

# P104 Use of Mycobacterial Cell Wall–DNA Complex Immediately After Endovesical Surgery in the Treatment of Patients With Non–Muscle-Invasive Bladder Cancer

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## Introduction

- Intravesical (Ive) adjuvant chemotherapy is recommended within 24 hours after transurethral resection of bladder tumor (TURBT) in patients with non–muscle-invasive bladder cancer (NMIBC) to destroy residual cancer cells and prevent reimplantation<sup>1-3</sup> (Figure 1).

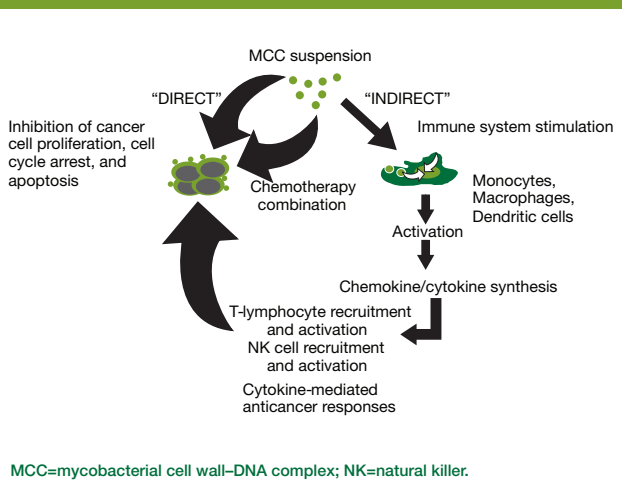
Figure 1. Intravesical Treatment Options After TURBT<sup>1-5</sup>

	Chemotherapy	Immunotherapy	Other Therapy
Status (in North America)	Available doxorubicin, epirubicin, gemcitabine, mitomycin C, thiotepa, valrubicin In development apaziquone	Available BCG, interferon	In development mycobacterial cell wall–DNA complex
Efficacy	Prevents recurrence	Prevents recurrence and progression	Might prevent recurrence and progression in BCG-refractory disease
Sterility	Sterile	Not sterile	Sterile
Timing after surgery	Immediate	≥2 wk for BCG (to reduce risk of death from sepsis or cystitis)	Unknown

BCG=bacillus Calmette-Guérin; TURBT=transurethral resection of bladder tumor.

- Ive bacillus Calmette-Guérin (BCG) is preferred for treatment of NMIBC with elevated risk of progression.<sup>1,3</sup>
  - However, BCG cannot be instilled until at least 2 weeks (Figure 1) after surgery because of risk of serious complications (eg, sepsis).<sup>1-3</sup>
- Mycobacterial cell wall–DNA complex (MCC), a sterile suspension of cell wall and DNA fragments derived from the nonpathogenic *Mycobacterium phlei*, has recently been shown to reduce recurrences in patients for whom BCG previously failed.<sup>4,5</sup>
  - MCC exhibits a dual mechanism of action, with immunomodulatory and chemotherapeutic effects (Figure 2).<sup>6,7</sup>

Figure 2. Dual Mechanism of Action of MCC



MCC=mycobacterial cell wall–DNA complex; NK=natural killer.

## Objective

- This analysis reviewed data from a phase III clinical trial to determine whether MCC can be safely instilled immediately after TURBT or bladder biopsy.

## Methods

### Study Design

- Open-label, single-treatment-arm, multinational study that evaluated the efficacy and safety of Ive MCC as induction and maintenance therapy in patients with NMIBC who were refractory to adequate Ive BCG therapy and at high risk of progression.
- BCG refractory was defined as evidence of
  - Persistent high-grade NMIBC ≥6 months after the start of a full BCG induction course (with or without maintenance or retreatment at 3 mo)
  - Recurrent high-grade NMIBC ≤2 years from the start of a full BCG induction course and after achieving a disease-free status 6 months postinduction; recurrence must be evident ≤6 months after receiving BCG maintenance therapy.
- All sites received institutional review board approval, and patients provided informed consent.

### Treatment

- 6 weekly Ive MCC (8 mg) instillations (induction), with the first instillation starting 7–56 days after TURBT/biopsy, followed by 3 once-weekly instillations at 3, 6, 12, 18, and 24 months (maintenance).
  - At their discretion, and considering their previous experience with MCC, some investigators instilled MCC within 1 day postsurgery (TURBT or biopsy).
- A second 6-week MCC induction course was allowed at 3 months at investigator discretion.
- After the 24-month treatment course, patients were followed up for up to an additional 36 months.

## Inclusion and Exclusion Criteria

- Adults (aged ≥18 y) with high-grade urothelial carcinoma (papillary Ta/T1, carcinoma in situ) who were BCG refractory, had surgery (TURBT or biopsy) within 56 days of starting study treatment, no urothelial carcinoma involving the upper urinary tract or prostatic urethra (≤12 mo from beginning of study treatment), and a life expectancy of >5 years were included.

## Primary Study Assessments

- Efficacy assessments: cystoscopy, urine cytology, and biopsy
- Clinical response definitions (assessed by Central Pathologist)
  - Failure: biopsy-confirmed diagnosis of NMIBC or muscle-invasive bladder cancer (MIBC) (urothelial carcinoma in upper urinary tract or prostatic urethra was not considered a treatment failure)
  - Progression: biopsy-confirmed diagnosis of MIBC
  - Disease-free: all other findings

## Primary Endpoints

- Efficacy endpoint: 1-year disease-free survival (DFS) in the intent-to-treat population estimated using Kaplan-Meier analysis
- Safety endpoint: frequency of treatment delays or discontinuations due to treatment-related AEs (TRAEs)

## Postsurgical (TURBT or Bladder Biopsy) Analysis

- A retrospective analysis was performed for patients who received MCC immediately (within 24 h) after undergoing bladder cancer–related surgery.
  - Postsurgical analysis included the description of any AEs, their severity, and their relationship to MCC.

## Results

### Timing of MCC Administration After TURBT or Biopsy

- Between November 2006 and April 2009, 129 patients were enrolled at 25 US and Canadian sites. Patient baseline characteristics are shown in Table 1.

Table 1. Patient Baseline Characteristics\*

Mean (SD) age, y	68.5 (11.2)
Men, n (%)	95 (74)
Race, n (%)	
White	129 (100)
Central pathologist diagnosis, n (%)	
Papillary only	34 (26)
CIS only	54 (42)
CIS + papillary	32 (25)
Missing/no tumors†	9 (7)
BCG instillations previously received, n (%)	
≤6	31 (24)
7–12	53 (41)
13–20	18 (14)
≥21	27 (21)

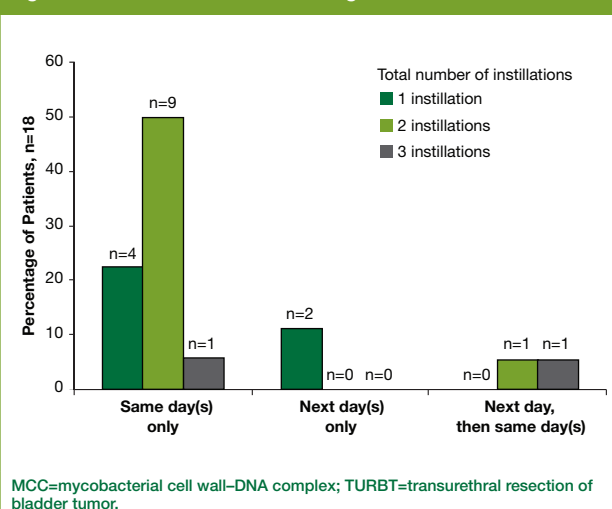
BCG=bacillus Calmette-Guérin; CIS=carcinoma in situ.

\*Overall intent-to-treat population (n=129).

†2 patients did not have a pathology assessment and another 7 patients did not have any malignant tumors at study entry. For these patients, central pathology results were imputed from local pathology results (4=papillary; 5=CIS only [no concurrent papillary disease]).

- Overall, 18 of 129 patients (14%) received a total of 32 MCC instillations within 24 hours of surgery (Figure 3). Within this group of 18 patients
  - 14 (78%) received MCC on day of the TURBT/biopsy; 2 (11%) received their first MCC treatment on the day after surgery and then, following a subsequent surgery, received a second MCC instillation on the same day as surgery; 2 (11%) other patients received MCC only on the day after surgery.
  - 6 (33%) had only a single postsurgical MCC administration, 10 (56%) had 2 postsurgical instillations, and 2 (11%) had 3 postsurgical instillations.
- In summary, 16 of 129 patients (12%) received a total of 28 instillations on the day of surgery and 4 (3%) patients received a total of 4 instillations on the day after surgery (this includes the 2 patients who had both a day-after and a subsequent same-day postsurgical administration [Figure 3]).

Figure 3. MCC Administration Timing Post-TURBT



MCC=mycobacterial cell wall–DNA complex; TURBT=transurethral resection of bladder tumor.

## Safety of MCC Administration After TURBT or Biopsy

- Same day of surgery administration: 5 of 16 patients (31.3%) experienced AEs following 5 of 28 instillations (17.9%) (Table 2).
  - 4 patients experienced local bladder/urological symptoms, which were mild to moderate in severity and considered unrelated to MCC.
  - 1 patient experienced systemically related AEs (rigor, nausea, headache) of moderate severity, which were possibly related to MCC.
  - 3 of these 5 patients received an instillation on the day of surgery at another time without experiencing any AEs.
  - None of these AEs resulted in treatment delays (ie, postponements) or discontinuation; none was serious.

Table 2. Safety of Ive MCC Administration Within 1 Day After TURBT/Biopsy

	Patients With an AE on the Day of Administration, n (%) n=16	Instillations Associated With an AE on the Day of Administration, n (%) n=28
Timing of MCC administration		
Same day as surgery	5 (31.3)	5 (17.9)
Type of AE		
Hematuria	2 (12.5)	2 (7.1)
Urinary frequency	2 (12.5)	2 (7.1)
Dysuria	1 (6.3)	1 (3.6)
Suprapubic cramps	1 (6.3)	1 (3.6)
Headache	1 (6.3)	1 (3.6)
Nausea	1 (6.3)	1 (3.6)
Rigor	1 (6.3)	1 (3.6)
More than 1 AE reported,* n (%)	2 (12.5)	2 (7.1)

AE=adverse event; Ive=intravesical; MCC=mycobacterial cell wall–DNA complex; TURBT=transurethral resection of bladder tumor.

\*2 patients reported multiple AEs on the day of administration (patient 1: rigor, nausea, headache; patient 2: urinary frequency, suprapubic cramps, dysuria) after a single instillation. Patient 2 had received a previous day of TURBT instillation with no AEs reported.

- Day after surgery administration: 4 patients reported no AEs on the day of the instillation.

## Overall MCC Efficacy and Safety

- The 1-year DFS rate was 25%, and median DFS was 177 days.
- Most TRAEs were mild or moderate. The most common TRAEs were dysuria (26%), hematuria (23%), fatigue (16%), increased urinary frequency (14%), micturition urgency (12%), and urinary tract infection (8%). 2 serious AEs were considered possible TRAEs (hematuria, urinary tract infection).

## Conclusion

- In the limited number of patients studied, Ive MCC was well tolerated when instilled immediately after TURBT or bladder biopsy.
- Further investigation is needed to determine whether Ive MCC, like cytotoxic agents, can be administered in the perioperative setting to prevent reimplantation of circulating tumor cells and potentially reduce the rate of recurrence.

## References

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