A Phase 3, Randomized, Open-Label, Multicenter, Global Study of Durvalumab and Bacillus Calmette-Guérin (BCG) Versus BCG Alone in High-Risk, BCG-Naïve Non–Muscle-Invasive Bladder Cancer (NMIBC) Patients (POTOMAC)

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Introduction

- Urothelial carcinoma (UC) is the most common type of cancer of the bladder, ureter, urethra, and urachus, accounting for approximately 90% of primary malignancies of the urinary tract.^{1,2}
- Standard treatment for patients with high-risk non–muscle-invasive tumors is transurethral resection of bladder tumor (TURBT) followed by intravesical administration of BCG.³
- Several randomized studies have demonstrated the efficacy of BCG in NMIBC, but recurrence rates are as high as 50% in the first 3 years of follow-up and can be even higher for aggressive histologic subtypes.^{4,5}
- Results of nonclinical and clinical studies of monoclonal antibodies (mAbs) targeting the programmed cell death ligand-1/programmed cell death-1 (PD-L1/PD-1) pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti–PD-L1 antibody may therapeutically enhance antitumor immune response in patients with cancer.^{6–8}
- Response rates doubling those with traditional chemotherapy have been reported for immunotherapies targeting PD-1 and PD-L1 in trials of patients with metastatic UC who progressed after platinum-based chemotherapy.
- Durvalumab (D) is a selective, high-affinity, engineered human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80 with a manageable safety and tolerability profile.
- PD-L1 inhibition with D in combination with other immunotherapies, including standard-of-care BCG, may improve response rate and duration of tumor response.

Figure: Study design

BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; D, durvalumab, G, histologic grade; HG, high grade; I, induction; M, maintenance; NMIBC, non–muscle-invasive bladder cancer; OS, overall survival; Q4W, every 4 weeks; T1, tumor invading the lamina propria.

Methods

Study Design

- This is a randomized, open-label, multicenter, global study to determine the efficacy and safety of D+BCG (I+M) and D+BCG (I only) versus BCG (I+M) alone in the treatment of patients with histologically confirmed high-risk NMIBC following complete resection of papillary tumors (patients with residual CIS are eligible) and who are BCG naïve (**Figure**).
- Approximately 975 patients aged ≥18 years will be randomized (1:1:1) to 1 of 3 treatment arms.
- The primary objective is to assess the efficacy of D+BCG (I+M) compared with BCG (I+M) alone as measured by disease-free survival using investigator disease assessments.
- Several secondary and safety objectives will also be explored (**Table**).
- Treatment will be discontinued if there is high-risk persistent disease or high-risk disease recurrence, disease progression, or unacceptable toxicity.
- Unless discontinuation criteria are met, treatment will continue for ~2 years for the D+BCG (I+M) and BCG (I+M) alone groups and for ~1 year for the D+BCG (I only) group.

Table: Additional objectives

Objectives
Secondary objectives
Efficacy of D+BCG (I only) compared with BCG (I+M) alone
Efficacy of D+BCG (I+M) compared with D+BCG (I only)
Disease-related symptoms and health-related quality of life in patients with NMIBC treated with D+BCG (I+M) and D+BCG (I only) compared with BCG (I+M) alone and compared with each
Safety objective
Safety and tolerability profile of D+BCG (I+M) and D+BCG (I only) compared with BCG (I+M) alone

Study Population: Inclusion and Exclusion Criteria

Inclusion	Exclusion
BCG naïve (patients who have not received prior intravesical BCG or who previously received but stopped BCG >3 years before study entry)	Evidence of muscle-invasive, locally advanced, metastatic, and/or extravesical bladder cancer
Local histological confirmation of high-risk transitional cell carcinoma of the urothelium of the urinary bladder confined to the mucosa or submucosa	Known or documented absolute and/or relative contraindication of adjuvant intravesical BCG treatment
Complete resection of all Ta/T1 papillary disease prior to randomization, with most recent TURBT occurring ≤2 months prior to consent for study	Concurrent extravesical, non–muscle-invasive transitional cell carcinoma of the urothelium
No prior radiotherapy to the bladder	Concurrent treatment with systemic immunostimulatory agents prior to first dose of study treatment
WHO/ECOG performance status of 0 or 1 at screening	Predominantly variant histology (other than urothelial) as assessed by pathology
No prior exposure to immune-mediated cancer therapy, including, but not limited to, other anti–CTLA-4, anti–PD-1, anti–PD-L1, and anti-programmed cell death ligand-2 antibodies	
Adequate organ and marrow function	

Conclusions

- There remains a significant unmet medical need for innovative, effective therapies for NMIBC that can significantly reduce recurrence and progression rates.
- Existing efficacy data and PD-L1 expression data support the potential therapeutic effect of durvalumab in earlier stages of bladder cancer, including high-risk NMIBC.
- PD-L1 inhibition through exposure to durvalumab in combination with the standard-of-care drug BCG, may increase both the long-term response rate and frequency of response by preventing the NMIBC tumor cells from evading immune-mediated antitumor response.
- The addition of durvalumab to BCG treatment may counteract acquired BCG resistance⁹; the combination could provide dual benefit by decreasing recurrence rates and increasing duration of response.

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Acknowledgments

This study was funded by AstraZeneca. The authors would like to thank the patients, their families and caregivers, and all investigators involved in this study. Medical writing support, which was in accordance with Good Publication Practice (GPP3) guidelines, was provided by Anne-Marie Manwaring of Parexel (Littlehampton, UK) and was funded by AstraZeneca. **Contact Email:** maria.de-santis@charite.de

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