

Pembrolizumab in bacillus Calmette-Guérin unresponsive nonmuscle-invasive bladder cancer; a difficult to treat disease (KEYNOTE-057)

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SUMMARY

KEYNOTE-057 is an open-label, single-arm, multicenter, phase 2 trial, published in *Lancet Oncology*, evaluating the efficacy of pembrolizumab as monotherapy for the treatment of high-risk nonmuscle-invasive bladder cancer (NMIBC) unresponsive to bacillus Calmette-Guérin (BCG). It has 2 cohorts; cohort A included high-risk NMIBC patients aged ≥ 18 years with BCG-unresponsive carcinoma-in-situ (Carcinoma in situ), with or without papillary tumors, with an ECOG 0-2. These patients were either noneligible for radical cystectomy (RC) or refused the surgery. Cohort B included patients with BCG-unresponsive high-grade Ta or any grade T1 papillary disease without CIS.

All enrolled patients received pembrolizumab 200 mg intravenous every 3 weeks for up to 24 months or until confirmed disease persistence, recurrence, or progression; unacceptable toxic effects; or withdrawal of consent. The primary endpoint was the clinical complete response (CR) rate (absence of high-risk NMIBC or progressive disease). Patients were evaluated by cystoscopy and urine cytology 3 months after the first dose. The patients underwent regular follow-up every 3 months for the first 2 years and every 6 months for 5 years.

101 patients with a median of 12 previous BCG instillations received at least 1 dose of pembrolizumab. 96 patients were included in the efficacy analysis. Median follow-up was 36.4 months and 39 (41%) of 96 patients with BCG-unresponsive CIS bladder with or without papillary tumors had a CR at 3 months. Among these 39, 18 patients continued with the CR for 12 months, and 20 developed recurrence after initial CR. 11 patients experienced CR at a median follow-up of 36.4 months. The median CR duration was 16.2 months and it was irrespective of PD-L1 status. The median duration of pembrolizumab treatment was 4.2 months with a median of 7 administrations. 59%

of patients were nonresponders (57/96). 40% of those who choose RC after discontinuing pembrolizumab upstaging was seen in only 8%, thus preserving the window of opportunity for curative-intent surgery.

At 12 months, the estimated PFS to worsening grade or stage of death was 83%, and the estimated PFS to T2, M1 or death was 97%. Overall survival was 98% at 12 months, 95% at 24 months, and 91% at 36 months. Grade 3/4 toxicity was seen in 13% of patients, the most common being arthralgia and hyponatremia seen in 2% and 3%, respectively. Serious treatment-related adverse events occurred in 8% of patients. There were no deaths that were considered treatment related.

The authors concluded that pembrolizumab monotherapy was tolerable with promising antitumor activity and should be considered a clinically active nonsurgical treatment option in this difficult-to-treat population.

COMMENTS

BCG “unresponsiveness” represents a significant population. After complete TURBT and adjuvant therapy with intravesical BCG for high-grade NMIBC, around 84% of CIS patients initially achieve a CR and around 50% fail to maintain a durable response.^[1] RC is recommended for BCG unresponsive disease, but many patients prefer bladder sparing therapies as this procedure is associated with significant morbidity. There are various options other than radical cystectomies such as valrubicin, gene therapy, sequential intravesical chemotherapy with or without enhanced drug delivery, and immune checkpoint inhibitors. Valrubicin is Food and Drug Administration (FDA) approved for BCG refractory NMIBC, but response rates are suboptimal and not durable.^[1]

A novel alternative intravesical gene therapy using nadofaragene firadenovec is a replication-deficient recombinant adenovirus that delivers human interferon α -2b complementary DNA into the bladder epithelium. 53.4% of patients with CIS showed a CR within 3 months

of the first dose (75 ml), maintained in 45.5% patients at 12 months.^[2]

Intravesical gemcitabine and docetaxel are also well-tolerated and effective rescue therapy for this population. 276 patients with a median follow-up of 22.9 months who received this treatment, high-grade recurrence-free survival rates were 65% and 52% at 1 and 2 years, respectively. 15.6% went on to cystectomy, of which 4% had progression to muscle invasion.^[3]

The evaluation of BCG failure patients has revealed PD-L1 overexpression in the BCG-induced bladder granulomas, indicating that it may facilitate the progression of the disease and prevent BCG success by neutralizing the T cell responses.^[4]

Pembrolizumab, a PD-1 inhibitor in this open-label, single-arm, phase 2 multicenter trial done in 14 countries, showed a durable response of 16.2 months in BCG unresponsive high-risk NMIBC patients with level 2 evidence. The study design consisted of a homogeneous patient population which was considered acceptable in the absence of any nonsurgical comparator group.^[5] The trial design used was framed in AUA and FDA workshop held in 2014, which suggested a CR rate of 40%–50% at 6 months and a response rate of at least 30% at 18–24 months to be considered clinically meaningful for approval of novel agents in BCG unresponsive NMIBC. The 2 prespecified interim analysis and their results reviewed by the external monitoring committee further improve the trial’s validity.

Median PFS to T2, M1 or death and OS was not reached in this analysis. Furthermore, many patients discontinued treatment due to persistent or recurrent disease and were censored early in the follow-up period. This right censoring in this trial design was dealt with the Kaplan–Meier method for survival analysis. The trial also surfaces a critical 59% nonresponder population which poses a significant challenge in the management and needs further research.

There were no unexpected safety concerns in RC that can be attributed to previous pembrolizumab treatment. Hence, pembrolizumab with a manageable safety profile can be used as an alternative for RC. This study is limited by the absence of a direct comparator group and a small sample size. Further trials with suitable comparators, randomization, and blinding can provide a better level of evidence.

This treatment is associated with significant expense; a single dose of this drug usually costs more than a complete

treatment with RC at present. Hence, real-world Indian data is required to judge the risk-benefit ratio more effectively in our population and justify its high cost. Until then, we can only expect a slow adoption of these novel agents.

REFERENCES

1. Kamat AM, Lerner SP, O'Donnell M, Georgieva MV, Yang M, Inman BA, *et al.* Evidence-based assessment of current and emerging bladder-sparing therapies for non-muscle-invasive bladder cancer after bacillus Calmette-Guérin therapy: A systematic review and meta-analysis. *Eur Urol Oncol* 2020;3:318-40.
2. Boorjian SA, Alemozaffar M, Konety BR, Shore ND, Gomella LG, Kamat AM, *et al.* Intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive non-muscle-invasive bladder cancer: A single-arm, open-label, repeat-dose clinical trial. *Lancet Oncol* 2021;22:107-17.
3. Steinberg RL, Thomas LJ, Brooks N, Mott SL, Vitale A, Crump T, *et al.* Multi-institution evaluation of sequential gemcitabine and docetaxel as rescue therapy for nonmuscle invasive bladder cancer. *J Urol* 2020;203:902-9.
4. Inman BA, Sebo TJ, Frigola X, Dong H, Bergstralh EJ, Frank I, *et al.* PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: Associations with localized stage progression. *Cancer* 2007;109:1499-505.
5. Jarow JP, Lerner SP, Kluetz PG, Liu K, Sridhara R, Bajorin D, *et al.* Clinical trial design for the development of new therapies for nonmuscle-invasive bladder cancer: Report of a food and drug administration and American urological association public workshop. *Urology* 2014;83:262-4.


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Received: 07.06.2021, **Revised:** 06.08.2021,

Accepted: 14.09.2021, **Published:** 01.10.2021

Financial support and sponsorship: Nil.

Conflicts of interest: There are no conflicts of interest.

Access this article online	
Quick Response Code:	Website: www.indianjurol.com
	DOI: 10.4103/iju.iju_244_21

How to cite this article: Kumar B. Pembrolizumab in bacillus Calmette-Guérin unresponsive nonmuscle-invasive bladder cancer; a difficult to treat disease (KEYNOTE-057). *Indian J Urol* 2021;37:367-8.