Pembrolizumab for the Treatment of Patients With High-Risk Non–Muscle-Invasive Bladder Cancer Unresponsive to Bacillus Calmette-Guérin: Extended Follow-Up of KEYNOTE-057 Cohort A

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*At the time of this analysis

Background

- Standard of care for high-risk (HR) non–muscle-invasive bladder cancer (NMIBC) is transurethral resection of the bladder tumor followed by intravesical Bacillus Calmette-Guérin (BCG) immunotherapy, although many patients will become BCG unresponsive and experience recurrence within 12 months[1-3]
- On January 8, 2020, pembrolizumab was approved by the US Food and Drug Administration (FDA) for the treatment of patients with BCG-unresponsive HR NMIBC with carcinoma in situ (CIS) with or without papillary tumors who are ineligible for or have elected not to undergo cystectomy[4]
- With more than 3 years of follow-up, we present updated results from cohort A of KEYNOTE-057 (NCT02625961), an open-label, single-arm, multicenter phase 2 study

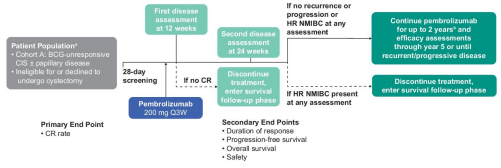
Objective

- To evaluate the efficacy and safety and tolerability of pembrolizumab after 3 years of follow-up in patients with HR NMIBC with CIS at baseline

Methods

Study Design

Figure 1. Study Design



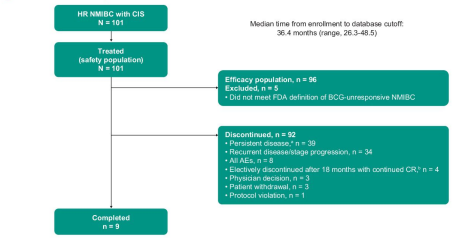
CR, complete response; Q3W, every 3 weeks.
[a]Cohort B: Papillary tumors only, without CIS—enrolling.
[b]Patients with continued CR can electively discontinue pembrolizumab after 18 months.

- Enrollment cutoff date: April 1, 2018
- Database cutoff date: May 25, 2020
- Analysis populations
  - Efficacy: all enrolled patients who received ≥1 dose of study medication by the enrollment cutoff date and underwent pre-enrollment cystoscopy and baseline computed tomography
  - Safety: all enrolled patients who received ≥1 dose of study medication by the enrollment cutoff date

Results

Patient Disposition

Figure 2. Patient Disposition



AE, adverse event.
[a]Includes patients who had CIS (± papillary tumor) at baseline and discontinued the study treatment and had CIS ± papillary tumor at month 3.
[b]Patients with CR who were allowed per protocol to discontinue study treatment after 18 months.

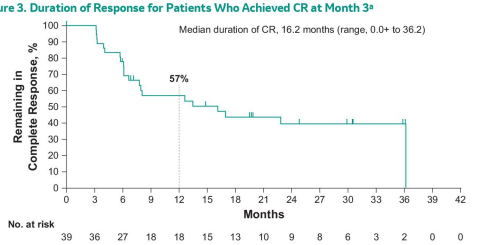
Efficacy

Table 1. Overall Response Rate by Central Review at Month 3

N = 96	n	%	95% CI
CR	39	40.6	30.7-51.1
Non-CR	56	58.3	47.8-68.3
Persistent[b]	40	41.7	31.7-52.2
Recurrent[b]	6	6.3	2.3-13.1
NMIBC stage progression[c]	9	9.4	4.4-17.1
Non–bladder malignancy[d]	1	1.0	0.0-5.7
Progression to T2	0	0	NA-NA
Nonevaluable[e]	1	1.0	0.0-5.7

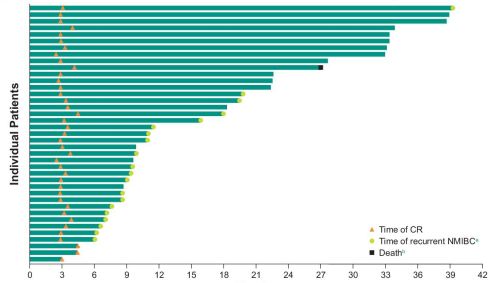
NA, not applicable.
[a]Defined as patients who at first evaluable assessment had CIS ± papillary tumor.
[b]Defined as pathologically confirmed appearance of papillary tumor (high-grade Ta or T1) without CIS at first evaluable assessment.
[c]Increase in stage from CIS and/or high-grade Ta at baseline to T1 disease.
[d]Patient developed new liver lesions (substantiated by imaging) and later had a second primary malignancy of pancreatic cancer. Subsequent review of the baseline imaging showed subtle findings that, in retrospect, could be attributed to pancreatic cancer. Clinical course and laboratory values further supported the diagnosis of metastatic pancreatic cancer.
[e]Patients whose protocol-specified efficacy assessments were missing or who discontinued the study medication for reasons other than progressive disease are considered nonresponders.

Figure 3. Duration of Response for Patients Who Achieved CR at Month 3[a]



[a]Month 0 = time point when initial CR was achieved.
+ indicates ongoing response.

Figure 4. Time to CR and Recurrence of HR NMIBC in Patients Who Have Experienced CR



[a]Pathologically confirmed reappearance of HR NMIBC (CIS and/or high-grade Ta and/or T1 disease) after a disease-free interval (at each month or afterward).
[b]1 patient died of congestive cardiac failure (not related to treatment).

Subsequent Treatment After Pembrolizumab and Pathological Upstaging

Table 2. Summary of Subsequent Treatments for Bladder Cancer by Responder Status[a]

	Cohort A N = 96		
	CR n = 14	Initial CR No Longer Ongoing n = 25	Never CR n = 57
Receiving subsequent treatment;[b] n (%)			
Cystectomy	0	11 (44.0)	29 (50.9)
Therapy or procedure (excluding cystectomy)[c,d]	1 (7.1)	12 (48.0)	30 (52.6)
Local procedures	1 (7.1)	9 (36.0)	17 (29.8)
Intravesical therapies	0	10 (40.0)	20 (35.1)
Systemic therapies	0	1 (4.0)	9 (15.8)
No or unknown subsequent therapy	13 (92.9)	3 (12.0)	8 (14.0)

[a]Status of patient at the time of the last on-study efficacy assessment.
[b]Subsequent treatment includes any new anticancer 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 or were not performed to treat bladder cancer.
[c]Patients might have received multiple therapies or undergone multiple procedures and might be counted more than once. Eleven patients received other therapies in addition to cystectomy and are counted in the Cystectomy and Therapy or Procedure (excluding cystectomy) rows.
[d]1 patient in the CR group achieved initial CR but subsequently withdrew consent for study treatment because of persistent low-grade AEs and entered survival follow-up, during which time the patient underwent a local biopsy procedure.

Table 3. Pathological Staging at Time of Radical Cystectomy in Patients Who Discontinued Pembrolizumab

	Patient, n n = 38[a]	Maximum T Stage	N Stage[b]	Achieved Initial CR, n	Interval Between Last Dose of Pembrolizumab and Radical Cystectomy, days
NMIBC	6	pT0	N0 = 5 Nx = 1	4	134.5 (60-149)[c]
	5	pTa	N0 = 5	0	103 (70-819)[c]
	18	pTis	N0 = 16 Nx = 2	6	76.5 (42-861)[c]
	6	pT1	N0 = 6	0	133 (51-566)[c]
MIBC	2	pT2	N0 = 1 N1 = 1[d]	0	60 86
	1	pT3	N1	0	457

Tumor node classification based on the guidelines in the *AJCC Cancer Staging Manual*, 8th edition.[5]
[a]TNM staging was not available for 2 of 40 participants who had undergone radical cystectomy.
[b]Nx = lymph node dissection not performed.
[c]In a patient with pT2N1 disease, a single perivesical lymph node was involved.
[d]Median (range).

Safety

- Of 101 patients, 67 (66.3%) experienced ≥1 treatment-related AE
  - Grade 3 or 4 treatment-related AEs occurred in 13 patients (12.9%)
  - No patient died of a treatment-related AE
- Treatment-related AEs led to pembrolizumab interruption in 13 patients (12.9%) and discontinuation in 7 (6.9%)

Table 4. Treatment-Related AEs of Any Grade (≥5% of the population) and Corresponding Grade 3 or 4 Treatment-Related AEs

Treatment-Related AEs, n (%)	N = 101		
	Any Grade	Grade 3[a]	Grade 4[b]
Any	67 (66.3)	11 (10.9)[c]	2 (2.0)
Diarrhea	11 (10.9)	0	0
Fatigue	11 (10.9)	0	0
Pruritus	11 (10.9)	1 (1.0)	0
Hypothyroidism	7 (6.9)	0	0
Arthralgia	6 (5.9)	2 (2.0)	0
Rash, maculopapular	6 (5.9)	0	0
Hyperthyroidism	5 (5.0)	0	0
Rash	5 (5.0)	0	0
Nausea	5 (5.0)	0	0

[a]Other grade 3 treatment-related AEs were hyponatremia (n = 2), adrenal insufficiency (n =1), adrenocorticotropic hormone deficiency (n = 1), cholestatic hepatitis (n = 1), decreased lymphocyte count (n = 1), dermatitis (n = 1), hypophosphatemia (n = 1), pulmonary embolism (n = 1), malaise (n = 1), and syncope (n = 1).
[b]Grade 4 treatment-related AEs were hyponatremia (n = 1) and type 1 diabetes mellitus (n = 1).
[c]1 patient experienced grade 3 adrenal insufficiency, grade 3 adrenocorticotropic hormone deficiency, and grade 3 hyponatremia, and 1 patient experienced both grade 3 cholestatic hepatitis and grade 3 decreased lymphocyte count.

Table 5. Immune-Mediated Adverse Events[a]

Immune-Mediated AE, n (%)	Cohort A N = 101		
	Any Grade	Grade 1 or 2	Grade 3 or 4
Any	22 (21.8)	19 (18.8)	3 (3.0)
Hypothyroidism	8 (7.9)	8 (7.9)	0
Hyperthyroidism	5 (5.0)	5 (5.0)	0
Pneumonitis	3 (2.0)	3 (3.0)	0
Colitis	2 (2.0)	2 (2.0)	0
Adrenal insufficiency	1 (1.0)	0	1 (1.0)
Autoimmune hepatitis	1 (1.0)	1 (1.0)	0
Autoimmune nephritis	1 (1.0)	1 (1.0)	0
Hypophysitis	1 (1.0)	1 (1.0)	0
Pruritus	1 (1.0)	0	1 (1.0)
Type 1 diabetes mellitus	1 (1.0)	0	1 (1.0)
Uveitis	1 (1.0)	1 (1.0)	0

[a]Immune-mediated AEs were based on a list of terms specified by the sponsor and included by the investigator regardless of attribution to study treatment or immune relatedness.

Conclusions

- With more than 3 years of follow-up data, pembrolizumab continues to show clinically meaningful, antitumor activity in patients with BCG-unresponsive HR NMIBC with CIS (with or without papillary disease) who are ineligible for or have elected not to undergo cystectomy
  - 40.6% CR rate at first evaluable assessment
  - Duration of CR, median (range): 16.2 months (0.0+ to 36.2)
- Use of pembrolizumab did not seem to limit the opportunity to undergo radical cystectomy or other subsequent therapies
- Rates of pathological upstaging to MIBC were low for patients who underwent radical cystectomy after discontinuation of pembrolizumab
- Pembrolizumab monotherapy had a manageable safety profile consistent with what has been reported[4]
- Results from this analysis provide compelling evidence that pembrolizumab should be considered an effective nonsurgical treatment option in patients with BCG-unresponsive CIS (with or without Ta/T1) of the bladder who are ineligible for or decline to undergo radical cystectomy

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