# Pembrolizumab monotherapy for the treatment of high-risk non-muscle-invasive bladder cancer unresponsive to BCG (KEYNOTE-057): an open-label, single-arm, multicentre, phase 2 study

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## Summary

**Background** Standard treatment for high-risk non-muscle-invasive bladder cancer is transurethral resection of bladder tumour followed by intravesical BCG immunotherapy. However, despite high initial responses rates, up to 50% of patients have recurrence or become BCG-unresponsive. PD-1 pathway activation is implicated in BCG resistance. In the KEYNOTE-057 study, we evaluated pembrolizumab, a PD-1 inhibitor, in BCG-unresponsive non-muscle-invasive bladder cancer.

**Methods** We did this open-label, single-arm, multicentre, phase 2 study in 54 sites (hospitals and cancer centres) in 14 countries. In cohort A of the trial, adults aged 18 years or older with histologically confirmed BCG-unresponsive carcinoma in situ of the bladder, with or without papillary tumours, with an Eastern Cooperative Oncology Group performance status of 0–2, and who were ineligible for or declined radical cystectomy were enrolled. All enrolled patients were assigned to receive pembrolizumab 200 mg intravenously every 3 weeks for up to 24 months or until centrally confirmed disease persistence, recurrence, or progression; unacceptable toxic effects; or withdrawal of consent. The primary endpoint was clinical complete response rate (absence of high-risk non-muscle-invasive bladder cancer or progressive disease), assessed by cystoscopy and urine cytology approximately 3 months after the first dose of study drug. Patient follow-ups were done every 3 months for the first 2 years and every 6 months thereafter for up to 5 years. Efficacy was assessed in all patients who received at least one dose of the study drug and met BCG-unresponsive criteria. Safety was assessed in all patients who received at least one dose of the study drug. This trial is registered with ClinicalTrials.gov number, NCT02625961, and is ongoing.

**Findings** Between Dec 9, 2015, and April 1, 2018, we screened 334 patients for inclusion. 186 patients did not meet inclusion criteria, and 47 patients were assigned to cohort B (patients with BCG-unresponsive high grade Ta or any grade T1 papillary disease without carcinoma in situ; results will be reported separately). 101 eligible patients were enrolled and assigned to receive pembrolizumab. All 101 patients received at least one dose of the study drug and were included in the safety analysis. Five patients had disease that did not meet the US Food and Drug Administration definition of BCG-unresponsive non-muscle-invasive bladder cancer and were therefore not included in the efficacy analysis (n=96). Median follow-up was 36·4 months (IQR 32·0–40·7). 39 (41%; 95% CI 30·7–51·1) of 96 patients with BCG-unresponsive carcinoma in situ of the bladder with or without papillary tumours had a complete response at 3 months. Grade 3 or 4 treatment-related adverse events occurred in 13 (13%) patients; the most common were arthralgia (in two [2%] patients) and hyponatraemia (in three [3%] patients). Serious treatment-related adverse events occurred in eight (8%) patients. There were no deaths that were considered treatment related.

**Interpretation** Pembrolizumab monotherapy was tolerable and showed promising antitumour activity in patients with BCG-unresponsive non-muscle-invasive bladder cancer who declined or were ineligible for radical cystectomy and should be considered a a clinically active non-surgical treatment option in this difficult-to-treat population.

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## Introduction

Bladder cancer is the tenth most common cancer globally and accounts for 2·1% of all cancer deaths worldwide.[1] Urothelial carcinoma of the bladder constitutes approximately 90% of all bladder cancer cases. Around three-quarters of patients with urothelial carcinoma of the bladder present with tumour that is confined to the urothelium (stage Ta or carcinoma in situ) or lamina propria (stage T1), collectively described as non-muscle-invasive bladder cancer.[2,3] Carcinoma in situ of the bladder

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## Research in context

### Evidence before this study

We searched PubMed using the keywords "non-muscle-invasive bladder cancer" OR "carcinoma in situ" AND "bacillus Calmette-Guerin relapsing" OR "bacillus Calmette-Guerin intolerant" OR "bacillus Calmette-Guerin refractory" OR "bacillus Calmette-Guerin resistant" OR "bacillus Calmette-Guerin failure" for papers published in English between Jan 1, 2000, and Jan 29, 2021, which yielded 207 results. From these, we identified 18 clinical trials in patients with non-muscle-invasive bladder cancer who received previous BCG treatment. These studies evaluated common intravesical regimens including mitomycin C chemotherapy, gemcitabine monotherapy or in combination with docetaxel or everolimus, and valrubicin. Other trials investigated novel treatments including adenovirus CG0070 and the tyrosine-kinase inhibitor dovitinib. Of these therapies, only valrubicin has been approved for the treatment of non-muscle-invasive bladder cancer. Although most studies reported promising efficacy, there was noteworthy heterogeneity between the enrolled patient populations, especially in the timing and amount of previous BCG exposure (eg, at least one previous course of BCG *vs* two induction courses of BCG *vs* at least two previous courses of intravesical therapy) and endpoints (disease-free survival *vs* recurrence-free survival *vs* complete response rate) between studies. Furthermore, most of these studies were in early clinical development with few patients enrolled. In 2018, the US Food and Drug Administration (FDA) published official guidance for study design in non-muscle-invasive bladder cancer, which provided a standardised definition of BCG-unresponsive disease as a well established clinical complete response rate and duration of complete response as the appropriate key endpoints for patients with carcinoma in situ. These searches highlight the unmet need for new treatment options for patients with BCG-unresponsive non-muscle-invasive bladder cancer.

### Added value of this study

In our trial, patients who received pembrolizumab had a complete response rate of 41%, with a median duration of complete response of 16·2 months, and 46% of initial responders had a complete response that lasted for 12 months or longer at the time of data cutoff. The safety profile of pembrolizumab in patients with BCG-unresponsive non-muscle-invasive bladder cancer was manageable and consistent with previous reports of pembrolizumab monotherapy.

### Implications of all the available evidence

Results of KEYNOTE-057 cohort A from a data cutoff date of May 24, 2019, led to FDA approval of pembrolizumab for the treatment of patients with BCG-unresponsive carcinoma in situ, with or without papillary tumours, who are ineligible for or choose not to undergo radical cystectomy on the basis of promising antitumour activity and a favourable safety profile. Targeting the PD-1–PD-L1 pathway could represent a new treatment option for this patient population. Future trials should explore potential markers and mechanisms of resistance to identify patients who are most likely to respond to PD-1 or PD-L1 immunotherapy. Combination strategies should also be considered to further improve upon the action of pembrolizumab.

affects approximately 10% of patients with non-muscle-invasive bladder cancer and is an aggressive form of urothelial carcinoma that carries an increased risk of recurrence and progression.[4] Standard treatment for most patients with high-risk non-muscle-invasive bladder cancer (high-grade Ta, carcinoma in situ, or any T1) is transurethral resection of bladder tumour (TURBT) followed by intravesical BCG immunotherapy.[2,3] Despite high initial efficacy, with complete response rates approaching 75%, approximately half of patients will have recurrence within 5 years or will be considered BCG-unresponsive after two courses of treatment.[5–7] Patients who are BCG-unresponsive are at an especially high risk of progression, with a 20–40% risk for progression to muscle-invasive bladder cancer within 5 years, which carries a 50% risk for the development of incurable metastatic disease.[2,6,8,9] For patients with BCG-unresponsive non-muscle-invasive bladder cancer, radical cystectomy with pelvic lymph node dissection and urinary diversion is the standard recommended treatment.[2,3] However, radical cystectomy is major surgery that is associated with much morbidity and mortality and can negatively affect quality of life.[10,11] As a result, many patients decline to undergo radical cystectomy despite it being a highly curative treatment. Moreover, many patients are unable to undergo radical cystectomy because of advanced age, frailty, or a chronic medical condition such as clinically significant heart, lung, liver, or kidney disease.[12]

For more than 20 years, only valrubicin was approved in the USA for the treatment of BCG-refractory carcinoma in situ, a decision made on the basis of a trial that showed modest efficacy in a heterogeneous patient population.[13] To boost clinical trial development, the US Food and Drug Administration (FDA) and the American Urological Association (AUA) convened a workshop in 2013 to develop a framework for clinical trial design in the BCG-unresponsive setting.[14] In 2018, the FDA published official guidance for study design in non-muscle-invasive bladder cancer.[15] In the population with BCG-unresponsive carcinoma in situ with or without papillary tumours, a single-arm study design with complete response rate and duration of response as key efficacy endpoints was acceptable given the absence of a suitable and commonly used non-surgical comparator, assuming that the study eligibility criteria stringently defined a homogeneous patient population.[14]

Pembrolizumab, a PD-1 inhibitor, is approved as second-line therapy for advanced urothelial carcinoma and

as first-line treatment for selected cisplatin-ineligible patients.[16,17] Activation of the PD-1–PD-L1 pathway has been implicated in resistance to BCG in non-muscle-invasive bladder cancer, and markedly increased PD-L1 expression was observed in tumours that relapsed after BCG treatment compared with BCG-naive tumours.[18] Moreover, high PD-L1 expression has been associated with subsequent recurrence and progression.[18]

In this KEYNOTE-057 study, we hypothesised that pembrolizumab could induce a clinical complete response in BCG-unresponsive high-risk non-muscle-invasive bladder cancer. The study included two cohorts: patients with carcinoma in situ with or without papillary tumours (cohort A) and patients without carcinoma in situ (cohort B). In January, 2020, on the basis of interim results from cohort A,[19] the FDA approved pembrolizumab for the treatment of patients with BCG-unresponsive carcinoma in situ, with or without papillary tumours, who are ineligible for or choose not to undergo radical cystectomy. We report further results from cohort A of this clinical trial.

## Methods

### Study design and participants

This open-label, single-arm, multicentre, phase 2 study was done at 54 sites (hospitals and cancer centres) in 14 countries (Australia, Canada, Finland, France, Greece, Italy, Japan, the Netherlands, Russia, South Korea, Sweden, Turkey, the UK, and the USA; appendix pp 2–4). Eligible patients were aged 18 years or older with histologically confirmed, BCG-unresponsive, high-risk non-muscle-invasive bladder cancer of predominantly (>50%) urothelial histology who were ineligible for or declined to undergo radical cystectomy. Eligible patients in cohort A had carcinoma in situ with or without papillary tumours, an Eastern Cooperative Oncology Group performance status of 0–2, and adequate organ function. Laboratory tests (ie, haematology and a comprehensive biochemistry panel) were required within 10 days before study initiation (appendix p 15). To be eligible, patients with concomitant Ta and T1 tumours had undergone complete TURBT, defined as per standard of care as a visually complete resection (residual carcinoma in situ, which is traditionally not amenable to complete transurethral resection, was acceptable), and the most recent cystoscopy or TURBT must have been done within 12 weeks before study initiation. Presence of detrusor muscle on pathology samples was required to ensure sample adequacy. A second TURBT was recommended but not required for patients with T1 tumours. The use of either white-light cystoscopy or blue-light cystoscopy was permitted, but the same technique had to be used in a patient throughout the trial.

BCG-unresponsive disease was defined as stage progression at 3 months (or up to 4 weeks either side) despite adequate BCG induction therapy alone, persistent high-risk non-muscle-invasive bladder cancer at 6 months (or up to 4 weeks either side) after adequate BCG therapy, or recurrent high-risk non-muscle-invasive bladder cancer within 9 months after the last BCG instillation despite adequate BCG therapy. Adequate BCG therapy was defined as at least five induction instillations (adequate induction) and at least seven instillations of BCG within 9 months of the first instillation, which is consistent with the FDA-recommended definition (≥5 of 6 doses of an initial induction course plus ≥2 of 3 doses of maintenance therapy or ≥2 of 6 doses of a second induction course).[15,20] Eligible patients had not received intervening intravesical chemotherapy or immunotherapy from the time of most recent cystoscopy or TURBT to study initiation (a single dose of intravesical chemotherapy given as part of the most recent cystoscopy or TURBT during the screening period, per local or regional practices, was permitted). Patients with histologically confirmed muscle-invasive carcinoma, locally advanced unresectable or metastatic urothelial carcinoma, or with concurrent extravesical (prostatic urethra, distal urethra, ureter, or renal pelvis) urothelial carcinoma were excluded. Also excluded were patients who received systemic chemotherapy, targeted small molecule therapy, or radiotherapy within 2 weeks before study drug initiation; patients with unresolved adverse events from a previously administered agent; and patients who had previous treatment with an immune checkpoint inhibitor. Patients were excluded if they had history of HIV infection, active hepatitis B or C infection, active pneumonitis, or a history of non-infectious pneumonitis that necessitated the use of steroids.

See Online for appendix

The protocol and its amendments were approved by the appropriate ethics committee at each centre, and the trial was done per Good Clinical Practice guidelines and in accordance with the principles of the Declaration of Helsinki. All patients provided written, informed consent. The trial protocol is available in the appendix.

### Procedures

All enrolled patients received intravenous pembrolizumab 200 mg every 3 weeks for up to 24 months or until centrally confirmed disease persistence, recurrence, or progression; unacceptable toxic effects; or withdrawal of consent. Patients with evidence of high-risk non-muscle-invasive bladder cancer at any efficacy evaluation, including at 3 months, had to discontinue treatment without the possibility of retreatment; patients with low-grade Ta recurrence could remain in the study after complete resection. After 18 months of treatment, patients with no evidence of disease on at least two consecutive evaluations could consider stopping treatment without being considered as withdrawing from the study. Patients were removed from the study if they withdrew informed consent or were lost to follow-up. Treatment interruptions were permitted in the case of medical or surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, or patient vacation or holidays). Patients resumed study therapy within 3 weeks

of the scheduled interruption unless otherwise discussed with the sponsor. Dose reductions were not permitted.

Disease assessment was based on integrated evaluation of local cystoscopy and centrally assessed urine cytology, biopsy (when applicable), and radiological findings (when applicable). Complete response was assessed at the first evaluable efficacy assessment (usually at 3 months). At screening, patients provided urine cytology specimens and formalin-fixed, paraffin-embedded tumour samples for central pathology review to substantiate grade or stage (assuring high-risk diagnosis and absence of muscle invasion) and for PD-L1 assessment by immunohistochemistry. Cystoscopy and urine cytology were done every 3 months for the first 2 years and every 6 months thereafter for up to 5 years. Directed biopsies were done in the case of abnormal cystoscopy findings, and random biopsies were done for abnormal cytology findings; these were centrally assessed. CT urography of the abdomen and pelvis was done every 6 months for the first 2 years, then once per year up to year 5, or more frequently if there was evidence of recurrence on cystoscopy, pathology, or urine cytology.

Monitoring of disease status continued until recurrence, disease progression, initiation of a new anticancer therapy, withdrawal of consent, or death. All patients were followed up for survival status until death or withdrawal of consent. Adverse events and immune-related adverse events were monitored throughout the study and for 30 days after the last dose of study drug (90 days for serious adverse events). Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Immune-related adverse events were defined by the use of a list of terms specified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator. Routine haematological and biochemistry panel tests were done within 3 days of the beginning of each treatment cycle, at treatment discontinuation, and at the safety follow-up (30 days after last dose). Vital signs, electrocardiograms, and physical examinations were assessed at regular intervals during the study, and any abnormalities and noteworthy changes from baseline were investigated. Additional and more frequent tests could be requested at the investigator's discretion.

Patients who did not have a complete response at the first assessment (usually at 3 months) had to discontinue study treatment and were categorised as having persistent or recurrent disease, non-muscle-invasive bladder cancer stage progression to T1, progression to muscle-invasive bladder cancer (T2), or extravesical or metastatic disease. Persistent disease was defined as the presence of carcinoma in situ at the first efficacy assessment; recurrent disease was defined as pathologically confirmed appearance of a papillary tumour (high-grade Ta or T1) without carcinoma in situ; non-muscle-invasive bladder cancer stage progression was defined as pathologically confirmed increase in stage from carcinoma in situ or high-grade Ta at baseline to T1; progression to muscle-invasive bladder cancer was defined as pathologically substantiated progression to T2 disease; and extravesical disease was defined as radiographic findings of possible locally advanced or metastatic bladder cancer or upper tract urothelial carcinoma.

### Outcomes

The primary endpoint was complete response rate of high-risk disease, defined as the absence of high-risk disease or progressive disease. The primary endpoint was centrally reviewed. Secondary endpoints included safety; complete response rate of any disease (defined as the absence of low-grade Ta, high-risk disease, and progressive disease); duration of response for high-risk disease and any disease (defined as time from first documented evidence of complete response until centrally confirmed recurrence of high-risk non-muscle-invasive bladder cancer or progressive disease or any disease); progression-free survival to worsening of grade or stage or death (defined as time from enrolment to worsening of grade or stage or death from any cause, whichever occurred first); progression-free survival to muscle-invasive or metastatic disease or death (defined as time from enrolment to muscle-invasive or metastatic disease or death from any cause, whichever occurred first); overall survival (defined as time from enrolment to death from any cause); and 6-month and 12-month rates of progression-free survival to worsening of grade or stage or death, progression-free survival to muscle-invasive or metastatic disease or death, and overall survival. Additional time-point assessments were made post hoc. An exploratory endpoint was to evaluate changes in health-related quality of life assessments from baseline using the Functional Assessment of Cancer Therapy–Bladder Cancer (FACT-Bl) questionnaire (consisting of general cancer-specific subscales [FACT-G] and a bladder cancer-specific subscale and symptom index) and Core Lower Urinary Tract Symptom Score (CLSS).[21,22] Utility scores were characterised using the 3-level version of the EuroQoL EQ-5D questionnaire (EQ-5D-3L).[23]

### Statistical analysis

For the primary endpoint, the study had approximately 97% power to reject the null hypothesis with the lower bound of the two-sided 95% CI excluding 20%, assuming full cohort enrolment of approximately 130 participants. The point estimates and 95% CIs for complete response rates were evaluated using the exact binomial method, comparing the lower bound of the 95% CI with the historical control rate of 20% from the valrubicin study, which led to its FDA approval.[24] The Kaplan-Meier method was used to estimate duration of response, progression-free survival to worsening of grade or stage or death, progression-free survival to muscle-invasive or metastatic disease or death, and overall survival. An estimate of the

treatment effect and 95% CI was used to establish whether treatment was consistent between clinically relevant subgroups (age [younger than 65 years *vs* 65 years or older], sex [female *vs* male], ethnicity [White *vs* non-White], Eastern Cooperative Oncology Group performance score [0 *vs* 1 or 2], PD-L1 status (positive *vs* negative), tumour stage at baseline [Ta, T1, or Tis with carcinoma in situ], pattern of failure [persistent *vs* progressive *vs* recurrent high-risk non-muscle-invasive bladder cancer], and geographical region [USA *vs* non-USA and EU *vs* non-EU]). The study had two prespecified interim analyses (when at least 20 patients completed the 3-month assessment and when at least 50 patients had an opportunity for a 6-month assessment). The efficacy and safety results from both interim analyses were reviewed by an external data monitoring committee to ensure adequate antitumor activity to allow the study to continue enrolment. On the basis of the promising antitumour activity observed in the second interim analysis (Nov 1, 2017), discussions with the FDA were initiated regarding what would constitute an adequate sample size to be able to make a suitable assessment of benefit and risk. A sample size of approximately 100 participants with BCG-unresponsive carcinoma in situ with at least 12 months of follow-up was deemed acceptable. Safety and tolerability was assessed by clinical review of all relevant parameters, including adverse events, laboratory tests, and vital signs. Summary statistics (counts and percentages) were provided for the safety endpoints. For patient-reported outcome endpoints, descriptive statistics (mean, 95% CI) of observed data with no imputation for missing data were plotted. A prespecified analysis timepoint of 45 weeks was selected based on the latest timepoint where the approximate overall completion rate was 60% and the compliance was 80% for the analytical population. At week 45, patients' post-baseline instrument or subscale scores of FACT-Bl were classified as improved, stable, or deteriorated. Patients with a 7-point change from baseline were classified as improved (7-point increase) or deteriorated (7-point decrease). For FACT-G physical wellbeing, those patients who had a 3-point change from baseline were classified as improved (3-point increase) or deteriorated (3-point decrease). The full statistical analysis plan can be found in the appendix.

Safety was assessed in all patients who received at least one dose of study treatment as of the enrolment cutoff. Efficacy was assessed in all patients who received at least one dose of study treatment as of the enrolment cutoff and met BCG-unresponsive criteria. Patients whose protocol-specified efficacy assessments were missing or who discontinued from the trial for reasons other than progressive disease were considered not evaluable for efficacy and were categorised as non-responders. Quality of life was evaluated in all patients who received at least one dose of treatment and completed at least one quality of life assessment. All statistical analyses were done with SAS (version 9.4). This study is registered with ClinicalTrials.gov, NCT02625961.

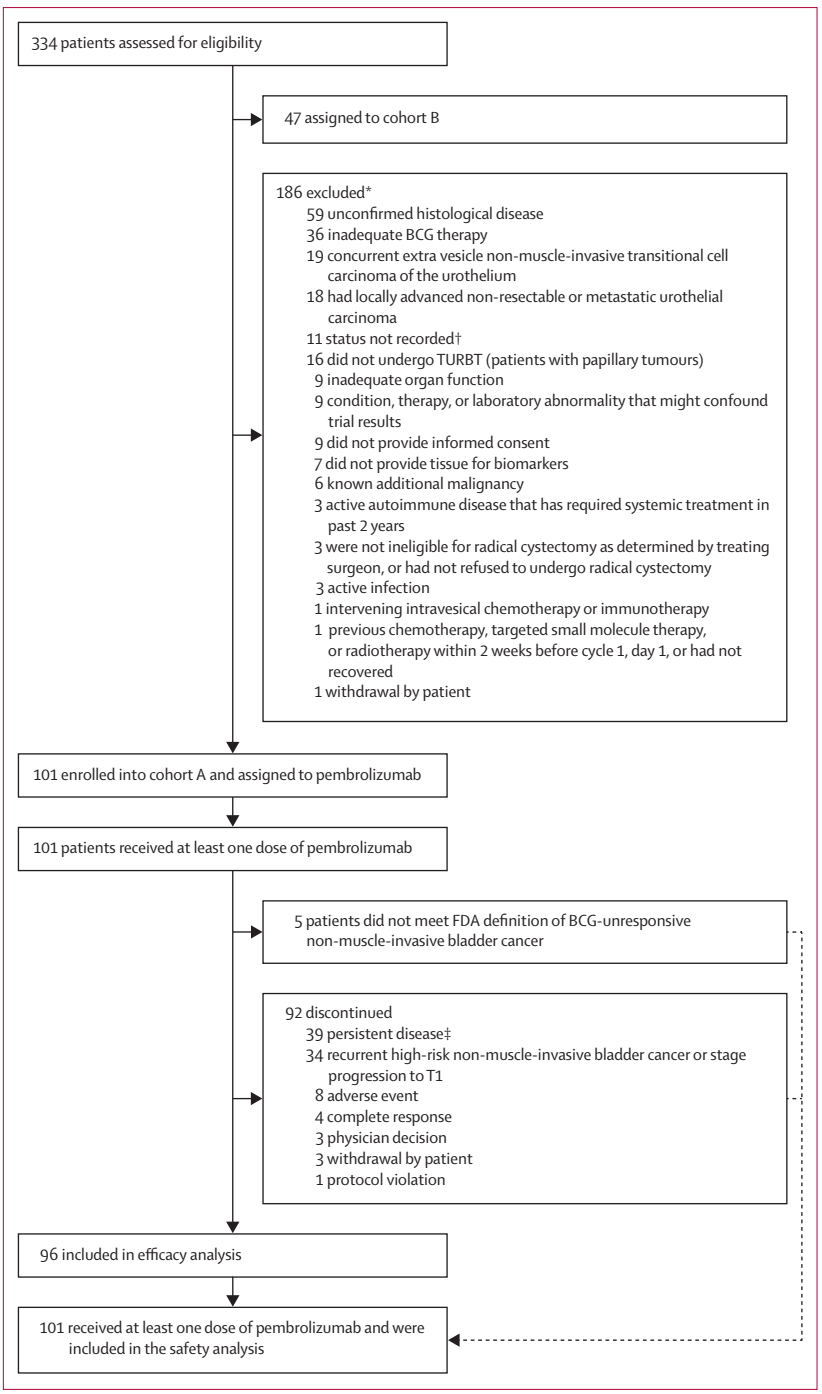


***Figure 1:*** **Trial profile**
FDA=US Food and Drug Administration. TURBT=transurethral resection of bladder tumour. *Patients could have more than one reason for screen failure. †Four consented and were in screening at data cutoff date, six consented after database cutoff date, and one was a screening failure not documented because of data entry error. ‡Includes patients in cohort A with carcinoma in situ at baseline who at month 3 also had carcinoma in situ with or without papillary tumour.

## Role of the funding source

The funders contributed to the study design, data analysis, and data interpretation in collaboration with the authors;

| | Cohort A (n=101) |
|---|---|
| Age | |
| Median age, years (IQR) | 73 (63–79) |
| ≥65 years | 71 (70%) |
| Sex | |
| Male | 85 (84%) |
| Female | 16 (16%) |
| ECOG performance status | |
| 0 | 74 (73%) |
| 1 | 27 (27%) |
| Previous BCG instillations, median (IQR) | 12·0 (9·0–16·5) |
| Tumour stage | |
| Carcinoma in situ with T1 | 12 (12%) |
| Carcinoma in situ with high-grade Ta | 25 (25%) |
| Carcinoma in situ alone | 64 (63%) |
| PD-L1 status* | |
| Combined positive score ≥10 | 38 (38%) |
| Combined positive score <10 | 58 (57%) |
| Not evaluable | 5 (5%) |
| Reason for not undergoing cystectomy | |
| Declined | 96 (95%) |
| Ineligible | 3 (3%) |
| Other | 2 (2%) |
| BCG failure category | |
| Persistent disease† | 26 (26%) |
| Recurrent disease‡ | 70 (69%) |
| Not classified§ | 5 (5%) |

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. *Combined positive score was computed as the ratio of the number of tumour cells, lymphocytes, and macrophages expressing PD-L1 (numerator) to the total number of viable tumour cells in the biopsy specimen (denominator) × 100. †Defined as persistent carcinoma in situ with or without papillary tumour at or before 6 months after receiving adequate BCG therapy. ‡Defined as recurrence within 9 months of the last BCG instillation despite receiving adequate BCG therapy. §Did not meet the US Food and Drug Administration definition of BCG-unresponsive non–muscle-invasive bladder cancer.

***Table 1:*** **Baseline characteristics**

| | Cohort A efficacy population (n=96)* |
|---|---|
| Complete response | 39 (41%, 30·7–51·1) |
| Non-complete response | 56 (58%, 47·8–68·3) |
| Persistent disease†‡ | 40 (42%, 31·7–52·2) |
| Recurrent disease | 6 (6%, 2·3–13·1) |
| Non-muscle-invasive bladder cancer stage progression§ | 9 (9%, 4·4–17·1) |
| Non-bladder malignancy¶ | 1 (1%, 0·0–5·7) |
| Progression to muscle-invasive disease (T2) | 0 (NA–NA) |
| Non-evaluable‖ | 1 (1%, 0·0–5·7) |

Data are n (%, 95% CI). NA=not applicable. *Patients with high-risk non-muscle-invasive bladder cancer who received at least one dose of the study drug, had baseline evaluations, and had at least one post-baseline disease assessment. †Defined as patients with carcinoma in situ at baseline who also had carcinoma in situ with or without papillary tumour at month 3. ‡Defined as pathologically confirmed appearance of papillary tumour (high-grade Ta or T1) without carcinoma in situ at month 3. §Defined as an increase in stage from carcinoma in situ or high-grade Ta at baseline to T1 disease. ¶For this patient, new liver lesions were found on imaging; later, a second primary malignancy of pancreatic cancer was found. 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 further supported the diagnosis of metastatic pancreatic cancer. ‖Patients whose protocol-specified efficacy assessments were missing or who discontinued from the trial for reasons other than progressive disease were not evaluable for efficacy and considered non-responders.

***Table 2:*** **Best overall response at month 3 by central review in patients with BCG-unresponsive carcinoma in situ**

all authors had full access to the data. The funder had no role in data collection. An external data monitoring committee made recommendations about the overall risk and benefit to trial participants. Investigators and site personnel collected data, which were housed on Merck's database. The funder provided financial support for editorial and writing assistance.

## Results

Between Dec 9, 2015, and April 1, 2018, we screened 334 patients for eligibility. 186 patients were excluded (the most common reasons for exclusion were unconfirmed histological disease [n=59] and inadequate BCG therapy [n=36]; figure 1) and 47 patients were allocated to cohort B (patients who met criteria for BCG-unresponsive high grade Ta or any grade T1 papillary disease without carcinoma in situ; data will be reported elsewhere). 101 eligible patients were enrolled and assigned to receive pembrolizumab in cohort A. The data cutoff date was May 25, 2020. 101 patients in cohort A received pembrolizumab and were included in the safety analysis. Five patients had disease that did not meet the FDA definition of BCG-unresponsive non-muscle-invasive bladder cancer and were excluded from the efficacy analysis; thus, the efficacy population comprised 96 patients.

At baseline, the median age of patients was 73 years (IQR 63–79), and patients received a median of 12·0 previous BCG instillations (9·0–16·5; table 1). Two patients had previously received systemic treatment before study initiation (one doxifluridine, one tegafur-uracil).

Median follow-up, defined as the time from enrolment to database cutoff, was 36·4 months (IQR 32·0–40·7). 39 (41%; 95% CI 30·7–51·1) of 96 patients with BCG-unresponsive carcinoma in situ with or without papillary tumours given pembrolizumab had a complete response at 3 months (table 2). Median duration of complete response from time of onset was 16·2 months (95% CI 6·7–36·2), and 18 (46%) of 39 responders remained in complete response for 12 months or longer (patients who remained in complete response for 12 months were enrolled in the study for approximately 15 months; figure 2A). Of the 39 patients with a complete response, 11 (28%) continued to be followed up for efficacy and had an ongoing response at the time of data cutoff and 20 (51%) had recurrent disease after an initial complete

response (figure 2B). One (3%) of these 39 patients had recurrence immediately after two or more consecutive non-evaluable assessments, three (8%) started new anticancer treatment before confirmed recurrence, three (8%) withdrew consent to be followed up for efficacy analysis but had not started a new anticancer treatment, and one (3%) died due to congestive heart failure, which was considered unrelated to treatment.

Complete response rates were generally consistent across protocol-prespecified subgroups (appendix p 5). The complete response rate and median duration of response in patients with any disease were the same as the complete response rate and duration of response in patients with high-risk non-muscle-invasive bladder cancer (appendix p 16).

16 (17%) of 96 patients had a progression-free survival to worsening of grade, worsening of stage, or death event (median not reached, 95% CI 25·1 months to not reached). Nine (9%) of 96 patients had a progression-free survival to muscle-invasive disease, metastatic disease, or death event (median 39·9 months, 95% CI 26·4–39·9; appendix pp 6–7). At 12 months, the estimated progression-free survival to worsening of grade or stage or death was 83% (95% CI 70·2–90·4), and estimated progression-free survival to muscle-invasive or metastatic disease or death was 97% (86·0–99·2). At the data cutoff, nine (9%) of 96 patients had died; median overall survival was not reached (95% CI not reached to not reached). Overall survival was 98% (95% CI 91·9–99·5) at 12 months, 95% (87·8–97·8) at 24 months, and 91% (83·7–95·7) at 36 months (appendix p 8).

The median duration of pembrolizumab treatment was 4·2 months (IQR 3·4–9·1), with a median of seven administrations (5–14). Nine (9%) of 101 patients completed pembrolizumab treatment as of the analysis cutoff date. 92 (91%) of 101 patients discontinued treatment; the primary reasons for discontinuation were persistent disease (39 patients) and recurrent disease or stage progression to T1 disease (34 patients). Four patients chose to discontinue treatment after maintaining a complete response for 18 months, as allowed per protocol. Of these four patients, one had carcinoma in situ-only disease at baseline, one had carcinoma in situ and T1 disease at baseline, and two had carcinoma in situ and high-grade Ta at baseline. Three of the four patients have ongoing complete responses since discontinuation of pembrolizumab, with duration of response ranging from 20–36 months at the time of data cutoff. One patient with carcinoma in situ and high-grade Ta at baseline recurred with high grade Ta approximately 1 year after discontinuing treatment and was treated with TURBT. No patients discontinued study treatment because of progression to muscle-invasive or metastatic disease by study-specified disease assessments.

67 (66%) of 101 patients in the safety population had treatment-related adverse events (table 3). 13 (13%) of 101 patients had grade 3 or 4 treatment-related adverse events, of which the most common were hyponatraemia (three [3%] patients) and arthralgia (two [2%] patients). 11 serious treatment-related adverse events occurred in eight patients (8%; one patient each with colitis, adrenocorticotropic hormone deficiency, adrenal insufficiency, autoimmune nephritis, cholestatic hepatitis, hyperthyroidism, hyponatraemia, lymphocyte count decrease, pulmonary embolism, syncope, and type 1 diabetes [one patient had hyperthyroidism, cholestatic hepatitis, and lymphocyte count decrease and

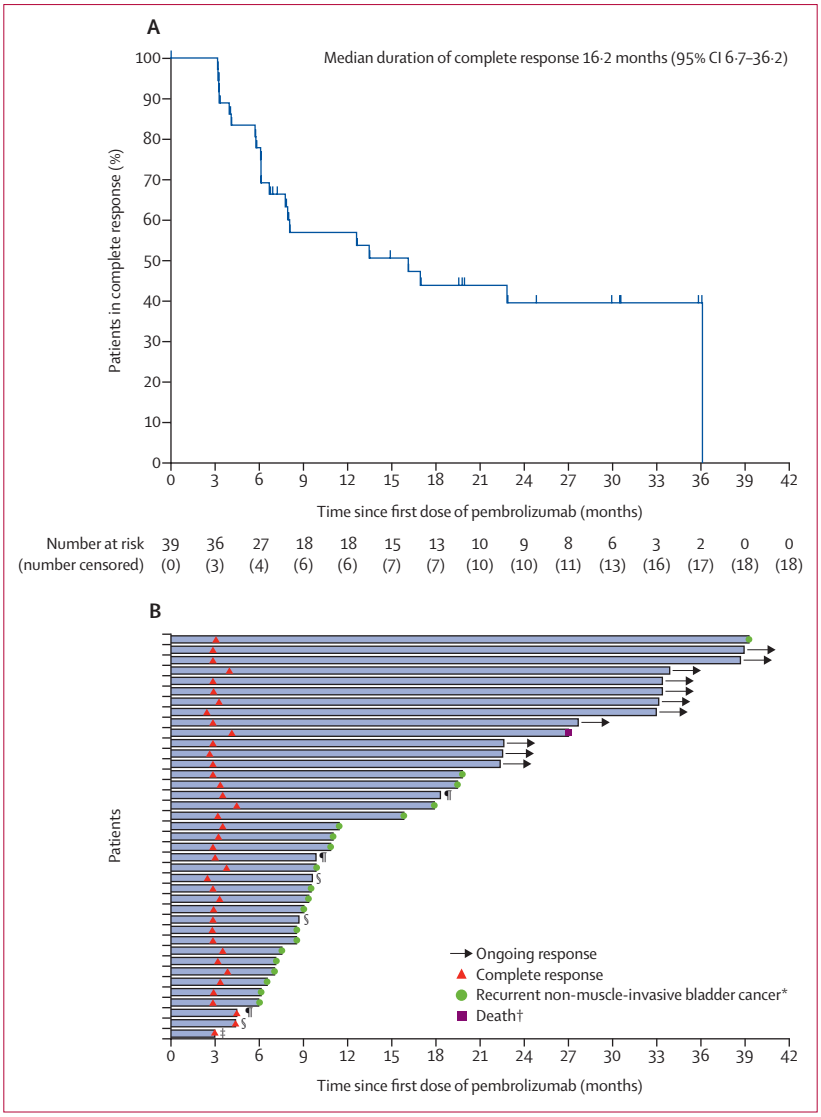


***Figure 2:*** **Duration of response from first dose of pembrolizumab**
(A) Kaplan-Meier estimates of duration of complete response of high-risk non-muscle-invasive bladder cancer among patients with a complete response as assessed from the first administration of pembrolizumab. (B) Time to complete response and recurrence of high-risk non-muscle-invasive bladder cancer in patients with a complete response. *Reappearance of high-risk non-muscle-invasive bladder cancer (carcinoma in situ or high-grade Ta or T1 disease) after a disease-free interval (at each month or after). †One patient died of congestive cardiac failure (not treatment related). ‡Patient experienced recurrence immediately after two or more consecutive non-evaluable assessments. §Patient started new anticancer treatment before confirmed recurrence. ¶Withdrew consent for efficacy follow-up.

| | Grade 1 or 2 | Grade 3* | Grade 4† |
|---|---|---|---|
| Any | 54 (53%) | 11 (11%) | 2 (2%) |
| Diarrhoea | 11 (11%) | 0 | 0 |
| Fatigue | 11 (11%) | 0 | 0 |
| Pruritus | 10 (10%) | 1 (1%) | 0 |
| Hypothyroidism | 7 (7%) | 0 | 0 |
| Rash maculo-papular | 6 (6%) | 0 | 0 |
| Hyperthyroidism | 5 (5%) | 0 | 0 |
| Rash | 5 (5%) | 0 | 0 |
| Nausea | 5 (5%) | 0 | 0 |
| Arthralgia | 4 (4%) | 2 (2%) | 0 |
| Dry mouth | 3 (3%) | 0 | 0 |
| Pneumonitis | 3 (3%) | 0 | 0 |
| Rash pruritic | 3 (3%) | 0 | 0 |
| Abdominal pain | 2 (2%) | 0 | 0 |
| Alanine aminotransferase increased | 2 (2%) | 0 | 0 |
| Asthaenia | 2 (2%) | 0 | 0 |
| Blood thyroid-stimulating hormone decreased | 2 (2%) | 0 | 0 |
| Colitis | 2 (2%) | 0 | 0 |
| Constipation | 2 (2%) | 0 | 0 |
| Eczema | 2 (2%) | 0 | 0 |
| Haematuria | 2 (2%) | 0 | 0 |
| Influenza-like illness | 2 (2%) | 0 | 0 |
| Malaise | 2 (2%) | 1 (1%) | 0 |
| Myalgia | 2 (2%) | 0 | 0 |
| Neuropathy peripheral | 2 (2%) | 0 | 0 |
| Pyrexia | 2 (2%) | 0 | 0 |
| Dermatitis | 1 (1%) | 1 (1%) | 0 |
| Hyponatraemia | 0 | 2 (2%) | 1 (1%) |

Data are n (%). The table shows treatment-related adverse events that occurred in two or more patients. *In addition to the grade 3 events listed, one patient each experienced grade 3 adrenal insufficiency, cholestatic hepatitis, decreased lymphocyte count, syncope, adrenocorticotropic hormone deficiency, hypophosphataemia, and pulmonary embolism. †In addition to the grade 4 events listed, one patient experienced grade 4 type 1 diabetes.

***Table 3:*** **Treatment-related adverse events (n=101)**

one patient had adrenocorticotropic hormone deficiency and adrenal insufficiency]). Treatment-related adverse events led to pembrolizumab interruption in 13 (13%) of 101 patients (two patients with diarrhoea, one patient with alanine aminotransferase increase, two patients with arthralgia, one patient with colitis, two patients with hyponatraemia, two patients with pruritus, one patient with abdominal pain, one patient with adrenal insufficiency, one patient with adrenocorticotropic hormone deficiency, one patient with aspartate aminotransferase increase, one patient with autoimmune hepatitis, one patient with dermatitis, one patient with eczema, one patient with maculo-papular rash [one patient had both diarrhoea and eczema; one patient had aspartate aminotransferase increase, alanine aminotransferase increase, and autoimmune hepatitis; and one patient had adrenocorticotropic hormone deficiency, adrenal insufficiency, and hyponatraemia]), and discontinuation in seven (7%) patients (two patients with pneumonitis, one patient with autoimmune nephritis, one patient with cholestatic hepatitis, one patient with hyponatraemia, one patient with myalgia, and one patient with type 1 diabetes). Three (3%) patients died of adverse events unrelated to study treatment (one each of respiratory failure caused by methicillin-resistant *Staphylococcus aureus* pneumonia, congestive cardiac failure, and metastatic pancreatic cancer). The remaining six deaths occurred during survival follow-up and were due to causes unknown (three patients), senile atrophy (one patient), progressive disease (one patient), and cardioembolic stroke not considered an adverse event (one patient).

22 (22%) of 101 patients had immune-related adverse events of any grade, three of which were grade 3 or 4 (appendix p 18). Common immune-related adverse events were hypothyroidism (eight [8%] patients; all grade 1 or 2), hyperthyroidism (five [5%] patients; all grade 1 or 2), and pneumonitis (three [3%] patients; all grade 1 or 2). Seven patients required treatment with systemic corticosteroids (≥10 mg per day prednisone or equivalent, with five patients receiving ≥40 mg per day) because of immune-mediated adverse events (two pneumonitis, one adrenal insufficiency, one colitis, one hepatitis, one hypophysitis, and one nephritis); none of these patients required other immunosuppressive agents (appendix p 19).

Of the 96 patients who were included in the efficacy analysis, 57 (59%) were non-responders (never had complete response on study) at the time of data cutoff. Overall, 40 (49%) of 82 initial responders (n=25) and non-responders (n=57) who discontinued pembrolizumab subsequently underwent radical cystectomy. Of the 25 initial responders who subsequently had confirmed recurrence (20 patients), recurrence immediately after two or more consecutive non-evaluable assessments (one patient), died (one patient), or started a new anti-cancer treatment before recurrence (three patients), 11 (44%) underwent radical cystectomy after discontinuation; this was the first treatment for ten (40%) of 25 patients after pembrolizumab discontinuation (appendix pp 20–22). Of 57 non-responders, 29 (51%) underwent radical cystectomy; this was the first subsequent treatment for 22 (39%) patients. Of the 40 patients who underwent radical cystectomy after pembrolizumab discontinuation, 35 (88%) had no pathological upstaging to muscle-invasive bladder cancer and two (5%) did not have data available. Three (8%) patients had evidence of muscle-invasive bladder cancer after pembrolizumab discontinuation (all three were non-responders to pembrolizumab); one patient had pT2N0 at 60 days after the last pembrolizumab dose, one had pT2N1 at 86 days after the last pembrolizumab dose, and one had pT3N1 at 457 days after the last pembrolizumab dose (table 4).

No unexpected safety concerns were reported in patients who opted for radical cystectomy.

Three patients who did not undergo radical cystectomy after pembrolizumab discontinuation (one had an initial complete response but subsequently recurred, and two were non-responders) and instead opted for alternative non-surgical therapies later progressed to muscle-invasive bladder cancer or metastatic disease. All three patients had reported disease progression at least 1 year after study discontinuation (approximately 23, 29, and 20 months after last dose of pembrolizumab).

Of the 96 patients in the efficacy evaluable population, 27 (28%) underwent local procedures, 30 (31%) received additional intravesical therapy, and ten (10%) received systemic therapy after treatment discontinuation. 11 (11%) patients received both radical cystectomy and other subsequent therapies or procedures. 24 (25%) patients received no or unknown subsequent therapy, 11 of whom continue to be followed up for efficacy and remain in complete response (appendix pp 20–22). Two patients remained in complete response at study discontinuation but withdrew consent for efficacy follow-up, two had recurrence after initial response, one died after initial response, and eight were non-responders.

Of the three patients who had recurrence or died after initial complete response, one patient remained in clinical complete response until death due to congestive heart failure, one patient was being followed up for survival but had not received subsequent therapy at data cutoff, and one patient had centrally confirmed recurrence with carcinoma in situ but local pathology showed no disease. The patient who had no disease by local pathology was categorised as having recurrence after an initial complete response because of the centrally confirmed carcinoma in situ recurrence, but continued to receive pembrolizumab on study and had a centrally confirmed complete response at the subsequent efficacy assessment (and has remained in complete response for approximately 38 months). Of the eight non-responders, one patient was lost to follow-up, two patients died secondary to non-treatment-related adverse events (pneumonia and pancreatic cancer), and five patients continued in survival follow-up without receiving any subsequent therapy for more than 1 year.

Health-related quality of life remained stable during pembrolizumab treatment. At a prespecified analysis timepoint of 45 weeks, 28 (70%) of 40 patients who were either responders or were non-evaluable for efficacy and completed at least one quality of life assessment had improved or stable FACT-G total scores from baseline and 33 (83%) had improved or stable FACT-G physical wellbeing scores from baseline (appendix p 9). Consistent findings for empirical mean change from baseline to week 51 were observed in the FACT-Bl, FACT-G, FACT-G physical wellbeing, CLSS, and EQ-5D-3L visual analogue scale scores over time (appendix pp 10–14). In non-responders (53 for FACT Bl, FACT-G, and FACT-G physical wellbeing; 52 for CLSS; and 54 for EQ-5D-3L visual analogue scale), health-related quality-of-life and symptom scores also were stable from baseline to week 15 (data were only available up to week 15 because non-responders discontinued treatment around month 3; appendix pp 10–14).

| | Patients (n=38)* | N stage† | Achieved initial complete response | Interval between last dose of pembrolizumab and radical cystectomy, days | Number of pembrolizumab doses |
|---|---|---|---|---|---|
| **Non-muscle-invasive bladder cancer** | | | | | |
| pT0 | 6 | N0=5, Nx=1 | 4 | 135 (91–138) | 11·5 (7·0–14·0) |
| pTa | 5 | N0=5 | 0 | 103 (79–209) | 5·0 (5·0–6·0) |
| pTis | 18 | N0=16, Nx=2 | 6 | 77 (61–176) | 6·0 (6·0–7·0) |
| pT1 | 6 | N0=6 | 0 | 133 (77–170) | 6·5 (6·0–7·0) |
| **Muscle-invasive bladder cancer** | | | | | |
| pT2 | 2 | N0=1, N1=1‡ | 0 | 60§,86§ | 3·5 (3·0–4·0) |
| PT3 | 1 | N1 | 0 | 457§ | 6·0§ |

Data are n, or median (IQR). Tumour-node classification based on the guidelines in the American Joint Committee on Cancer Cancer Staging Manual, 8th edition.[25] *TNM staging was not available for two of the 40 participants who had undergone radical cystectomy. †Nx=lymph node dissection not performed. ‡In a patient with pT2N1 disease, a single perivesical lymph node was involved. §These data are only for one patient each, and therefore do not have IQR.

*Table 4:* **Pathological staging at time of radical cystectomy in patients who discontinued pembrolizumab by maximum T stage**

## Discussion

The FDA approval of pembrolizumab for patients with BCG-unresponsive carcinoma in situ in January, 2020, represents a substantial advancement in a difficult-to-treat disease setting with few approved therapeutic options. Despite being highly curative, many patients make the informed decision not to undergo radical cystectomy. One of the key premises of KEYNOTE-057 was to identify an alternative treatment option for these patients. Pembrolizumab fulfils an unmet need for efficacious, non-surgical therapies in BCG-unresponsive carcinoma in situ and provides a clinically meaningful option for patients who are ineligible for or decline radical cystectomy.

In 2016, the International Bladder Cancer Group (IBCG) recommended an initial complete response rate of 50% at 6 months and durable response rates of 30% at 12 months and 25% at 18 months for novel agents in patients with BCG-unresponsive carcinoma in situ.[20] Similarly, the outcome of a joint workshop between the FDA and AUA representatives on trial design for BCG-unresponsive non-muscle-invasive bladder cancer that was published in 2014 suggested a complete response rate of 40–50% at 6 months and a response rate of at least 30% at 18–24 months to be considered clinically meaningful in the context of review of a single-arm study for approval.[14] These benchmarks were considered aspirational, designed to encourage new trials of novel agents and to challenge existing treatment approaches previously established from older studies that were done when a uniform definition of BCG-unresponsive non-muscle-invasive bladder cancer did not exist, and

study populations included participants satisfying various definitions of BCG failure. The IBCG agreed that all evidence should be evaluated, including drug mechanism of action, the toxicity of the therapy, and other measures of antitumour effect. The final 2018 FDA guidance for non-muscle-invasive bladder cancer reflected this nuanced approach and stated that clinical response rate should be considered in the context of duration of response, but specific benchmarks were not identified.[15] Results of the analysis of this trial showed a clinical complete response rate of 41% at the first evaluable efficacy assessment, which exceeds that observed with currently approved intravesical therapies.[20,24,26] Equally important is the durability of response, a hallmark of pembrolizumab.[27] After more than 2 years of follow-up, 28% of complete responders who continued to be followed up for efficacy had an ongoing response and 46% had at least a 12-month duration of response at the time of data cutoff. Although complete responses were observed irrespective of tumour PD-L1 status, definitive conclusions cannot be drawn because of the small sample size and the overlapping CIs in this subgroup analysis. Patients maintained health-related quality of life over time during treatment with pembrolizumab.

In this analysis, median progression-free survival to disease worsening or death and overall survival were not reached. Median progression-free survival to muscle-invasive or metastatic disease or death was 39·9 months. Notably, there were few progression-free survival events, and achieving a median duration for progression-free survival is probably an artifact of many patients discontinuing treatment due to persistent or recurrent non-muscle-invasive bladder cancer, resulting in their being censored early in the follow-up period. Less than half of patients underwent radical cystectomy after they discontinued pembrolizumab on trial, including three patients who subsequently developed muscle-invasive or metastatic disease, suggesting that patients might continue to decline this surgery despite its clear medical indication. Importantly, if a patient continues to decline radical cystectomy, the subsequent development of metastatic disease probably represents the natural history of untreated disease and would not be attributed to lack of efficacy by pembrolizumab. Nevertheless, in the approximately 40% of patients who chose to undergo radical cystectomy, the window of opportunity for curative intent surgery was preserved, as suggested by the fact that only three (8%) of those patients were pathologically upstaged to muscle-invasive bladder cancer at the time of radical cystectomy. Furthermore, the safety of radical cystectomy did not seem to be affected by previous pembrolizumab treatment because no unexpected safety concerns were reported in patients who opted for radical cystectomy after pembrolizumab discontinuation.

In this study, pembrolizumab monotherapy had a manageable safety profile consistent with that previously reported,[19] and no new risks associated with its use were identified. Grade 3 and 4 immune-related adverse events were rare, and immune-related adverse events were managed with appropriate intervention as outlined in the product information.[19] Although rare, life-threatening immune-related adverse events have been reported with pembrolizumab; thus, early recognition and management remain important.[28]

This single-arm study is limited by the absence of a direct comparator group, although it should be noted that few efficacious treatment options other than radical cystectomy are available for this patient population.[2,3] Valrubicin is approved in this treatment setting, but it is not recommended in current National Comprehensive Cancer Network treatment guidelines.[29] Furthermore, comparison with off-label treatments is complicated by historical inconsistencies in the definition of adequate BCG therapy, differences in BCG dosing schedules, heterogeneity in patient populations and monitoring or surveillance plans, and other selection and confounding biases. Only a few trials have been done specifically in patients with FDA-defined, BCG-unresponsive carcinoma in situ.[15] Because of the absence of a suitable comparator, single-arm clinical trial designs are the most appropriate for the BCG-unresponsive carcinoma in situ population at this time.[20] The study design followed recommendations published by the FDA and guidelines and clinical practice from the AUA and Society of Urologic Oncology.[2,29] For example, random biopsies were not required at pre-specified timepoints on study but were triggered clinically by suspicious findings on cystoscopy or abnormal urine cytology. Recognising this potential limitation, the study required independent central review of all pathology and urine cytology specimens at screening and while on study, ensuring a consistent and rigorous disease evaluation process.

In conclusion, our results support the use of pembrolizumab as a clinically active non-surgical treatment option in patients with BCG-unresponsive carcinoma in situ of the bladder who are ineligible for or decline radical cystectomy. FDA approval of pembrolizumab fulfils a major unmet need and establishes a foundation and benchmark for future trials that could provide higher and more durable responses for patients with BCG-unresponsive carcinoma in situ with or without papillary tumours.

**Contributors**

AVB, AMK, TF, and RdW contributed to the conception and design of the study. GSK, EMU, JLB, LEMK, EAS, HN, BRK, EK, and RdW contributed to acquisition of the data. GSK contributed to provision of study materials. AVB and RdW had access to and verified the data. AVB, AMK, LEMK, DFB, BRK, KN, EK, and TF contributed to data analysis. AVB, AMK, LEMK, EMU, GSK, JLB, EAS, DFB, PG, HKS, HN, BRK, HL, KN, EK, TF, and RdW contributed to data interpretation. AVB, AMK, KN, EK, and TF drafted the manuscript. All authors contributed to revising of the manuscript and provided final approval to submit the manuscript for publication.The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication.

### Declaration of interests

AVB has received research funding from AstraZeneca/MedImmune, Genentech/Roche, Merck Sharp & Dohme, and Seattle Genetics; has been a consultant to AstraZeneca/MedImmune, Cerulean Pharma, Genentech/Roche, Incyte, Merck Sharp & Dohme, Pfizer/EMD Serono, and Seattle Genetics/Astellas; and has received honoraria from AstraZeneca/MedImmune, Genentech/Roche, and Merck Sharp & Dohme. AMK has received research funding from FKD Industries and Merck Sharp & Dohme; has received honoraria from UroToday Publishing and EAU (EU Oncology); has been a consultant to Merck Sharp & Dohme, Bristol Myers Squibb, Imagin, Eisai, Arquer, MDX Health, Photocure, AstraZeneca, Tesaro, Abbott Molecular, US Biotest, Ferring, and BioClinica; has received travel expenses from Pfizer Japan; holds patents for CyPRIT-Cytokine Panel for Response to Intravesical Immunotherapy; and is the president of the International Bladder Cancer Group and the International Bladder Cancer Network. GSK has served on advisory boards for Merck, Bristol Myers Squibb, Roche, Ferring, Janssen, and Theralase and has received honoraria from AbbVie, TerSera, Sanofi, and Biosyent. EMU has received research funding from Merck, Pfizer, Astellas, Dendreon, Myriad, Janssen, Bayer, and Blue Earth. JLB has received research funding from Decipher Biosciences and has been a consultant to Bristol Myers Squibb, Ismar Healthcare, Ambu, Roche, Merck Sharp & Dohme, and Janssen. MR has been a consultant to Invectys, Arquer, and Janssen, and has received honoraria from Ipsen, Ferring, AstraZeneca, Pierre Fabre, and Astellas. LEMK has received honoraria from and has been a consultant for Ipsen, Bristol Myers Squibb, Merck Sharp & Dohme, Astellas, Bayer, Novartis, and Pfizer; has provided expert testimony for Ipsen; has participated in a speakers' bureau for Merck Sharp & Dohme, Bristol Myers Squibb, and Ipsen; and has received travel expenses from Bristol Myers Squibb, Merck Sharp & Dohme, Ipsen, and Astellas. EAS has received research support (clinical trial) from Astellas/Medivation. PG has been a consultant to AstraZeneca, Bayer, Bristol Myers Squibb, Clovis Oncology, Driver, EMD Serono, Exelixis, Foundation Medicine, GlaxoSmithKline, Genentech, Genzyme, Heron Therapeutics, Janssen, Merck, Mirati Therapeutics, Pfizer, Roche, Seattle Genetics, and QED Therapeutics; has participated in an educational programme for Bristol Myers Squibb; and received institutional research funding from AstraZeneca, Bavarian Nordic, Bayer, Bristol Myers Squibb, Clovis Oncology, Debiopharm, Genentech, GlaxoSmithKline, Immunomedics, Kure It Cancer Research, Merck, Mirati Therapeutics, Oncogenex, Pfizer, and QED Therapeutics. HKS has been a consultant to Merck Sharp & Dohme, Genentech/Roche, Bristol Myers Squibb, Boehringer Ingelheim, and Janssen; and has received research funding from Merck Sharp & Dohme, AstraZeneca, Genentech/Roche, Bristol Myers Squibb, Baselia, and Astellas. HN has received research funding from Astellas, Ono Pharmaceuticals, and Takeda Pharmaceuticals and has participated in speakers' bureaus for Merck Sharp & Dohme and Chugai Pharmaceuticals. BRK has received research funding from Genomic Health, Merck Sharp & Dohme, Bristol Myers Squibb, and Photocure and has been a consultant to Photocure, Pacific Edge, TARIS Biomedical, Boston Scientific, and NxTHERA. HL, KN, and EK are employed by Merck Sharp & Dohme. TF is an employee of Merck Sharp & Dohme; has stock ownership in Merck Sharp & Dohme, Amicus, GlaxoSmithKline, and AstraZeneca; and has a spouse who is an employee of Amicus Therapeutics and who is on the board of directors for VenatoRx. RdW has received research funding from Bayer and Sanofi; has been a consultant to Astellas, Merck Sharp & Dohme, Roche/Genentech, and Sanofi; and has received honoraria from Astellas, Bayer, Janssen, Merck Sharp & Dohme, Roche/Genentech, and Sanofi. DFB declares no competing interests.

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### Data sharing

Merck Sharp & Dohme, a subsidiary of Merck & Co, Kenilworth, NJ, USA, is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company's clinical trials for the purpose of legitimate scientific research. Merck Sharp & Dohme is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The Merck Sharp & Dohme data sharing website outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of Merck Sharp & Dohme subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with Merck Sharp & Dohme before data access is granted. Data will be made available for request after product approval in the USA and EU or after product development is discontinued. There are circumstances that might prevent Merck Sharp & Dohme from sharing requested data, including country or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and Merck Sharp & Dohme subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, Merck Sharp & Dohme will either perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

For more on the **Merck Sharp & Dohme data sharing website** see http://engagezone.msd.com/ds_documentation.php

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