



February 17, 2022

Steven D. Pearson, MD, MSc, FRCP  
President  
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RE: ICER Bladder Cancer Review Follow-up

Dear Dr. Pearson:

Thank you for the opportunity to submit comments on evidence and/or information.

The updated results from cohort A of KEYNOTE-057 (NCT02625961), with more than 3 years of follow up further 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 (RC) [1, 2].

With the updated database cutoff date of May 25, 2020 (median follow-up 36.4 months, range 26.3–48.5), the complete response (CR) rate and median duration of response remained the same as previously reported (database cutoff date 24Sep2019) [3], with 18 (46%) of 39 responders remaining in CR for 12 months or longer. With a minimum of more than 2 years of follow-up, 11 (28%) of the complete responders continued to be followed for efficacy and had an ongoing response at the time of database cutoff.

Overall, 40 (49%) of 82 patients who discontinued pembrolizumab, including initial responders (n=25) and non-responders (n=57), subsequently underwent RC. Of these, 35 patients (88%) had no pathological upstaging to muscle-invasive bladder cancer (MIBC), 3 (8%) patients (all non-responders) had evidence of MIBC after pembrolizumab discontinuation, and 2 (5%) patients did not have data available. Notably, 6 participants had pT0 at time of RC.

At 12 months, the estimated PFS from enrolment to worsening of grade or stage (e.g., to T1) or death (whichever occurred first) was 83% (95% CI 70.2–90.4), and estimated PFS from enrolment to MIBC or metastatic disease or death (whichever occurred first) was 97% (86.0–99.2).

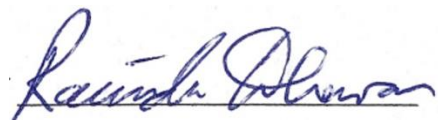
Nine (9%) of 96 patients had died, including 3 (3%) deaths due to adverse events unrelated to study treatment, and 6 deaths that occurred during survival follow-up (unknown causes n=3, senile atrophy n=1, progressive disease n=1, and cardioembolic stroke n=1). Median overall survival (median OS, defined as time from enrolment to death from any cause) was not reached.

OS rates were 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.

Results from the updated analysis suggest that pembrolizumab continues to show clinically meaningful antitumor activity in patients with BCG-unresponsive HR NMIBC with CIS (+/- papillary disease) who are ineligible for or have elected not to undergo RC. Use of pembrolizumab did not seem to limit the opportunity to undergo RC or other subsequent therapies. Rates of pathological upstaging to MIBC were low for patients who underwent RC after discontinuation of pembrolizumab. Pembrolizumab monotherapy had a manageable safety profile consistent with what has been reported before.

Again, we would like to thank ICER for the opportunity to submit additional evidence.

Sincerely,



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## References

- 1 de Wit R, Kulkarni GS, Uchio EM, et al. 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. *Lancet Oncol.* 2021 Jul;22(7):919-930. doi: 10.1016/S1470-2045(21)00147-9. Epub 2021 May 26
- 2 Balar AV, Kamat AM, Kulkarni GS et al. Pembrolizumab for the treatment of patients with high-risk (HR) non-muscle-invasive bladder cancer (NMIBC) unresponsive to Bacillus Calmette-Guérin: Extended follow-up of KEYNOTE-057 cohort A. Crossref DOI link: [https://doi.org/10.1200/JCO.2021.39.6\\_SUPPL.451](https://doi.org/10.1200/JCO.2021.39.6_SUPPL.451)
- 3 Presentation at the Oncologic Drugs Advisory Committee (ODAC) Meeting, December 17, 2019 <https://www.fda.gov/media/133956/download>