance. Forty patients (41%; 95% CI 31%, 52%) had a CR at the first disease assessment. The median duration of response was 16.2 months (1 day+, 30 months+). With an updated data cutoff of 24-SEPT-2019, 19 patients remained in response for at least one year. This corresponds to 48% of responding patients and 20% of all treated patients. Thirty-eight patients with either no CR or CR followed by recurrent disease underwent subsequent cystectomy. Progression to muscle-invasive disease (T2) was demonstrated in 3 (8%) of these patients.

ISSUE #1: While FDA guidance states that CR rate and duration of response in a single-arm trial are appropriate efficacy endpoints to evaluate a treatment for BCG-unresponsive NMIBC for approval, an advisory committee has not previously discussed what magnitudes of these endpoints may be considered clinically meaningful.

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QUESTION (cont.)

SAFETY

The most common ($\geq 15\%$) adverse events in KEYNOTE-057 Cohort A included diarrhea, fatigue, hematuria, pruritis, and cough. Twenty-nine percent of patients experienced Grade 3-4 AEs, the most common ($\geq 2\%$) of which included pneumonia, hyperglycemia, hyponatremia, pulmonary embolism, urinary tract infection, arthralgia, and cellulitis. Pembrolizumab was discontinued due to an adverse event in 10% of patients. Twenty-one percent of patients experienced immune-related adverse events (irAEs), including 3% of patients who experienced Grade 3-4 irAEs. Two patients died on study due to pneumonia and pancreatic cancer. With a minimum follow-up of 14 months from last patient enrolled to data cut-off and a median follow-up of 24 months, no patient in Cohort A experienced progression to muscle-invasive or extra-vesical disease prior to cystectomy.

ISSUE #2: Pembrolizumab is a systemic therapy with immune-related toxicities. While the safety profile of pembrolizumab has been well-characterized, the benefit/risk in the setting of the observed CR rate and duration in patients with BCG-unresponsive NMIBC containing CIS should be considered.

QUESTION

1. **VOTE:** Do the observed complete response rate and duration represent a favorable risk/benefit profile in patients with BCG-unresponsive high-risk NMIBC with CIS treated with pembrolizumab?