Oncologic Drugs Advisory Committee (ODAC) Meeting

December 17, 2019

NDA/BLA# 125514s-066

Drug name: pembrolizumab

Applicant: Merck Sharp & Dohme Corp.

Combined FDA and Applicant ODAC Briefing Document

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Applicant and the Food and Drug Administration (FDA) for the panel members of the advisory committee. We have brought the drug pembrolizumab (also known as Keytruda®) to this advisory committee to gain the committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues the Agency identified for the advisory committee's discussion. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

This document is available for public release without redaction.

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Glossary

Abbreviation	Definition
2L	Second-line
AE	Adverse event
AEOSI	Adverse events of special interest

Abbreviation	Definition
APaT	All participants as treated
AUA	American Urological Association
BCG	Bacillus Calmette-Guerin
BLA	Biologics licensing application
bx	Biopsy
CI	Confidence interval
CIS (or TIS)	carcinoma in situ
CPS	Combined positive score
CR	Complete response
CTU	Computed tomography urography
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
FAS	Full analysis set
FDA	Food and Drug Administration
f/u	Follow-up
HR-NMIBC	High-risk Non-muscle invasive bladder cancer (T1, high grade Ta, and/or CIS)
HRQoL	Health-related quality of life
IBCG	International Bladder Cancer Group
IgG4	Immunoglobulin G4
ITT	Intent-to-treat
mAB	Monoclonal antibody
MIBC	Muscle-invasive bladder cancer
MRSA	Methicillin-resistant Staphylococcus Aureus
NCCN	National Comprehensive Cancer Network
NMIBC	Non-muscle invasive bladder cancer
ODAC	Oncologic Drugs Advisory Committee
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed cell death ligand 1
QD	Once daily
QoL	Quality of life
Q3W	Every 3 weeks
RC	Radical cystectomy
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious AE
SLR	Systematic literature review
SUO	Society of Urologic Oncology
TURBT	Transurethral resection of a bladder tumor
UC	Urothelial carcinoma
U.S.	United States

Representatives of FDA:	Jamie Brewer, MD, Medical Officer, Division of Oncology 1
	Joyce Cheng, PhD, Statistician
	Shenghui Tang, PhD, Statistician
	Daniel Suzman, MD, Cross Disciplinary Team Leader, Division of Oncology 1
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1 INTRODUCTION

This briefing document presents results from ongoing study KEYNOTE-057 as of the data cutoff of 24-May-2019 with updated duration of response based on a data cutoff of 24-September-2019 and includes all participants who enrolled on or prior to 01-Apr-2018. This briefing document includes the Applicant's position followed by the FDA's position as a new pilot format to reduce redundancy and improvement readability.

1.1 **Applicant** Proposed Indication

Proposed Indication: KEYTRUDA is indicated for the treatment of patients with Bacillus Calmette-Guerin-unresponsive, high-risk, non-muscle invasive bladder cancer with carcinoma in-situ with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy.

1.2 **FDA** Purpose of the Meeting

There are limited options for management of patients with Bacillus Calmette-Guerin (BCG)-unresponsive non-muscle invasive bladder cancer (NMIBC). However, clinical trial conduct in this setting is challenging due to difficulties in trial design, risk stratification, adequacy of prior BCG exposure, and appropriate comparators. Prior discussion in workshops that included FDA, academic urologists, and patient advocates regarding trial design and appropriate endpoints resulted in publication of FDA guidance for the evaluation of drugs and biologics in BCG-unresponsive NMIBC (FDA Guidance for Industry, 2018).

KEYNOTE-057 evaluated pembrolizumab monotherapy in two cohorts of patient with high-risk NMIBC who were considered unresponsive to treatment with BCG. Cohort A enrolled patients with carcinoma in-situ (CIS) (with or without papillary tumors) while Cohort B enrolled patients with high-grade Ta or any grade T1 papillary tumors without CIS. The primary endpoint of Cohort A, which is the focus of this briefing document, was the complete response rate. Response duration was a secondary endpoint.

The single-arm trial design of KEYNOTE-057 evaluating CR and duration of CR in Cohort A (patients with high-risk CIS-containing BCG-unresponsive NMIBC) follows the recommendations of the FDA guidance. The FDA additionally agrees with the definition of adequacy of prior BCG therapy in this trial that was used to define BCG-unresponsiveness.

While the prior workshops discussed benchmarks for what values of CR rate and durability would constitute a clinically meaningful result, these were not advisory committee meetings, and further discussion is needed (Jarow et al, Urology 2014; Kamat et al, JCO 2016).

The purpose of this advisory committee meeting is to discuss whether the magnitude of the observed complete response (CR) rate and duration of CR in patients with NMIBC with CIS with or without papillary tumors provides a benefit that outweighs the risks associated with systemic therapy. FDA seeks input from the committee on whether the available data from KEYNOTE-057 present a favorable benefit in tumors outcomes that sufficiently outweighs the risks of systemic therapy in patients with BCG-unresponsive, high-risk, NMIBC with CIS (with or without papillary tumors).

2 EFFICACY

2.1 Description of Clinical Setting

The Applicant's Position:

2.1.1 Overview of High-risk NMIBC

Urothelial carcinoma is considered the 6th most common cancer and the 9th leading cause of cancer death in the U.S., with an estimated 81,190 new cases and approximately 17,240 deaths from bladder cancer in the U.S. in 2018 [Ref. 5.4: 04MRQC]. Global incidence in men is 34.3 and in women is 8.3 per 100,000 person-years. Urothelial carcinoma becomes more common with age, and the median age is 73 years at diagnosis [Ref. 5.4: 04MRQC], [Ref. 5.4: 04XBKC].

Approximately 75% of newly diagnosed bladder cancer cases are classified as NMIBC [Ref. 5.4: 04XBKC], which includes Ta (70%), T1 (20%), and CIS (10%) [Ref. 5.4: 04T4M2]. NMIBC is a public health burden, characterized by frequent recurrences, high morbidity, and high per patient cost due to frequent office visits and procedures. According to the IBCG classification, NMIBC is stratified as low, intermediate, and high-risk disease, with high-risk defined as the presence of high-grade Ta, any T1, or CIS. High-risk NMIBC has the highest risk of progression to muscle invasive and metastatic disease.

The FDA's Position:

FDA agrees with the sponsor regarding the incidence and risk stratification of urothelial carcinoma.

High-risk NMIBC may include CIS with or without papillary tumors or may include only papillary tumors. The prognosis for patients with high-risk NMIBC is poor with approximately 20% of patients progressing to muscle-invasive disease and 14% of patients dying from bladder cancer. The majority of these events occur relatively early, within approximately four years (van den Bosch and Witjes, Eur Urol 2011). The presence of CIS is considered a high-risk feature and may associated with even greater risk for progression in the setting of high-grade T1 tumors (Gontero et al Eur Urol 2015). The standard of care for patients with BCG-unresponsive high-risk NMIBC remains radical cystectomy, regardless of the presence of CIS. In the FDA guidance for BCG-unresponsive NMIBC, the FDA considered that visible papillary tumors may be resected via TURBT and thus objective response rate may only be assessed in the population with CIS-containing tumors. Patients with resected papillary tumors alone could only be assessed via a time-to-event endpoint, which would require randomization.

2.1.2 Overview of BCG-unresponsive High-Risk NMIBC

The Applicant's Position:

Standard treatment for high-risk NMIBC includes TURBT followed by immunotherapy with intravesical BCG that includes induction and maintenance therapy for up to 3 years [Ref. 5.4: 04XBKC], [Ref. 5.4: 04XB8Z] [Ref. 5.4: 04XBKC]. Intravesical BCG therapy is a mainstay of treatment for patients with CIS tumors as well as for preventing recurrence of high-risk stage Ta or T1 papillary tumors [Ref. 5.4: 04T3FN]. While BCG therapy is often successful at preventing early tumor recurrences in patients with high-risk NMIBC, most patients do not maintain sustained remissions [Ref. 5.4: 04XCFL]. BCG treatment eventually fails in up to 50% of patients, and approximately 50% of those failures occur within the first 6 months [Ref. 5.4: 055YP3].

BCG-unresponsive high-risk NMIBC is defined as persistent disease despite adequate BCG therapy, disease recurrence after initially achieving a tumor-free state after adequate BCG, or T1 tumors following a single induction course of BCG [Ref. 5.4: 04XC2B], [Ref. 5.4: 052J5M]. Adequate BCG therapy is defined as a minimum of 5 of 6 doses of an induction course (adequate induction) plus 2 of 3 doses of a maintenance course, or 2 of 6 doses of a second induction course [Ref. 5.4: 052J5M].

Ultimately, failure of BCG to prevent tumor recurrences presents a significant clinical challenge in the BCG-unresponsive population, where progression to muscle-invasive disease is observed in 40% of patients [Ref. 5.4: 04CTF5], [Ref. 5.4: 04DQ2F]. Progression to metastatic disease

occurs in 20-30% of individuals who progress to muscle-invasive disease, with death due to bladder cancer in nearly all of these patients [Ref. 5.4: 04CTF5], [Ref. 5.4: 04DQ2F].

The FDA's Position:

FDA agrees with the sponsor regarding the definition of BCG-unresponsive high-risk NMIBC. This definition is concordant with that in the FDA guidance.

2.1.3 Unmet Medical Need

2.1.3.1 Current Therapies for BCG-unresponsive NMIBC – Radical Cystectomy

The Applicant's Position:

Because of the high rate of progression to muscle-invasive disease in patients with high-risk NMIBC who do not respond to BCG therapy, RC is the standard of care in the U.S. (as recommended by the AUA/SUO/NCCN) and globally [Ref. 5.4: 04T57S], [Ref. 5.4: 04XBKC]. While RC is considered curative, it is associated with a high rate of perioperative morbidity and mortality due to the complexity and invasiveness of the surgery, especially in elderly patients who often have multiple comorbidities. In addition, patients who have this surgery report a negative impact on various QoL metrics [Ref. 5.4: 052JKF]. As a result, many patients are ineligible for, or decline to undergo RC.

RC is associated with mortality rates between 1.4% - 6.9% and complication rates of approximately 60% within 90 days following surgery [Ref. 5.4: 055YNQ], [Ref. 5.4: 055YRX], [Ref. 5.4: 057SWG]. Significant post-operative complications included systemic infections (25%), ileus (16%), wound infection (9.2%), anemia requiring transfusion (8.1%), intestinal obstruction (7.2%), deep venous thrombosis (5.3%), wound dehiscence (4.6%), pulmonary embolism (3.2%), urinary extravasation (2.6%), and intestinal anastomotic leak (0.9%) [Ref. 5.4: 055YRX]. Long-term morbidities include metabolic abnormalities, stenosis of the conduit or ureters, chronic kidney disease, infections, calculi, sexual dysfunction, and rectal dysfunction including fecal urgency and leakage [Ref. 5.4: 052KY5], [Ref. 5.4: 055YQZ], [Ref. 5.4: 055YRX]. There is a significant association between age and the incidence of higher severity grade (Grade 3 to 5) complications [Ref. 5.4: 055YRX].

RC is associated with reduced HRQoL. In a study of the general urothelial cancer population, RC significantly affected 6 HRQoL domains or scales. Of these 6 domains, 3 (fatigue, appetite loss, and role functioning) had QoL score changes that were greater than 10 points [Ref. 5.4: 052JKF]. Smith et al (2018) [Ref. 5.4: 052JKN] reported that patients undergoing RC reported significant HRQoL decrements across nearly all physical domains (including physical component summary, physical functioning, physical and general health) and across several mental health domains (including role emotional, vitality and social functioning scores).

Because of the significant risk of morbidity, mortality, and decreased HRQoL associated with RC, many patients decline to undergo this surgery [Ref. 5.4: 052JKF], [Ref. 5.4: 052JKN]. The

median age at diagnosis is 73 years for the bladder cancer population [Ref. 5.4: 04XBKC], and elderly patients often have co-morbidities that preclude surgical intervention, or electively seek nonsurgical alternative therapy options [Ref. 5.4: 04T3DT], [Ref. 5.4: 057K8P]. Although no comparable data are available for BCG-unresponsive, high-risk NMIBC patients, in a study of elderly patients (≥75 years of age) with MIBC, 20.6% received RC, 13.1% received chemoradiation, and 66.3% did not receive either of these treatments [Ref. 5.4: 057K8P]. This high proportion of patients not treated with definitive therapy such as RC highlights the ineligibility and/or hesitancy of early-stage bladder cancer patients to be treated with these curative therapies.

Both physicians and patients are seeking treatment options for the common clinical situation of a patient who is medically unfit and ineligible for RC or who has made an informed decision not to undergo RC for high-risk NMIBC that is unresponsive to BCG. There are no currently approved standard therapies for patients in this clinical situation. While the FDA approved intravesical valrubicin for this population of patients more than 2 decades ago, it is not part of current treatment guidelines [Ref. 5.4: 04T57S], [Ref. 5.4: 04XBKC], and new therapies are desperately needed. Systemic immune checkpoint inhibitors are a potential treatment option for high-risk NMIBC that is unresponsive to BCG in patients who are ineligible for or decline RC.

The FDA's Position:

FDA agrees that radical cystectomy is generally considered the standard of care for patients with BCG-unresponsive high-risk NMIBC. FDA additionally agrees that radical cystectomy is a procedure with high rates of morbidity and mortality, particularly in elderly patients with co-morbidities, and may adversely affect quality of life. While there is no consistent definition regarding ineligibility for cystectomy, the FDA agrees with the reference cited above that there exists a large proportion of patients for whom cystectomy is indicated who do not receive this therapy.

2.1.3.2 Current Therapies for BCG-unresponsive NMIBC – Systemic and Intravesical Therapies

The Applicant's Position:

There are currently no well-accepted systemic or intravesical treatments for patients who no longer respond to BCG therapy. The only standard of care option for patients with BCG-unresponsive high-risk NMIBC is RC with urinary diversion, and those patients who decline or are ineligible for this surgery currently lack treatment options.

An SLR and meta-analysis were performed to estimate the historical CR rate and DOR from prior studies of systemic and intravesical therapies in BCG-unresponsive high-risk NMIBC [Ref. 5.4: 058DGZ]. Twenty-eight studies were identified in the literature review. Criteria for inclusion in the meta-analysis were:

1) CR rate was assessed in patients with CIS (with or without papillary tumors). This criterion is consistent with the proposed indication.

2) The treatment was available for use in U.S. practice, even if the treatment had not received marketing approval for use in high-risk NMIBC (studies of investigational treatments were not included).

Of the 28 studies, 4 satisfied criteria for inclusion [Ref. 5.4: 052JK5], [Ref. 5.4: 052L2P], [Ref. 5.4: 055YPX], [Ref. 5.4: 052J5F]. The studies were single arm trials that included the following treatments: valrubicin (2 studies), docetaxel, and nab-paclitaxel. Valrubicin was approved in the U.S. on 25-SEP-1998, for intravesical administration in patients with BCG-refractory CIS of the bladder for whom immediate RC would be associated with unacceptable morbidity or mortality; however, due to marginal efficacy, it is not currently recommended in bladder cancer treatment guidelines [Ref. 5.4: 04T57S], [Ref. 5.4: 04XBKC]. The CR rate at 6 months was 18% in both valrubicin studies.

The meta-analysis demonstrated a pooled CR rate of 21% (95% CI: 15%, 27% using a random effects model) for 197 subjects included in the analysis. Durability data were limited for these studies, and therefore, a formal meta-analysis was not conducted for DOR. Additionally, most of these studies were conducted in relatively small patient populations and further investigations are needed to confirm efficacy.

In summary, there is a significant unmet need for patients with BCG-unresponsive high-risk NMIBC with CIS, as few nonsurgical treatment options exist. In the absence of pharmacologic intervention or RC, BCG-unresponsive CIS with or without resected disease will persist and progress [Ref. 5.4: 052J5M].

Despite the urgent need for new therapies for patients with BCG-unresponsive NMIBC who decline to undergo or are considered ineligible for RC, clinical trial development in this space had been, until recently, extremely limited due to lack of consensus around appropriate study design and endpoints, as well as a standardized definition for adequate BCG and what constitutes BCG-unresponsive disease. Recognizing the significant unmet medical need in this space and to spur drug development in NMIBC, a combined workshop with the FDA and AUA was held in 2013, where clinical trial design, endpoints, and potential efficacy thresholds were discussed [Ref. 5.4: 04T3D2]. Subsequently, draft FDA guidance for industry was published in 2015 outlining recommendations for clinical trial development and conduct in BCG-unresponsive NMIBC. This guidance was further updated, and a final version was published in February 2018 [Ref. 5.4: 052J5M]. KEYNOTE-057 was designed to follow the recommendations by FDA and clinical experts in the field and is consistent with the recommendations outlined in the FDA/AUA workshop and the FDA guidance.

The FDA's Position:

FDA agrees that there are limited treatment options aside from radical cystectomy for the treatment of BCG-unresponsive high-risk NMIBC and that this disease setting represents an

unmet medical need. FDA agrees with the presented CR rate for valrubicin. In the study of patients with BCG-refractory CIS (n=90), the median duration of response for valrubicin per the USPI was 13.5 months if measured until last available bladder biopsy or 21 months if measured until time of documented recurrence. The FDA agrees that the design of KEYNOTE-057 (Cohort A) was concordant with the FDA guidance and is adequate to evaluate the efficacy of pembrolizumab in this setting.

2.1.4 Rationale for Pembrolizumab in the Treatment of NMIBC

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This blockade enhances functional activity of the target lymphocytes to facilitate tumor regression and, ultimately, immune rejection.

In advanced bladder cancer (locally advanced/metastatic urothelial cancer), pembrolizumab has demonstrated efficacy and is approved for marketing in certain patients in the second-line and first-line setting based on results of the KEYNOTE-045 and KEYNOTE-052 studies (see [Sec. 2.1.4.1] below and [Ref. 5.4: 046FK6], [Ref. 5.4: 04NZLS], [Ref. 5.4: 04RS09]). Also, results from a study of MIBC provide emerging evidence that the anti-tumor activity of pembrolizumab may extend across all UC settings [Ref. 5.4: 055TLY] [Sec. 2.1.4.1].

These findings support the rationale for investigating the efficacy and safety of checkpoint inhibitors in the treatment of patients with BCG-unresponsive high-risk NMIBC. Also, a systemic agent such as pembrolizumab, with known activity against advanced bladder cancer, may protect against more invasive, advanced disease in patients with high-risk NMIBC.

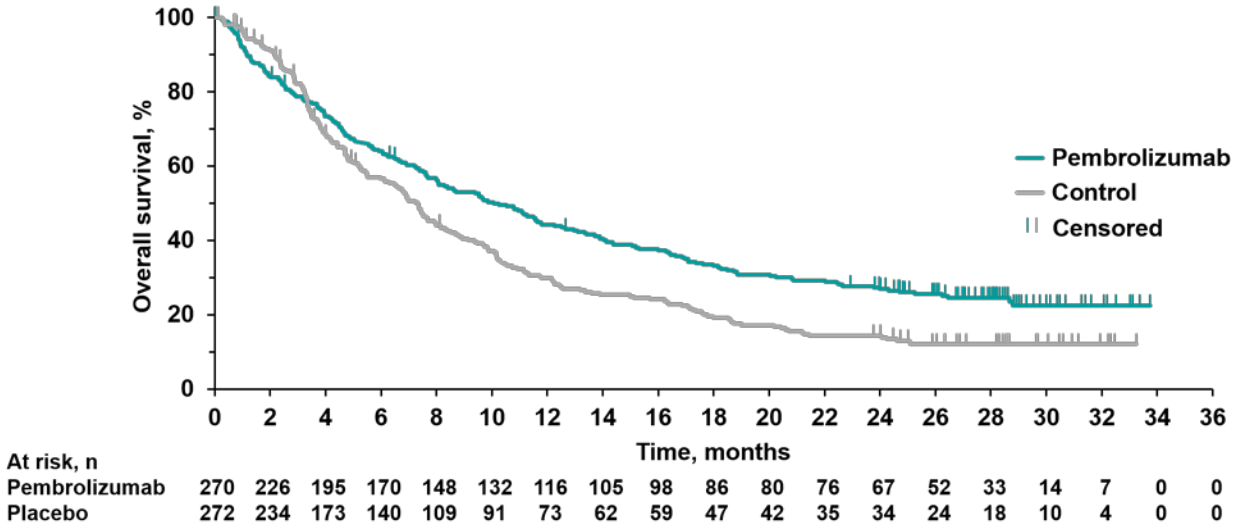
The FDA's Position:

The FDA agrees that there was adequate clinical rationale to conduct KEYNOTE-057.

2.1.4.1 **Advanced/Metastatic Urothelial Cancer - KEYNOTE-045 and KEYNOTE-052 Overview**

Pembrolizumab was the first checkpoint inhibitor to demonstrate an OS benefit versus chemotherapy in the second-line treatment of patients with locally advanced/metastatic urothelial carcinoma in KEYNOTE-045 [Figure 1]. Based on these data, pembrolizumab monotherapy was granted FDA approval in May 2017 for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

Figure 1:
KEYNOTE-045 Kaplan-Meier Estimates of Overall Survival
All Subjects (ITT Population)



Control arm is investigator's choice of paclitaxel, docetaxel or vinflunine.
(Database cutoff date: 26OCT2017
Source: [P045V02MK3475: analysis-adsl; adtte]

Pembrolizumab provided meaningful objective response rate and duration of response in the first-line treatment of cisplatin ineligible patients with locally advanced/metastatic urothelial carcinoma in KEYNOTE-052 [Table 1]. These data led to FDA approval for pembrolizumab monotherapy in May 2017 (revised in June 2018) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are not eligible for cisplatin-containing chemotherapy whose tumors express PD-L1 [CPS ≥10] as determined by an FDA-approved test, or in patients who are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

Table 1:
KEYNOTE-052: Summary of Best Overall Response with Confirmation Based on RECIST 1.1 per Central Radiology Assessment
All Subjects (APT Population)

Response Evaluation	Pembrolizumab (N=370)
Objective Response	
Objective response rate (95% CI[+])	29% (24, 34)
Complete response	9%
Partial response	20%
Duration of Response	
Median in months (range)	30.1 (1.4+ to 35.9+)
+ denotes ongoing. Database Cutoff Date: 26SEP2018	

Source: [P052V03MK3475: analysis-adsl; adopa]

In addition to the demonstrated efficacy of pembrolizumab monotherapy in KEYNOTE-045 and KEYNOTE-052 in advanced/metastatic bladder cancer, there are preliminary data for

pembrolizumab monotherapy for the neoadjuvant treatment of MIBC in published results of the investigator-initiated PURE-01 study (n = 50). Substantial clinical activity as measured by pathologic complete response was observed; the pathologic complete response rate was 42% (95% CI: 28.2, 56.8) for participants receiving 3 cycles of neoadjuvant pembrolizumab [Ref. 5.4: 055TLY]. These findings in MIBC taken together with results of KEYNOTE-045 and KEYNOTE-052 suggest activity of pembrolizumab across all urothelial cancer settings.

The FDA's Position:

FDA agrees that pembrolizumab has demonstrated activity in advanced/metastatic urothelial carcinoma and is approved for the indications described above.

2.1.5 Regulatory History

The Applicant's Position:

KEYTRUDA (pembrolizumab) is approved in the United States and in many other countries across various tumor types, including locally advanced/metastatic urothelial carcinoma.

KEYTRUDA is indicated for the treatment of the following: melanoma, non-small lung cancer, small cell lung cancer, head and neck squamous cell carcinoma, classical Hodgkin's lymphoma, primary mediastinal large B-Cell lymphoma, urothelial carcinoma, microsatellite instability-high cancer, gastric cancer, esophageal squamous cell carcinoma, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cell carcinoma, and endometrial carcinoma.

The global registration status of KEYTRUDA is rapidly evolving. Applications are under regulatory agency review worldwide in multiple indications.

During the development of pembrolizumab for patients with BCG-unresponsive high-risk NMIBC, regulatory feedback was obtained from the FDA regarding KEYNOTE-057 protocol development and overall pembrolizumab clinical development in urothelial cancer.

The FDA's position:

FDA agrees that pembrolizumab is approved for the indications described above.

2.1.6 Overview of the Clinical Development Plan for Pembrolizumab in Urothelial Carcinoma

The Applicant's Position:

Pembrolizumab is undergoing clinical evaluation in NMIBC, MIBC, and advanced/metastatic urothelial cancer in studies sponsored by Merck or in collaboration with other companies or collaborative groups [Table 2].

Table 2: Select Merck-sponsored Studies of Pembrolizumab in Urothelial Carcinoma

Study/Status	Design/Dosage Regimen	Study Population
NMIBC		
KEYNOTE-057/ Ongoing	Multicenter, single arm, two-cohort open-label Phase 2 study/ Pembrolizumab	Participants with high-risk NMIBC unresponsive to BCG Cohort A (enrollment complete) – with CIS at baseline Cohort B (enrollment ongoing) – without CIS at baseline (high grade Ta or any grade T1)
KEYNOTE-676 Ongoing	Randomized, comparator-controlled, multi-site, open-label, parallel-group Phase 3 study/ **Treatment Arm 1**: Pembrolizumab + BCG **Treatment Arm 2**: BCG	Participants with high-risk NMIBC that is persistent or recurrent following adequate BCG induction
MIBC		
KEYNOTE-866 Ongoing	Randomized, placebo controlled, parallel group, multi-site, double-blind, Phase 3 study/ **Treatment Arm A:** Pre-operative: pembrolizumab, gemcitabine, cisplatin Post-operative: pembrolizumab **Treatment Arm B:** Pre-operative: placebo, gemcitabine, cisplatin Post-operative: placebo	Participants with previously untreated MIBC and are cisplatin eligible
KEYNOTE-905 Ongoing	Randomized, controlled, parallel-group, multi-site, open-label, Phase 3 study/ **Treatment Arm 1** Pre-operative pembrolizumab 200 mg Q3W for 3 cycles + cystectomy Cystectomy + postoperative pembrolizumab 200 mg Q3W for 14 cycles **Treatment Arm 2** Cystectomy alone	Participants with previously untreated MIBC and are cisplatin ineligible
Advanced/metastatic urothelial cancer		
KEYNOTE-045/ Ongoing	Randomized, controlled, open label Phase 3 study/	Participants with 2L+ UC (enrollment complete)

Study/Status	Design/Dosage Regimen	Study Population
	Treatment Arm 1: Pembrolizumab Treatment Arm 2: Investigator choice of paclitaxel, docetaxel, or vinflunine	
KEYNOTE-052/ Ongoing	Multicenter, single arm, open-label, Phase 2 study/ Pembrolizumab	Participants with cisplatin-ineligible UC (enrollment complete)
KEYNOTE-361/ Ongoing	Randomized, active-controlled, parallel group, multi-site, open-label, Phase 3 study/ **Treatment Arm 1**: Pembrolizumab only **Treatment Arm 2** : Pembrolizumab + cisplatin/carboplatin +gemcitabine **Treatment Arm 3**: Cisplatin/carboplatin + gemcitabine only	Participants with locally advanced or metastatic urothelial cancer (enrollment complete);
MK-7902-011 Ongoing	Randomized, placebo controlled, parallel group, multi-site, double-blind, Phase 3 study/ **Treatment Arm 1** Pembrolizumab, 200 mg intravenous Q3W +lenvatinib, 20 mg oral QD **Treatment Arm 2** Pembrolizumab, 200 mg intravenous Q3W + matching placebo for lenvatinib oral QD	Participants with locally advanced/metastatic urothelial cancer who are cisplatin ineligible whose tumors are PD-L1 positive, and participants that are ineligible for any platinum containing chemotherapy regardless of PDL1

2L = second-line; CIS = carcinoma in situ; MIBC = muscle-invasive bladder cancer; NMIBC = non-muscle-invasive bladder cancer; UC = urothelial carcinoma.

The FDA's Position:

FDA agrees that the sponsor is conducted several trials of pembrolizumab in multiple settings in urothelial carcinoma. The FDA notes the ongoing KEYNOTE-676 study in patients with high-risk NMIBC following BCG induction, but who are not considered BCG-unresponsive, may provide supportive evidence regarding the efficacy in patients with NMIBC. This study enrolls patients with CIS-containing and papillary-only NMIBC. The primary endpoint is CR rate in patients with CIS-containing tumors. Time-to-event endpoints, including recurrence-free survival, are secondary endpoints.

2.2 Summary of Clinical Trials Supporting Efficacy

2.2.1 KEYNOTE-057 Trial Design

The Applicant's Position:

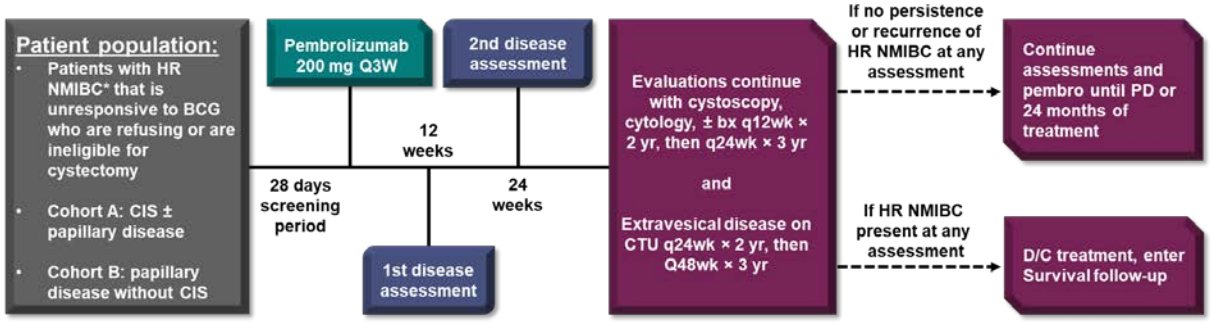
KEYNOTE-057 is an ongoing single-arm, multicenter, open-label, Phase 2 study of the efficacy and safety of pembrolizumab in participants with BCG-unresponsive high-risk NMIBC who are ineligible for or decline to undergo RC ([Figure 2] illustrates the study design). There were 102 participants in Cohort A who received at least one dose of pembrolizumab 200 mg Q3W as of

the enrollment cutoff 01-APR-2018. Disease assessments are performed every 12 weeks for the first 2 years and every 24 weeks thereafter through Year 5, and are based on an integrated evaluation of local cystoscopy and centrally-assessed urine cytology, imaging, and TURBT/biopsies as clinically indicated. Participants are required to discontinue from study treatment if there is confirmed high-risk disease recurrence or progression at any time point.

Participants are assigned to Cohort A or Cohort B as described in Figure 2. This briefing document presents results of Cohort A only because the proposed indication is for patients with CIS (with or without Ta or T1 papillary tumors).

The primary endpoint for Cohort A is the CR rate for BCG-unresponsive high-risk NMIBC, defined as the absence of high-risk NMIBC (CIS, high grade Ta or T1) or progressive urothelial carcinoma. DOR is a key secondary endpoint.

Figure 2: KEYNOTE-057 Study Design



Abbreviations: f/u = follow-up; HR NMIBC = high-risk NMIBC (T1, high grade Ta, and/or CIS); BCG = Bacillus Calmette-Guérin; CIS = carcinoma in situ; CTU= computed tomography urography; NMIBC = non–muscle-invasive bladder cancer; PD = progressive disease; Q3W = every 3 weeks; bx = biopsy; D/C= discontinue

The FDA's Position:

The trial design of KEYNOTE-057 (Cohort A), as described by the sponsor, was consistent with recommendations provided in the FDA Guidance to Industry on BCG-unresponsive Non-muscle Invasive Bladder Cancer: Developing Drugs and Biologics for Treatment. The FDA considers the design of KEYNOTE-057 acceptable to evaluate the activity of pembrolizumab in patients with BCG-unresponsive high-risk NMIBC. The study did not mandate random biopsies at any time point, which was recommended but not required by the guidance. The potential implications of not including random biopsies are discussed in the FDA position under Section 2.2.3.

2.2.2 KEYNOTE-057 Statistical Methods

The Applicant's Position:

The primary population for the analysis of efficacy data in this study was the FAS population, consisting of all enrolled participants who received ≥1 dose of study treatment as of the enrollment cutoff. Safety was analyzed in the APaT population. The APaT and FAS populations were identical for this study.

The point estimate for the CR rate and the associated 95% CI were provided using the binomial exact method and were compared with the historical control CR rate of 20% based on the valrubicin CR rate of 18% [Ref. 5.4: 052JK5]. This is also consistent with the pooled historical CR rate of 21% from a systematic literature review (see [Sec. 2.1.3.2]) and meta-analysis of published data [Ref. 5.4: 058DGZ].

For DOR, the Kaplan-Meier curve and median estimate from the Kaplan-Meier curve were provided. DOR was censored at the last assessment before the data cutoff date for responding patients who had not yet progressed.

The FDA's Position:

The applicant designed and sized the study (Cohort A) so that the lower bound of the 95% CI for the complete response rate would exclude a historical CR rate of 20%. However, for a single-arm study, efficacy based on CR rate needs to be supported by an adequate CR rate magnitude and a clinically meaningful duration of response.

2.2.3 Comparison of KEYNOTE-057 Study Design with Published Literature and FDA Guidance

The Applicant's Position:

Beginning with the workshop in 2013 co-sponsored by the FDA and AUA, recommendations for clinical trial design for drug development in NMIBC were published in the literature in 2014 and 2015; FDA issued a draft guidance in 2015, followed by a final guidance in 2018 [Ref. 5.4: 04T3D2], [Ref. 5.4: 05BFXR], [Ref. 5.4: 05BFXQ], [Ref. 5.4: 05BFXS], [Ref. 5.4: 052J5M].

The date of the first visit for the first participant in KEYNOTE-057 was 29-MAR-2016. Although the finalized FDA guidance was not available at the start of the study, the KEYNOTE-057 protocol was reviewed by the FDA and clinical experts in the field at different times during protocol development and their recommendations were incorporated. The study design is consistent with publications that were available during protocol development.

Important characteristics of the study protocol are consistent with the 2018 FDA guidance [Ref. 5.4: 052J5M] for patients with BCG-unresponsive high-risk NMIBC, including the following:

- At 3 months, participants with BCG-unresponsive CIS at study entry who have new, T1 high-grade disease with or without CIS and participants with persistent CIS who did not have a disease-free interval should discontinue the investigational drug. KEYNOTE-057 requires all

participants with any high-risk NMIBC at any efficacy evaluation, including month 3, to discontinue from study therapy.

- Single-arm trials are appropriate in this disease setting due to the lack of effective nonsurgical comparators. KEYNOTE-057 utilizes a single-arm trial design.
- The primary efficacy endpoint in single-arm trials of patients with BCG-unresponsive NMIBC should be CR rate in patients with CIS. Sponsors should consider the CR rate in the context of DOR. KEYNOTE-057 utilizes CR rate and DOR as key endpoints in patients with CIS.
- The lower bound of the 95% CI around the observed response rate should rule out a clinically unimportant complete response rate. KEYNOTE-057 was designed to determine whether the CR rate from pembrolizumab monotherapy was significantly higher than a historical control CR rate of 20%, ie, whether the lower bound of the 95% CI for CR was >20%. The CR rate of 20% was based on the published valrubicin CR rate of 18% [Ref. 5.4: 052JK5], which is also consistent the pooled CR rate of 21% from a meta-analysis of published data [Ref. 5.4: 058DGZ].
- Systemic therapies are expected to treat disease throughout the urinary tract; thus, evidence of disease in the upper tract should be counted as recurrence. In comparison, intravesical therapies are not expected to treat disease in the upper tract. In KEYNOTE-057, upper tract disease was considered a recurrence event.
- Participants should be followed every 3 months for 2 years, then every 6 months for 2 years, and then annually with cystoscopy, directed biopsies, and urine cytology. In KEYNOTE-057, efficacy assessments follow these recommendations, except that biopsies are required only if there are suspicious cytology and/or cystoscopy. Also, CTUs are required every 6 months or more frequently as needed.
- Prior BCG and NMIBC history must be carefully documented, as it is important to distinguish BCG-unresponsive disease from either inadequate therapy or BCG-intolerance because of difference in prognosis. In KEYNOTE-057, BCG treatment was collected (number of instillations and dose per instillation), and the definition of adequate BCG and BCG-unresponsive disease in KN057 is consistent with established definitions (see [Table 3]). The KEYNOTE-057 definition of BCG-unresponsive is more conservative than that in the FDA guidance, as recurrence of CIS must have been within 9 months of study entry instead of within 12 months.
- Sponsors should consult with the appropriate FDA review division regarding the need for central pathology review of biopsy specimens and/or cytology for all patients or a representative sample. In KEYNOTE-057 a central review of initial histology, grade, and stage was conducted, and disease assessments were based on an integrated evaluation of local cystoscopy and centrally-assessed urine cytology, imaging, and TURBT/biopsies as clinically indicated.

Table 3: Comparison of Definitions of BCG-unresponsive NMIBC in FDA Guidance and KEYNOTE-057

FDA Definition (Feb 2018)	KEYNOTE-057 protocol definition
BCG-unresponsive disease is defined as: • T1 high-grade disease at the first evaluation	BCG unresponsive disease is defined as: • T1 high-grade disease at the first evaluation

following an induction BCG course • *Persistent or recurrent (CIS) alone* or with *recurrent Ta/T1* (noninvasive papillary disease/tumor invades the subepithelial connective tissue) disease *within 12 months** of completion of adequate BCG therapy • *Recurrent high-grade Ta/T1* disease *within 6 months** of completion of adequate BCG therapy	after adequate BCG induction • Stage progression at 3 months (±4 weeks) despite adequate induction therapy (e.g., Ta to T1, or CIS to T1; note: adequate induction therapy only is required in this case); or • Persistent high-risk NMIBC at 6 months (±4 weeks) after adequate BCG; or • Recurrent high-risk NMIBC within 9 months of the last BCG instillation despite having received adequate BCG
Adequate BCG therapy is defined as ≥1 of the following: • At least 5 of 6 doses of an initial induction course plus ≥2 of 3 doses of maintenance therapy • At least 5 of 6 doses of an initial induction course plus≥2 of 6 doses of a 2nd induction course	Adequate BCG therapy must include: • An induction course with ≥5 instillations of BCG (adequate induction); and • At least 7 instillations of BCG within 9 months of the first instillation of adequate induction therapy
*Sponsors have some flexibility in the use of 6 and 12 months to define BCG-unresponsive NMIBC.	

The FDA's Position:

As discussed above, the FDA agrees that the design of KEYNOTE-057 is adequate to evaluate the efficacy and safety of pembrolizumab in this setting. As noted by the applicant, bladder biopsies in KEYNOTE-057 were prompted by visual detection of lesions on cystoscopy or abnormal urine cytology. Previous publications have reported that CIS is detected in approximately 15% of patients with NMIBC in which random biopsies were performed in the setting of negative cytology (Subiela et al 2018). Random bladder biopsies at specified time points were not required, which raises potential concern that recurrent disease could have been missed.

2.3 Efficacy Summary

2.3.1 KEYNOTE-057 Disposition, Demographics, and Baseline Characteristics

The Applicant's Position:

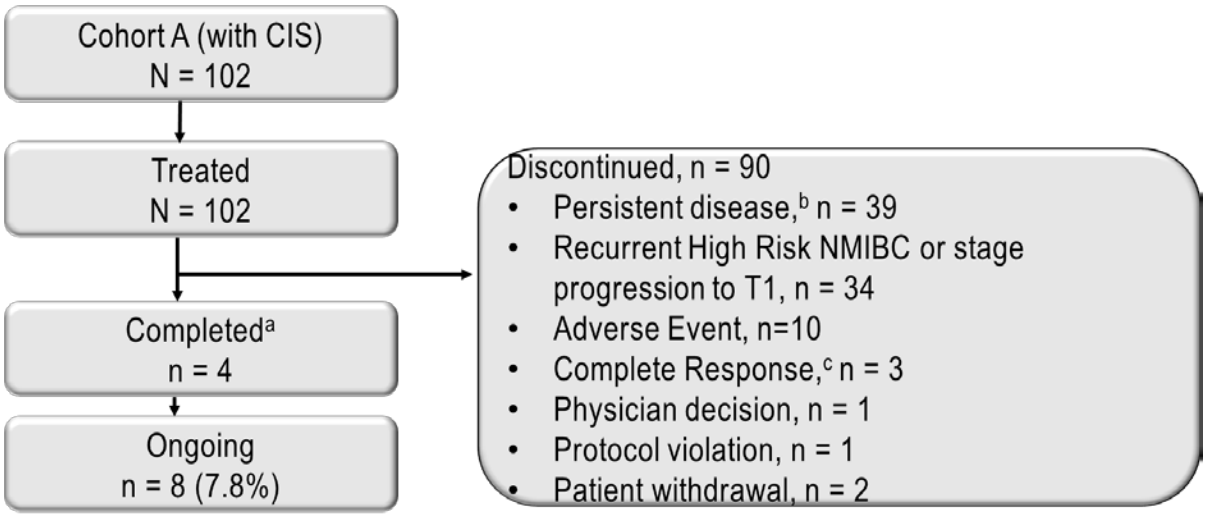
The median (range) follow-up duration for participants in Cohort A was 24.1 (4.6-36.5) months at the time of data cutoff (24-May-2019). The minimum follow-up for the study, from the last enrolled participant to database cutoff, was 14 months.

Seven participants had completed 2 years of study therapy with CR (4 participants) or had discontinued after 18 months due to continued CR as allowed per protocol (3 participants) at the time of data cutoff. The majority of participant discontinuations from study therapy were due to persistent or recurrent NMIBC or NMIBC stage progression to T1; based on study-specified assessments, no participants progressed to muscle invasive or advanced UC while on study treatment [Figure 3].

Key baseline characteristics are representative of patients with high-risk NMIBC [Table 4]. KEYNOTE-057 participants were predominately men (83.3%) and elderly (70.6% were ≥65 and

44.1% were ≥75 years of age). Approximately 95% of participants declined RC and approximately 5% were reported as medically ineligible for RC. Notably, 12 participants had CIS plus T1 disease at baseline, which is considered an especially high-risk population.

Figure 3: KEYNOTE-057 Participant Disposition



a Completed 35 cycles of study treatment, as defined per protocol.
b Includes participants with CIS at baseline and discontinued from study treatment because they continued to have CIS at the first evaluable efficacy assessment.
c Discontinued from study treatment after 18 months due to continued CR, as allowed per protocol.

Table 4: KEYNOTE-057 Participant Characteristics
All Participants (FAS Population)

	Pembrolizumab (Cohort A)	
	n	(%)
Subjects in population	102	
Gender		
Male	85	(83.3)
Female	17	(16.7)
Age (Years)		
< 65	30	(29.4)
>= 65	72	(70.6)
Median (range)	73 (44-92)	
Race		
Asian	27	(26.5)
White	69	(67.6)
Missing	6	(5.9)
ECOG		
[0] Normal Activity	75	(73.5)
[1] Symptoms, but ambulatory	27	(26.5)
[2] Ambulatory but unable to work	0	(0.0)
BCG history: Number of prior instillations of BCG		
Median (range)	12.0(6.0-45.0)	

	Pembrolizumab (Cohort A)	
	n	(%)
PD-L1 Status‡		
PD-L1 CPS <10	58	(56.9)
PD-L1 CPS >=10	39	(38.2)
Not Evaluable	5	(4.9)
Tumor pattern at study entry (bladder cancer stage prior to treatment)†		
Carcinoma in situ (TIS) with T1	12	(11.8)
Carcinoma in situ (TIS) with High grade TA	25	(24.5)
Carcinoma in situ (TIS)	65	(63.7)
Reason the Subject Did Not Receive Prior Cystectomy		
Subject Declined Cystectomy	97	(95.1)
Subject Ineligible	3	(2.9)
Other*	2	(2.0)
Baseline High-risk NMIBC Disease Status**		
Persistent high-risk NMIBC	26	(25.5)
Recurrent high-risk NMIBC	71	(69.6)
Progressive high-risk NMIBC	0	(0.0)
Not Classified	5	(4.9)
Geographic Region US		
US	36	(35.3)
Non-US	66	(64.7)

† Baseline values represent central pathology high-risk NMIBC T-Stage information from archival or fresh tissue obtained prior to or on first dose date.

‡ Participants whose PD-L1 status was not evaluable by the central vendor due to insufficient tumor cell quantity in sample received are considered Not Evaluable. PD-L1 testing was performed by immunohistochemistry (PD-L1 IHC 22C3 pharmDx test). A participant is considered “PD-L1 positive” if their tumor has a PD-L1 CPS ≥10. This is consistent with results of other studies by the Sponsor demonstrating that PD-L1 CPS ≥10 is an appropriate cutoff for participants with bladder cancer.

* These 2 participants were ineligible for cystectomy due to advanced age.

** In Baseline high-risk NMIBC Disease Status, 'Persistent HR NMIBC' is defined as CIS that persists without a tumor-free interval within 6 months +/- 4 weeks of completing adequate BCG therapy and remains present at study entry, 'Recurrent HR NMIBC' is defined as development of HR NMIBC within 9 months of the last BCG instillation despite receiving adequate BCG therapy, 'Progressive HR NMIBC' is defined as stage progression (eg. Ta to T1, or CIS to T1) at 3 months (+/- 4 weeks) despite receiving adequate induction BCG therapy, and 'Not Classified' did not meet inclusion criteria for BCG unresponsive HR NMIBC.

Database Cutoff Date: 24MAY2019.

Source: [P057V02MK3475: adam-adsl]+

The FDA’s Position:

FDA agrees with the sponsor’s presentation of the baseline demographic and disease characteristics of Cohort A. Of note, persistent high-risk NMIBC is generally considered a subgroup at higher risk for progression to MIBC than those with recurrent disease.

The FDA agrees with the statement that no patient in Cohort A progressed to MIBC or metastatic urothelial carcinoma prior to cystectomy while on trial with a minimum follow-up of 14 months from last patient enrolled to data cutoff and median follow-up of 24 months. Thirty-eight patients with persistent or recurrent disease following pembrolizumab underwent subsequent cystectomy. Of these, three patients, all of whom had persistent disease, rather than complete response and then recurrence, were noted to have muscle-invasive disease (T2) on pathologic examination of their cystectomy specimen. This rate of upstaging at cystectomy is generally consistent with that seen in other trials of high-risk NMIBC (Sternberg et al. BJU Int 2013), although the 38 patients who underwent cystectomy may represent a non-random sample of the overall population.

2.3.2 KEYNOTE-057 Efficacy Results

2.3.2.1 Primary Efficacy Endpoint - Complete Response

The Applicant's Position:

Primary efficacy endpoint results demonstrate that pembrolizumab monotherapy resulted in a CR rate of 41.2% (95% CI: 31.5%, 51.4%) in participants with BCG-unresponsive high-risk NMIBC [Table 5]. The lower bound of the 95% CI for the CR rate was greater than the historical control CR rate of 20%; therefore, the study results for pembrolizumab monotherapy met the pre-specified success criterion for the study. In addition, among participants whose disease recurred after achieving a CR or who did not achieve CR, none were reported to progress to muscle-invasive disease or metastatic bladder cancer while on treatment with pembrolizumab based on study-specified assessments.

The one participant with a best response to treatment of extravesical disease developed new liver lesions on imaging and was later found to have a second primary malignancy of pancreatic cancer. Subsequent review of the baseline scan showed subtle findings that, in retrospect, could be attributed to pancreatic cancer, and later scans showed metastases that were most likely from the pancreatic cancer. Clinical course and laboratory values (elevated carbohydrate antigen 19-9 and carcinoembryonic antigen levels) further supported the diagnosis of metastatic pancreatic cancer.

Table 5: KEYNOTE-057 Summary of Best Overall Response of High-risk NMIBC Per Central Assessment
All Participants in Cohort A (FAS Population)

Response Evaluation	Pembrolizumab (Cohort A) (N=102)		
	N	%	95% CI[†]
Complete Response (CR)	42	41.2	(31.5, 51.4)
Non-Complete Response (Non-CR)	58	56.9	(46.7, 66.6)
Persistent	41	40.2	(30.6, 50.4)
Recurrent	7	6.9	(2.8, 13.6)
NMIBC Stage Progression	9	8.8	(4.1, 16.1)
Progression to T2	0	0.0	(NA, NA)

Extravesical Disease	1	1.0	(0.0, 5.3)
Non-Evaluable (NE)	2	2.0	(0.2, 6.9)

[†] Based on binomial exact confidence interval method.
Persistent disease is defined as pathologically confirmed presence of CIS +/- papillary tumor (HG Ta or T1).
Recurrent disease is defined as pathologically confirmed appearance of papillary tumor (HG Ta or T1) without CIS.
NMIBC stage progression is defined as pathologically confirmed increase in stage from CIS +/- HG Ta at baseline to T1 disease.
Progression to T2 is defined as pathologically confirmed progression to muscle invasive bladder cancer.
Extravesical disease is defined as presence of lesions suspicious for locally advanced or metastatic bladder cancer on imaging.
NE: Participants without at least one complete protocol specified efficacy assessment due to adverse event, withdrawal of consent, administrative reasons, physician decision, lost to follow-up, or death are considered not evaluable for efficacy.
Database Cutoff Date: 24MAY2019.

Source: [P057V02MK3475: adam-adsl; adrs]

A sensitivity analysis of CR rate was performed that excluded participants (n = 5) who did not meet the definition of BCG-unresponsive NMIBC. Protocol deviations were recorded for these 5 participants. Results of this analysis were similar to the results in the overall population (CR rate = 41.2% [95% CI: 31.3%, 51.7%]).

The FDA's Position:

FDA's evaluation of efficacy is based on the 97 patients in Cohort A that met the FDA definition of BCG-unresponsive NMIBC. Five patients (of the 102 described by the applicant) did not have adequate documentation to confirm that they met the FDA definition of BCG-unresponsive NMIBC. However, the CR rate was similar in these five patients. Based on FDA calculation, the CR rate in the 97 BCG-unresponsive patients with CIS (with or without papillary tumors) was 41% (95% CI 31%, 52%) (Table 6).

Table 6: KEYNOTE-057 Summary of Best Overall Response of High-risk NMIBC Per Central Assessment Among 97 Patients with BCG-Unresponsive CIS-Containing NMIBC per FDA Guidance (Cohort A): DCO 24-May-2019

Response, n (%) [95% CI]	Pembrolizumab (Cohort A) (N=97)
Complete Response (CR)	40 (41.2) [31.3, 51.7]
Non-Complete Response (Non-CR)	56 (57.7) [47.3, 67.7]
Persistent	40 (41.2) [31.3, 51.7]
Recurrent	6 (6.2) [2.3, 13.0]
NMIBC Stage Progression	9 (9.3) [4.3, 16.9]
Progression to T2	0
Extravesical Disease	1 (1.0) [0.0, 5.6]
Non-Evaluable (NE)	1 (1.0) [0.0, 5.6]

FDA agrees with the sponsor's assessment of metastatic pancreatic cancer in the patient with extravesical disease.

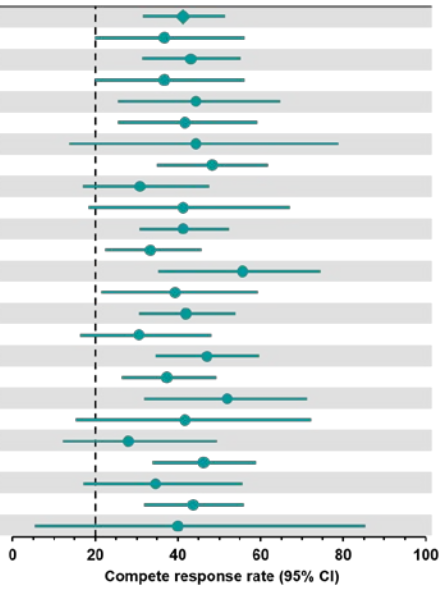
2.3.2.1.1 Subgroup Analysis of Complete Response Rate

The Applicant's Position:

The CR rate was generally consistent across subgroups, including in elderly participants (≥75 years of age; >40% of participants were in this subgroup) [Figure 4]. Complete responses were observed for 5 of 12 participants who had CIS plus T1 at study entry, which is considered an especially high-risk tumor pattern of NMIBC.

Figure 4: KEYNOTE-057 Complete Response Rate of High-risk NMIBC Per Central Assessment by Subgroup Factors – Cohort A (FAS Population)

Subgroup		# response/N	CRR (95% CI)
Overall		**42/102**	**41.2 (31.5, 51.4)**
Age, yr	<65	11/30	36.7 (19.9, 56.1)
	≥65	31/72	43.1 (31.4, 55.3)
Age group, yr	<65	11/30	36.7 (19.9, 56.1)
	≥65 to <75	12/27	44.4 (25.5, 64.7)
	≥75 to <85	15/36	41.7 (25.5, 59.2)
	≥85	4/9	44.4 (13.7, 78.8)
PD-L1 subgroup	PD-L1 CPS <10	28/58	48.3 (35.0, 61.8)
	PD-L1 CPS ≥10	12/39	30.8 (17.0, 47.6)
Gender	Female	7/17	41.2 (18.4, 67.1)
	Male	35/85	41.2 (30.6, 52.4)
Race	White	23/69	33.3 (22.4, 45.7)
	Non-White	15/27	55.6 (35.3, 74.5)
Geographic region EU	EU	11/28	39.3 (21.5, 59.4)
	Non-EU	31/74	41.9 (30.5, 53.9)
Geographic region US	US	11/36	30.6 (16.3, 48.1)
	Non-US	31/66	47.0 (34.6, 59.7)
ECOG status	0	28/75	37.3 (26.4, 49.3)
	1/2	14/27	51.9 (31.9, 71.3)
Tumor pattern at study entry	Carcinoma in situ (TIS) with T1	5/12	41.7 (15.2, 72.3)
	Carcinoma in situ (TIS) with high-grade TA	7/25	28.0 (12.1, 49.4)
	Carcinoma in situ (TIS)	30/65	46.2 (33.7, 59.0)
Baseline HR NMIBC dx status	Persistent high-risk NMIBC	9/26	34.6 (17.2, 55.7)
	Recurrent high-risk NMIBC	31/71	43.7 (31.9, 56.0)
	Not classified	2/5	40.0 (5.3, 85.3)



Database Cutoff Date: 24MAY2019.
Source: [P057V02MK3475: adam-adsl; adrs]

The FDA's Position:

Evaluation of CR rate across subgroups is considered exploratory; however, the FDA agrees that there were no clear outlying subgroups.

2.3.2.2 Key Secondary Efficacy Endpoint – Durability of Response

The Applicant's Position:

The CR rate was accompanied by clinically meaningful durability of CR for participants with BCG-unresponsive high-risk NMIBC who achieved a CR [Table 5] [Figure 5]. The median DOR was 16.2 months (range, 0.0+, 26.8+) at the time of data cutoff, measured from the time initial CR was achieved. The Kaplan-Meier estimate for the percentage of participants with DOR of

≥12 months was 57.4%. At the time of data cutoff, all responders in Cohort A had the opportunity for ≥9 months of durability follow-up, and all but 3 responders had the opportunity for ≥12 months of DOR follow-up. With continued follow-up, it is anticipated that the number of responders with durations of response of 12 months and longer will continue to increase. Responses were ongoing for 19 of 42 responders at the time of data cutoff [Table 7], and 15 of these responders are still being followed for DOR status (4 responders discontinued due to AE, withdrawal by participant, or physician decision).

Results of a sensitivity analysis of DOR that excluded participants (n = 5) who did not meet the definition of BCG-unresponsive NMIBC were similar to the results in the overall population (median DOR = 16.2 [95% CI = 0.0+ to 26.8+] months).

Table 7: KEYNOTE-057 Summary of Complete Response Duration of High-risk NMIBC Per Central Assessment in Participants with Complete Response – Cohort A (FAS Population)

		Pembrolizumab (Cohort A) (N=102)
Number of participants with Complete Response[†]		42
Complete Response Duration (months)		
Median [‡] (Range)[§]		16.2 (0.0+ - 26.8+)
Number (%) of Participants with Complete Response Duration and K-M Estimates (%[‡]):		
Duration	n (%)[*]	K-M estimates (%[*‡])
≥3 months	39 (92.9)	100.0
≥6 months	30 (71.4)	79.5
≥9 months	20 (47.6)	57.4
≥12 months	17 (40.5)	57.4
≥15 months	13 (31.0)	50.7
≥18 months	8 (19.0)	41.3

The DOR of high-risk NMIBC is defined as the time from first documented evidence of CR until evidence of recurrence or progression of high-risk NMIBC by central pathology review or progressive disease by radiology review.

[*] The n (%) column includes all 42 initial responders in the denominator, while the K-M estimate column censors ongoing responders when they complete the study, discontinue from the study, or at the time of last visit for participants still being followed for efficacy at the time of data cutoff (24-MAY-2019).

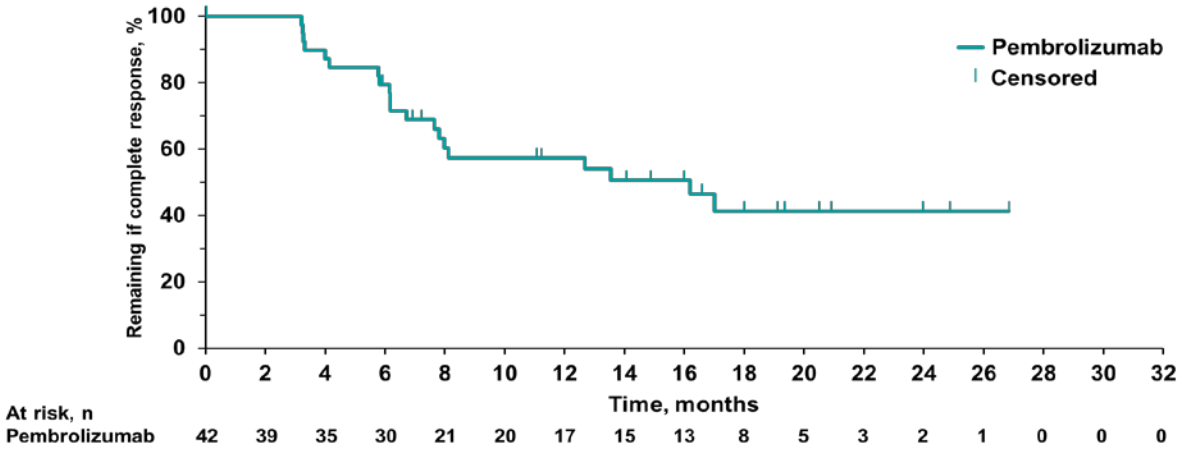
[†] Analysis of complete response duration is based on patients with a best overall response as complete response.

[‡] From product-limit (Kaplan-Meier) method for censored data.

[§] '+' indicates there is no persistent, recurrent or progressive disease by the time of last disease assessment, i.e., the duration of complete response is censored.

Database Cutoff Date: 24MAY2019. Source: [P057V02MK3475: adam-adsl; adtte]

Figure 5: KEYNOTE-057 Kaplan-Meier Estimates on Duration of Complete Response of High-risk NMIBC Per Central Assessment in Participants with Complete Response – Cohort A (FAS Population)



Database Cutoff Date: 24MAY2019.
Source: [P057V02MK3475: adam-adsl; adtte]

Table 8: KEYNOTE-057 Summary of Reasons Subjects with Complete Response are Censored from the DOR Analysis of High-risk NMIBC Per Central Assessment - Cohort A (FAS Population)

	Pembrolizumab (Cohort A) (N=102)
Number of Subjects with Complete Response[†]	42
Subjects Who have Non-Complete Response (Recurrent Disease, NMIBC Stage Progression, Progression to T2, Extravesical Disease) or Died[‡] (%)	**20 (47.6)**
Subjects Who have Recurrent Disease	20 (47.6)
Subjects Who have NMIBC Stage Progression	0 (0.0)
Subjects Who have Progression to T2	0 (0.0)
Subjects Who have Extravesical Disease	0 (0.0)
Subjects Who Died	0 (0.0)
Censored Subjects (%)	**22 (52.4)**
Subjects who have Non-Complete Response or Died immediately after 2 or more consecutive NE	1 (2.4)
Subjects who started new anti-cancer treatment	2 (4.8)
Subjects who were lost to follow-up	0 (0.0)
Ongoing response[§]	19 (45.2)

[†] Patients with a best overall response as complete response.
[‡] Includes all complete responders that go on to have recurrent disease, NMIBC stage progression, progression to T2, extravesical disease, or died without previously having 2 or more consecutive NE assessments. See footnote to [Table 5] for additional definitions.
[§] Ongoing response includes all complete responders who are alive, have not progressed, have not initiated new anti-cancer treatment, are not lost to follow-up.
NE: Participants without at least one complete protocol specified efficacy assessment due to adverse event, withdrawal of consent, administrative reasons, physician decision, lost to follow-up, or death are considered not evaluable for efficacy.
Database Cutoff Date: 24MAY2019.

Source: [P057V02MK3475: adam-adsl; adtte]

The FDA's Position:

The FDA agrees with the sponsor's above reporting for the 102-patient population above. For the 97-patient cohort, summary of complete response duration as of the 24-May-2019 data cutoff is presented in Table 9.

Table 9: KEYNOTE-057 Summary of Response Duration Among 97 Patients with BCG-Unresponsive CIS-Containing NMIBC per FDA Guidance (Cohort A): DCO 24-May-2019

Endpoint	Pembrolizumab (Cohort A) (N=97)
Complete Response Rate (95% CI)	41 (31, 52)
Duration of Response	
Median in months (range)	16.2 (0.0+, 26.8+)
% (n) with duration ≥12 months	40% (16)

Per FDA calculation, the median duration of response among the 40 patients (within the 97 patients in Cohort A with BCG-unresponsive NMIBC) who achieved a complete response was 16.2 months (range, 0.0+, 26.8+). At the time of data cut-off, all patients in complete response had been followed for at least 48 weeks following response. Three patients in complete response as of the data cut-off had not yet reached the one-year post-CR timepoint. 40% of patients with a CR (n=40) remained in CR for at least one year. This equates to 17% of the 97 patients in the primary efficacy population with durable CR of ≥ 1 year from the time of CR.

A summary of reasons for censoring in the 97-patient population is presented in Table 10.

Table 10: KEYNOTE-057 Summary of Reasons Subjects with Complete Response Among 97 Patients are Censored from the DOR Analysis of High-risk NMIBC Per Central Assessment - Cohort A

Number of Subjects, n (%)	Pembrolizumab (Cohort A) (N=97)
Complete Response	40 (41)
Non-Complete Response or Died	19 (48)
Recurrent Disease	19 (48)
Progression to T2	0
Extravesical Disease	0
Died	0
Censored Subjects	21 (53)
Non-Complete Response or Died Immediately After 2 or More Consecutive NE	1 (2.5)
Started New Anti-Cancer Treatment	2 (5)
Lost to Follow-Up	0
Ongoing Response	18 (45)

The Sponsor additionally updated duration of response based on a data cutoff of 24-September-2019. Based on this data cutoff, three additional patients in Cohort A remained in response for ≥1 year from response, resulting in 48% of responding patients and 20% of all treated patients with durable response for ≥1 year. The updated duration of response data are presented in Table 11.

Table 11: KEYNOTE-057 Summary of Response Duration Among 97 Patients with BCG-Unresponsive CIS-Containing NMIBC per FDA Guidance (Cohort A): DCO 24-SEPT-2019

Endpoint	Pembrolizumab (Cohort A) (N=97)
Complete Response Rate (95% CI)	41 (31, 52)
Duration of Response	
Median in months (range)	16.2 (0.0+, 30.4+)
% (n) with duration ≥12 months	48% (19)

2.3.2.3 **Interventions Administered Following Discontinuation of Pembrolizumab**

The Applicant's Position:

Among participants who achieved a CR and then developed recurrent disease, 10 of 23 (43.5%) underwent RC after discontinuation, and 9 of 23 (39.1%) received other subsequent therapy or procedures for the treatment of bladder cancer after discontinuation (any new systemic or intravesical anti-cancer therapy, radiation treatment or surgical procedure) [Table 12]. For all 10 who underwent RC, RC was the first subsequent treatment received (ie, they did not receive any other treatment between pembrolizumab discontinuation and RC). For participants whose first subsequent treatment was not RC (9 subjects), the most frequent (in ≥2 participants) next treatments were intravesical BCG and transurethral bladder resection.

For participants who never achieved a CR, 28 of 60 (46.7%) underwent RC, and 25 of 60 (41.7%) received other subsequent therapy or procedures for treatment of bladder cancer [Table 12]. Of these participants who never achieved CR, 5 (8.3%) received both RC and other subsequent therapies/procedures. RC was the first subsequent treatment received for 24 participants (40%). For subjects whose first subsequent treatment was not RC (24 subjects), the most frequent (in ≥2 participants) next treatments were transurethral bladder research, pembrolizumab, and intravesical BCG, mitomycin, and docetaxel.

These results suggest that many patients do not undergo RC despite disease recurrence and instead may opt for systemic or intravesical therapies. However, RC still remains an option for those patients who wish to pursue this surgery after treatment discontinuation, as demonstrated by the approximately 40% of participants who underwent RC after discontinuing from study therapy. As no participant was reported to progress to T2 disease based on protocol specified disease assessments, it appears that the window of opportunity for RC was not lost due to initial treatment with pembrolizumab.

Table 12: KEYNOTE-057 Summary of All Subsequent Treatments Received to Treat Bladder Cancer by Responder Status[†] – Cohort A (FAS Population)

Number of Subjects Receiving Subsequent Treatment [‡]	Pembrolizumab (Cohort A) N=102					
	CR		Initial CR - No Longer Ongoing		Never CR	
	N (%) = 19 (18.6)		N (%) = 23 (22.5)		N (%) = 60 (58.8)	
	N	%	N	%	n	%
Cystectomy	0	0.0	10	43.5	28	46.7
Therapy or Procedure (Excluding Cystectomy)[§]	1	5.3	9	39.1	25	41.7
Local Procedures/Radiation	0	0.0	5	21.7	12	20.0
Transurethral procedures						
Transurethral bladder resection	0	0.0	4	17.4	12	20.0
Transurethral prostatectomy	0	0.0	1	4.3	0	0.0
Other procedures	1	5.3	2	8.7	3	5.0
Biopsy bladder[‖]	1	5.3	1	4.3	1	1.7
Biopsy	0	0.0	1	4.3	1	1.7
Fulguration	0	0.0	0	0.0	1	1.7
Radiation	0	0.0	0	0.0	1	1.7
Intravesical therapies	0	0.0	6	26.1	21	35.0
BCG	0	0.0	5	21.7	5	8.3
carboplatin	0	0.0	0	0.0	1	1.7
docetaxel	0	0.0	0	0.0	3	5.0
epirubicin	0	0.0	0	0.0	1	1.7
gemcitabine	0	0.0	1	4.3	5	8.3
pirarubicin	0	0.0	0	0.0	2	3.3
valrubicin	0	0.0	0	0.0	2	3.3
mitomycin	0	0.0	0	0.0	8	13.3
oportuzumab monatox	0	0.0	1	4.3	1	1.7
Systemic therapies	0	0.0	0	0.0	4	6.7
pembrolizumab	0	0.0	0	0.0	3	5.0
Photodynamic therapy with TLD-1433 and TLC-3200 (coded as study drug [unspecified])	0	0.0	0	0.0	1	1.7
Number of Subjects Receiving No Subsequent Therapy or Unknown Subsequent Treatment	18	94.7	4	17.4	12	20.0

[†] Status of subject at the time of the last on-study efficacy assessment.
[‡] Subsequent treatment includes procedures (any new anti-cancer therapy, radiation treatment or surgical procedure) performed to treat BCG-unresponsive NMIBC that persisted or recurred after pembrolizumab treatment. It does not include procedures that were performed simultaneously with radical cystectomy and/or were not for treatment of bladder cancer.
[§] Subjects may have received multiple therapies or procedures and may be counted more than once. Five subjects in the Never CR group received other therapies in addition to cystectomy and are counted in both 'Cystectomy' and 'Therapy or Procedure (Excluding Cystectomy)' rows.
[‖] One subject in the CR group achieved an initial CR but subsequently withdrew consent for study treatment due to persistent low-grade AEs and entered survival follow-up (SFU). During SFU, it was reported that subject underwent local biopsy procedure.
Database Cutoff Date: 24MAY2019.

The FDA's Position:

FDA agrees with the presentation of data in Table 10 above for the 102-patient population. For the 97-patient cohort, a summary of subsequent treatments by responder status is shown in Table 13.

Table 13: KEYNOTE-057 Summary of All Subsequent Treatments Received to Treat Bladder Cancer by Responder Status Among 97 Patients with BCG-Unresponsive CIS-Containing NMIBC per FDA Guidance (Cohort A)

	Pembrolizumab (Cohort A) (N=97)		
Subsequent Treatment, n (%)	CR (N=18)	CR - no longer ongoing (N=22)	Never CR (N=57)
Cystectomy	0	9 (40.9)	27 (47.4)
Therapy or Procedure (Excluding Cystectomy)	1 (5.6)	9 (40.9)	25* (43.9)
Unknown or None	17 (94.4)	4 (18.2)	10 (17.5)

* Five subjects received other therapies in addition to cystectomy

Despite 95% of the population refusing cystectomy prior to study entry, 46% (N=36) of the 79 patients with persistent or recurrent disease following pembrolizumab therapy underwent subsequent cystectomy. The median time to cystectomy measured from the first dose of pembrolizumab was 6.1 months in patients that did not achieve a CR compared to 11.5 months in patients that achieved a CR and had disease recurrence. Although there were no patients identified on study with progression to MIBC or metastatic urothelial cancer prior to cystectomy, three patients who did not achieve an initial CR were found to have upstaging to MIBC after pathology review of their cystectomy specimen.

2.3.3 Efficacy Summary and Conclusions

The Applicant's Position:

KEYNOTE-057 was a well-conducted study that was designed to follow the recommendations by FDA and clinical experts in the field and intended to address the lack of effective nonsurgical therapy for patients with high-risk BCG-unresponsive NMIBC who are ineligible for or decline RC. The following are conclusions and efficacy summary statements:

- Pembrolizumab monotherapy resulted in a CR rate (41.2%; 95% CI: 31.5%, 51.4%) in participants with BCG-unresponsive high-risk NMIBC with CIS, with or without papillary tumors, that exceeds the CR rate of the FDA-approved therapy, valrubicin, as well as other existing nonsurgical therapies that are commonly used by physicians, based on results from

a meta-analysis (CR rate from meta-analysis of historical data: 21% [95% CI: 15%, 27%] [Ref. 5.4: 058DGZ]).

- Responders experienced clinically meaningful durability, with a median duration of CR of 16.2 months (range, 0.0+, 26. 8+).
- There were no reports of progression to muscle-invasive or metastatic bladder cancer while receiving study treatment, suggesting that even patients who did not achieve CR were not placed at undue risk of developing MIBC with pembrolizumab administration for 3 months. In addition, the opportunity for RC or other treatment was preserved, given that the majority of participants received subsequent therapies after treatment discontinuation. Fewer than 50% of participants had undergone RC subsequent to discontinuation of pembrolizumab at the time of the data cutoff, suggesting that patients still prefer to receive systemic or intravesical therapies instead of RC after disease recurrence, despite the curative potential of RC.

The FDA's Position:

Forty-one percent of patients with CIS achieved a CR with 20% of all treated patients continuing in CR for at least one year after response based on the 24-SEPT-2019 data cut-off. The median duration of response based on the updated data cutoff was 16.2 months (range, 0.0+, 30.4+). Considering that, based on the 24-MAY-2019 cutoff date, few patients progressed to MIBC and none had metastatic disease with a minimum of 14 months of follow-up from last patient enrolled to data cutoff and a median duration of follow-up of 24 month, these results may be clinically meaningful in the setting of radical cystectomy as the primary alternative. However, the 20% of patients with durable CR lasting ≥ 1 year is lower than the benchmarks discussed at prior workshops. While time to cystectomy was not an endpoint of this study and a minority of patients with persistent or recurrent disease underwent subsequent cystectomy, it may also be clinically meaningful that, in a responder analysis, patients experiencing a CR followed by recurrence delayed cystectomy by approximately 5 months compared to those with persistent disease as best response.

3 SAFETY

The Applicant's Position:

The current safety profile of pembrolizumab is well-characterized based on the extensive clinical trial program for pembrolizumab monotherapy (≥30,000 participants received pembrolizumab in clinical trials) as well as the extensive post marketing experience across the KEYTRUDA indications.

Adverse reactions that were identified across indications during clinical trials experience with KEYTRUDA are described in the Warnings and Precautions section of the product information [Ref. 5.4: 04VZML]. The majority of reported adverse reactions were Grade 1 to 2 in severity. The adverse reactions include immune-mediated events of hypothyroidism in 8.5% of

participants, hyperthyroidism in 3.4%, pneumonitis in 3.4%, colitis in 1.7%, hepatitis in 0.7%, hypophysitis in 0.6%, nephritis in 0.3%, type 1 diabetes mellitus (including diabetic ketoacidosis) in 0.2%, and infusion-related reactions in 0.2%. Skin adverse reactions and other clinically important immune-mediated adverse reactions are also described in the Warnings and Precautions section (see Sections 5.6 and 5.7 of the product information [Ref. 5.4: 04VZML]). Instructions regarding monitoring and management of immune-mediated events include treatment interruption, the use of hormone replacement therapy or oral or intravenous treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids, as outlined in the product information [Ref. 5.4: 04VZML].

In this briefing document, safety data for Cohort A of KEYNOTE-057 are compared to safety data from other pembrolizumab monotherapy studies in the reference safety dataset described in the product information (n = 2977) using descriptive statistics. The reference safety dataset includes pooled safety data from participants treated with pembrolizumab monotherapy, including 1567 participants with advanced melanoma from KEYNOTE-001, KEYNOTE-002, and KEYNOTE-006, and 1232 participants with NSCLC from KEYNOTE-001 and KEYNOTE-010. Data from the reference safety dataset are the basis for the adverse reaction frequencies described above. Cumulative data for pembrolizumab monotherapy across all approved indications has been shared with the FDA and has not resulted in meaningful changes to the reported frequency of adverse reactions.

The FDA's Position:

FDA agrees with the assessment of the safety of pembrolizumab monotherapy as described in the USPI.

3.1 Overall Extent of Exposure

The Applicant's Position:

Median exposure to pembrolizumab was similar for participants in KEYNOTE-057 Cohort A and the reference safety dataset: median (range) exposure values were 4 (range, 0 to 26) months and 4 (range, 0 to 30) months, respectively.

The FDA's Position:

FDA agrees with the above.

3.2 Summary of Adverse Events

The Applicant's Position:

KEYNOTE-057 results demonstrate that the safety profile of pembrolizumab monotherapy in high-risk NMIBC is generally consistent with the known safety profile of pembrolizumab monotherapy in the reference safety dataset [Table 14]. The most frequent (incidence ≥15%) AEs in KEYNOTE-057 were diarrhea, fatigue, hematuria, pruritus, and cough [Table 15]. Of note,

the incidence of hematuria was higher in KEYNOTE-057 relative to the RSD; this higher frequency is consistent with the underlying urothelial carcinoma, where hematuria is the most common presenting symptom, and can also be attributed to the frequent medical procedures that are performed in the target population (eg, cystoscopy) [Ref. 5.4: 0572SS], [Ref. 5.4: 0572SD].

The most frequent Grade 3 to 5 AEs (incidence ≥2% [≥2/102]) were pneumonia, hyperglycemia, hyponatremia, pulmonary embolism, urinary tract infection, arthralgia, and cellulitis; and the most frequent drug-related Grade 3 to 5 AEs (incidence ≥2%) were arthralgia and hyponatremia.

The most frequent (incidence ≥2% [≥2/102]) SAEs were pneumonia, pulmonary embolism, urinary tract infection, and cellulitis. No individual drug-related SAE (by preferred term) was reported in more than 1 patient. Four patients discontinued due to SAEs (cholestatic hepatitis, hyponatremia, nephritis, and type 1 diabetes mellitus). One patient died due to respiratory failure (resulting from MRSA pneumonia) and one death was secondary to metastatic pancreatic cancer, neither of which were considered related to therapy.

Table 14: KEYNOTE-057 Adverse Event Summary (APaT Population)

	KEYNOTE-057 Cohort A n (%)	Reference Safety Dataset for Pembrolizumab n (%)
Subjects in the population	102	2977
Any AE	99 (97.1)	2,727 (97.4)
Grade 3-5 AE	30 (29.4)	1,273 (45.5)
Serious AE	26 (25.5)	1,042 (37.2)
Death	2 (2.0)[a]	110 (3.9)
Discontinuation due to AE	10 (9.8)	334 (11.9)
Discontinuation due to serious AE	4 (3.9)	253 (9.0)

[a] Respiratory failure (n = 1) and metastatic pancreatic cancer (n = 1). None of the deaths was deemed related to treatment.

Table 15: KEYNOTE-057 Adverse Events by Decreasing Incidence (in ≥10% of participants) (APaT Population)

	KEYNOTE-057 Cohort A n (%)	Reference Safety Dataset for Pembrolizumab n (%)
Subjects in the population	102	2977
Any AE	99 (97.1)	2,727 (97.4)
Diarrhea	22 (21.6)	625 (22.3)
Fatigue	21 (20.6)	1044 (37.3)
Hematuria	21 (20.6)	39 (1.4)
Pruritus	19 (18.6)	562 (20.1))
Cough	18 (17.6)	615 (22.0)

	KEYNOTE-057 Cohort A n (%)	Reference Safety Dataset for Pembrolizumab n (%)
Nausea	15 (14.7)	685 (24.5)
Arthralgia	14 (13.7)	504 (18.0)
Constipation	12 (11.8)	498 (17.8)
Urinary tract infection	12 (11.8)	162 (5.8)
Nasopharyngitis	12 (11.8)	182 (6.5)

The FDA's Position:

FDA agrees with the above incidences of adverse events in Cohort A.

3.3 Summary of Adverse Events of Special Interest

The Applicant's Position:

Adverse events of special interest or AEOSIs are intended to capture immune-mediated events and infusion-related reactions associated with pembrolizumab. A prespecified list of preferred terms was developed by the Applicant to consistently characterize the nature and frequency of each AEOSI across the pembrolizumab clinical program, regardless of causality as reported by investigators. The frequencies of participants in KEYNOTE-057 who experienced AEOSIs were similar to the frequencies observed in the pembrolizumab reference safety dataset [Table 16] [Table 17].

The majority of AEOSIs reported were mild to moderate in severity (Grade 1 or 2). Grade 3 AEOSIs were adrenal insufficiency and pruritus (in 1 participant each). One participant had a Grade 4 AEOSI of type 1 diabetes mellitus. This participant with type 1 diabetes mellitus also had the event of metastatic pancreatic cancer described above.

No new indication-specific, immune-mediated AE causally associated with pembrolizumab was identified in this study. The majority of immune-related AEs were grade 1-2 and managed with recommended treatment (described above in [Sec. 3]).

Table 16: KEYNOTE-057 Adverse Event Summary for AEOSIs (APaT Population)

	KEYNOTE-057 Cohort A n (%)	Reference Safety Dataset for Pembrolizumab n (%)
Subjects in the population	102	2977
Any AEOSI	21 (20.6)	597 (21.3)
Grade 3-5 AEOSI	3 (2.9)	154 (5.5)
Serious AEOSI	5 (4.9)	161 (5.8)
Death due to AEOSI	0 (0.0)	4 (0.1)
Discontinuation due to AEOSI	4 (3.9)	83 (3.0)
Discontinuation due to serious AEOSI	2 (2.0)	68 (2.4)

Table 17: KEYNOTE-057 AEOSIs by Decreasing Frequency (APaT Population)

	KEYNOTE-057 Cohort A n (%)	Reference Safety Dataset for Pembrolizumab n (%)
Subjects in the population	102	2977
Any AEOSI	21 (20.6)	597 (21.3)
Hypothyroidism	8 (7.8)	237 (8.5)
Hyperthyroidism	5 (4.9)	96 (3.4)
Pneumonitis	3 (2.9)	94 (3.4)
Adrenal insufficiency	1 (1.0)	22 (0.8)
Colitis	1 (1.0)	48 (1.7)
Hepatitis	1 (1.0)	19 (0.7)
Hypophysitis	1 (1.0)	17 (0.6)
Nephritis	1 (1.0)	9 (0.3)
Type 1 diabetes mellitus	1 (1.0)	6 (0.2)
Severe skin reaction	1 (1.0)	38 (1.4)
Uveitis	1 (1.0)	14 (0.5)

The FDA's Position:

FDA agrees with the above incidences of immune-related adverse events in Cohort A.

3.4 Safety Summary and Conclusions

The Applicant's Position:

- The safety profile of pembrolizumab in NMIBC is consistent with the well-established safety profile of KEYTRUDA monotherapy, which has been continually assessed in a large clinical trial program (≥30,000 participants) and during extensive postmarketing experience over 5 years across KEYTRUDA indications.
- Types, frequencies, and severity of AEs as well as company defined pembrolizumab AEOSIs were generally similar between participants in KEYNOTE-057 and in the reference safety dataset for pembrolizumab.
- No new safety concerns were identified. AEs were effectively managed by standard clinical practice as applicable for pembrolizumab monotherapy (outlined in the product label [Ref. 5.4: 04VZML]).

The FDA's Position:

FDA agrees with the safety profile of pembrolizumab presented by the Applicant and has not identified any new safety signals in the review of pembrolizumab in KEYNOTE-057. No events of disease progression to MIBC or metastatic urothelial carcinoma were observed in the study with median follow-up duration of 24 months, suggesting that deferral of immediate radical cystectomy in lieu of treatment with pembrolizumab did not appear to worsen oncologic outcomes. Three patients out of the 38 with persistent or recurrent disease who underwent subsequent cystectomy were determined to have MIBC on their cystectomy specimens. This incidence of upstaging does not appear greater than expected in this population.

4 POINTS FOR THE ADVISORY COMMITTEE TO CONSIDER

The Applicant's Position:

4.1 Discussion of Benefits and Risks of Pembrolizumab in Patients with NMIBC

BCG-unresponsive high-risk NMIBC is a serious condition with significant unmet medical need. The only current standard of care option is RC with urinary diversion [Ref. 5.4: 04T57S], [Ref. 5.4: 04XBKC]. Although RC is considered curative for patients with high-risk NMIBC, it is associated with a high rate of perioperative morbidity and mortality, and a clinically relevant negative impact on HRQoL [Ref. 5.4: 052JKF] [Ref. 5.4: 052JKN]. Many patients, in particular elderly patients, either have comorbidities precluding surgical intervention or electively seek alternative nonsurgical therapy options [Ref. 5.4: 04T3DT], [Ref. 5.4: 057K8P]. Currently, intravesical or systemic therapies that provide an effective, durable treatment option for patients who decline RC or are ineligible are limited. New non-surgical therapies are urgently needed for this patient population.

Recognizing the significant unmet medical need and the lack of clinical trials in the BCG-unresponsive NMIBC space, a workshop with the FDA and AUA was held in 2013, where appropriate clinical trial design, endpoints, and potential efficacy thresholds were discussed for patients with BCG-unresponsive NMIBC who are ineligible for or decline RC [Ref. 5.4: 04T3D2]. As a result, a more standardized approach to clinical trials in this space was developed, resulting in publication of a final FDA guidance in 2018 that attempts to standardize approaches to clinical trials in this disease space [Ref. 5.4: 052J5M].

KEYNOTE-057 is a well-designed and well-conducted study that follows recommendations in FDA-AUA publications and FDA guidance. Results demonstrate that pembrolizumab is a clinically meaningful option for patients who decline or are ineligible for RC.

Efficacy findings at the time of data cutoff (24-May-2019) indicate that pembrolizumab monotherapy results in a compelling CR rate (41.2%) in patients with BCG-unresponsive CIS (with or without papillary tumors) that exceeds the CR rate of available nonsurgical therapies based on results of a SLR/meta-analysis (lower bound of the 95% CI was greater than the upper bound of the 95% CI for CR rate in the meta-analysis). Equally important is the durability of the complete responses, which demonstrates clinically meaningful improvements compared to

currently available intravesical treatment options. Durable responses are a hallmark of anti-PD-1 therapy with pembrolizumab across multiple types of solid tumors, including advanced/metastatic UC, and now including NMIBC, given these results from KEYNOTE-057.

Consistent with FDA guidance, all nonresponders discontinued pembrolizumab at Month 3 in KEYNOTE-057. It is notable that delayed responses to checkpoint inhibitors were observed in many studies [Ref. 5.4: 04RQDS], [Ref. 5.4: 05BTH3], [Ref. 5.4: 05BTH9], and anecdotally in KEYNOTE-057; therefore, discontinuation of treatment at Month 3 may lead to a conservative estimate of CR rate.

As no participant was reported to progress to muscle invasive disease or developed metastatic bladder cancer based on protocol specified disease assessments, the window of opportunity for RC is preserved for participants who subsequently elect to undergo RC after recurrence. Notably, less than 50% of patients had undergone cystectomy subsequent to discontinuation of pembrolizumab, suggesting that patients still decline RC and receive intravesical or systemic therapies despite disease recurrence. This is consistent with the overall patient population enrolled in KEYNOTE-057, where a majority of patients had initially elected not to undergo RC despite its curative potential.

KEYNOTE-057 safety data show a manageable safety profile for pembrolizumab monotherapy use in the target population for the proposed indication. No new risks associated with the use of pembrolizumab were identified. The AE profile is consistent with the safety profile of pembrolizumab monotherapy or considered related to underlying urothelial carcinoma or associated procedures. Pembrolizumab was generally well tolerated and AEOSIs were managed with appropriate intervention (treatment interruption, corticosteroid treatment, hormone replacement therapy as outlined in the product information [Ref. 5.4: 04VZML]).

4.1.1 Benefits and Risks Conclusions

In conclusion, the analysis of data from KEYNOTE-057 provides strong evidence that the benefits of pembrolizumab monotherapy outweigh the risks for patients with BCG-unresponsive high-risk NIMBC who are ineligible for or elect not to undergo RC. Treatment with pembrolizumab results in a CR rate that exceeds the CR rate of existing non-surgical therapies for patients with BCG-unresponsive CIS. Also, the observed durable clinical benefit among responders in KEYNOTE-057 suggests that pembrolizumab monotherapy provides patients an effective, durable treatment option. Given the observed manageable and well-understood safety profile of pembrolizumab in KEYNOTE-057, pembrolizumab is an attractive treatment option that does not appear to diminish the window of opportunity for RC for patients who subsequently choose to undergo RC after recurrence.

RC is a life-altering surgery with a negative impact on quality of life and significant morbidity and mortality. For this reason, many patients decline this surgery or are medically ineligible. Treatment with pembrolizumab in this disease setting fulfills a significant unmet medical need and provides a valuable treatment option for patients with BCG-unresponsive NMIBC with CIS who are ineligible for or decline RC, a clinical scenario for which no well-accepted treatment options are currently available.

The FDA's Position:

The Applicant is seeking an indication for the use of pembrolizumab for the treatment of adult 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 based on the CR rate and duration of CR from a single-arm, open-label study, KEYNOTE-057. While these endpoints have been determined by the FDA to be appropriate in this setting, the magnitude required to demonstrate clinical benefit has not been previously discussed in an ODAC. The Applicant conducted a study concordant with FDA guidance and demonstrated a CR rate of 40%; (95% CI 31%,52%; as calculated by FDA) of which 48% of CRs were maintained for at least one year subsequent to the CR. Thus, a total of 20% of the 97 patients experienced CR durable for at least one year, allowing deferral of radical cystectomy. Additionally, in a responder analysis, time to cystectomy in patients who achieved a CR but had subsequent disease recurrence was approximately 5 months longer than in those who had persistent disease as best response.

FDA agrees with the safety profile of pembrolizumab as described by the Applicant and agrees that there are no new safety signals identified in KEYNOTE-057. Pembrolizumab appeared to be well-tolerated in this patient population; however, it is a systemic therapy with potentially life-threatening toxicities. There was no detriment identified in progression to MIBC or metastatic urothelial carcinoma prior to cystectomy and only three patients who underwent subsequent cystectomy were pathologically upstaged to MIBC, suggesting that treatment with pembrolizumab might not compromise oncologic outcomes compared to immediate radical cystectomy. However, the duration of follow-up, with a minimum of 14 months and median of 24 months, may not yet be sufficient to allow definitive conclusions.

Although the efficacy results of KEYNOTE-057 show a significant improvement over available non-surgical therapies including valrubicin, it is not yet clear whether this improvement is sufficiently clinically meaningful to warrant approval in the setting of the toxicities of a systemic therapy.

5 DRAFT TOPIC FOR ADVISORY COMMITTEE DISCUSSION

Do the observed complete response rate and duration of response represent a favorable risk/benefit profile for patients with BCG-unresponsive high-risk NMIBC with CIS treated with pembrolizumab?

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