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Original article

An open label, single-arm, phase II multicenter study of the safety and efficacy of CG0070 oncolytic vector regimen in patients with BCG-unresponsive non–muscle-invasive bladder cancer: Interim results

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Abstract

Objectives: CG0070 is a replication-competent oncolytic adenovirus that targets bladder tumor cells through their defective retinoblastoma pathway. Prior reports of intravesical CG0070 have shown promising activity in patients with high-grade non–muscle invasive bladder cancer (NMIBC) who previously did not respond to bacillus Calmette-Guérin (BCG). However, limited accrual has hindered analysis of efficacy, particularly for pathologic subsets. We evaluated interim results of a phase II trial for intravesical CG0070 in patients with BCG-unresponsive NMIBC who refused cystectomy.

Patients and methods: At interim analysis (April 2017), 45 patients with residual high-grade Ta, T1, or carcinoma-in-situ (CIS) ± Ta/T1 had evaluable 6-month follow-up in this phase II single-arm multicenter trial (NCT02365818). All patients received at least 2 prior courses of intravesical therapy for CIS, with at least 1 being a course of BCG. Patients had either failed BCG induction therapy within 6 months or had been successfully treated with BCG with subsequent recurrence. Complete response (CR) at 6 months was defined as absence of disease on cytology, cystoscopy, and random biopsies.

Results: Of 45 patients, there were 24 pure CIS, 8 CIS + Ta, 4 CIS + T1, 6 Ta, 3 T1. Overall 6-month CR (95% CI) was 47% (32%–62%). Considering 6-month CR for pathologic subsets, pure CIS was 58% (37%–78%), CIS ± Ta/T1 50% (33%–67%), and pure Ta/T1 33% (8%–70%). At 6 months, the single patient that progressed to muscle-invasive disease had Ta and T1 tumors at baseline. No patients with pure T1 had 6-month CR. Treatment–related adverse events (AEs) at 6 months were most commonly urinary bladder spasms (36%), hematuria (28%), dysuria (25%), and urgency (22%). Immunologic treatment–related AEs included flu-like symptoms (12%) and fatigue (6%). Grade III treatment–related AEs included dysuria (3%) and hypotension (1.5%). There were no Grade IV/V treatment–related AEs.

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Conclusions: This phase II study demonstrates that intravesical CG0070 yielded an overall 47% CR rate at 6 months for all patients and 50% for patients with CIS, with an acceptable level of toxicity for patients with high-risk BCG-unresponsive NMIBC. There is a particularly strong response and limited progression in patients with pure CIS.

Keywords: Non-muscle invasive bladder cancer; Oncolytic adenovirus; Intravesical therapy; BCG unresponsive

1. Introduction

Guidelines define high-risk non–muscle-invasive bladder cancer (NMIBC) as carcinoma-in-situ (CIS) or high-grade Ta or T1 bladder tumors [1–3]. Intravesical bacillus Calmette-Guérin (BCG) is the most common adjuvant treatment for high-risk NMIBC [1–3]. However, BCG does not cure over 50% of these patients [4,5]. There are no standard second-line agents in this setting, although some intravesical agents have been recently evaluated [6].

CG0070 is a replication-competent oncolytic adenovirus that selectively replicates in retinoblastoma (Rb) pathway–defective bladder tumor cells [7]. The adenovirus also causes transgene expression of granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine that is critical for immune activation. There are 2 presumed mechanism of action for CG0070: (1) direct tumor lysis by selective replication in Rb pathway–defective tumor cells, and (2) immune-mediated killing resulting from immunogenic cell death and local GM-CSF production.

A phase I/II study assessed 35 patients who received CG0070, demonstrating a tolerable safety profile with some confirmation of mechanism of action—CG0070 replication in urine and GM-CSF transgene expression [7]. Patients with Rb pathway defects had higher clinical response compared to wild type (58% vs. 20%), suggesting replication specificity. The phase II/III randomized controlled BOND study was closed early, and preliminary results showed 29% CR at 15 months. An attractive tolerability profile was again demonstrated, but there was unclear correlation of defective Rb pathways and clinical response. Given concerns for lack of appropriate control or salvage treatments, recent consensus from the International Bladder Cancer Group supported the use of single-arm trials in the high-risk BCG-unresponsive setting [8]. We present interim 6-month response results from the single-arm BOND II study assessing the safety and efficacy of CG0070 in patients with high-risk BCG-unresponsive NMIBC who refuse cystectomy.

2. Patients and methods

2.1. Study design

This is an ongoing single-arm, phase II, multicenter study (clinicaltrials.gov NCT02365818) assessing the safety and efficacy of CG0070 in patients with NMIBC who failed BCG therapy and refused cystectomy. At the time of this interim analysis (April 2017), patients were enrolled at 18 sites from June 2015 through February 2017.

2.2. Patient selection

Patients were eligible for inclusion if they had high-grade NMIBC (Ta, T1, CIS, or CIS with Ta or T1, or all of these) and had previously failed BCG therapy and refused cystectomy. Patients without history of CIS or CIS at enrollment must have had disease recurrence within 12 months of most recent intravesical therapy of any kind, disease recurrence within 18 months of BCG maintenance, or disease recurrence within 24 months of BCG induction. Patients with T1 tumors required evidence of muscle in most recent biopsy. Pathology specimens for inclusion were confirmed by a central pathologist, and urothelial tumors with $<50\%$ variant histology were eligible. Patients must have received at least 2 or more prior courses of intravesical therapy per recommended schedules, with BCG as one of the prior therapies. The first course of BCG must have included at least 6 weekly treatments, and the second course at least 2 weekly treatments. BCG failure was defined as patients with BCG-refractory (failure to achieve a disease-free state (DFS) at 6 months following initial BCG therapy with either maintenance of retreatment at 3 months because of persistent or rapidly recurrent tumor), BCG-resistant (rapid recurrence or persistence at 3 months; patients achieve DFS at 6 months following a repeat induction cycle or TURBT), or BCG-relapsing disease (recurrence of disease after achieving DFS by 6 months) [9]. Radical cystectomy was declined by patients, with a clear understanding that delay of cystectomy may increase the risk of disease progression and subsequent serious and life-threatening consequences.

Additional inclusion criteria were age of 18 years or older, entry into the study within 10 weeks of most recent diagnostic procedure (positive urine cytology, biopsy, or TURBT), Eastern Cooperative Oncology Group performance status ≤ 2, adequate CBC, and renal and hepatic function (WBC $>$ 3,000 cells/mm^3, ANC $>$ 1,000 cells/mm^3, hemoglobin $>$ 9.5 g/dL, platelet count $>$ 100,000 cells/mm^3, serum creatinine $<$ 2.5 mg/dL, absolute lymphocyte count $\geq$ 800/μL, PT/INR/PTT/fibrinogen within normal limits, and bilirubin/AST/ALT within 2× upper limits of normal). Exclusion criteria included prior systemic chemotherapy or radiation for bladder cancer (prior intravesical therapy for superficial disease acceptable); pregnancy; known infection with HIV, HBV, or HCV; anticipated chemotherapy

or radiotherapy while on study; systemic treatment on any investigational clinical trial within 28 days or experimental vaccine trial within 1 year before registration; concurrent treatment with immunosuppressive or immunomodulatory agents including systemic steroids cyclosporine, antithymocyte globulin, or tacrolimus (but excluding inhaled or topically applied steroids, short or long term standard dose nonsteroidal anti-inflammatory drugs); and history of stage III or greater nonurothelial cancer. Basal or squamous cell skin cancers must have been adequately treated with disease-free status. Patients with history of stage I or II cancers must have been disease-free for $\geq$ 2 years at the time of registration. All infections must be resolved, and patients must remain afebrile while off antibiotics 7 days before study.

2.3. Treatment

As previously described, CG0070 is a replication-competent adenovirus (serotype 5) where an essential viral replication promoter (E1A) is controlled by an E2F-1 promoter, which enables selective lysis of Rb-defective tumor cells; immune stimulation is enhanced by encoding the human GM-CSF cytokine gene [7].

CG0070 was administered after 14 days from the most recent biopsy and in the absence of any evidence of hematuria or traumatic catheterization. All patients received intravesical CG0070 immediately following an intravesical rinse with 100 mL normal saline, pretreatment with 75 mL 0.1% dodecyl maltoside (DDM), and another saline rinse. DDM is a nonionic surfactant that acts as a mild detergent and solubilizing agent, used to enhance the transduction efficiency of CG0070 in the bladder. Instillation of CG0070 was performed within 2 hours of DDM pretreatment. A fixed dose of 1×10^{12} Vp CG0070 was administered in a 100 mL normal saline solution via a 100% silicone 3-way catheter. Dwell time was 45 to 50 minutes, and patients were encouraged to reposition to maximize bladder surface exposure. Intravesical CG0070 was instilled weekly for 6 weeks for both induction and maintenance treatments.

2.4. Patient evaluation

The predetermined primary outcome measure was durable complete response (CR) at 18 months. Given the available data at the data cutoff on April 2017, 6-month CR is the primary outcome for this interim analysis and includes all patients who received at least 1 dose of intravesical CG0070. Baseline characteristics and adverse event profile were assessed using intention-to-treat analysis for all 67 accrued patients to date. Response was assessed for the 45 patients with evaluable 6-month follow-up, given limited sample size for intention-to-treat analysis for this interim report.

CR was deemed by negative cystoscopy, urine cytology, and bladder biopsies. Biopsies were taken for visually positive lesions at the time of each cystoscopy. In addition, random bladder biopsies were mandated at 6 months. In the event of a positive urine cytology in the setting of no visual lesions on cystoscopy or positive random biopsies, a second urine cytology was obtained in 2 to 4 weeks. Patients with a negative second urine cytology were considered CR. If the second cytology was positive, the patient was considered a nonresponder, no longer followed on the trial, and received a recommendation to undergo further work-up for upper tract and urethral disease.

Response categories were determined by central review of pathology and cytology. Progressive disease (PD) was defined as evidence of any disease after a prior "negative" assessment, or progression to T2 or higher pathology. All other situations were considered stable disease (SD).

Low-grade Ta or T1 bladder lesions were not considered as local failures, and resection of these lesions was allowed with such patients classified as CR. In this setting, a re-TURBT was mandated for T1 lesions. If disease status was not assessed for any reason between 2 consecutive time points, the patients was considered to have failed treatment.

Clinical response was first evaluated after induction at 3 months with cystoscopy, bladder biopsy of visually positive lesions, and urine cytology. Patients with CR at 3 months underwent no intervention and were reevaluated at 6 months. Patients with SD received "accelerated maintenance" (AM) at 3 to 4 months, which involved administration of the 6-month maintenance doses at 3 to 4 months instead. Patients with PD were deemed nonresponders and strongly counseled to reconsider cystectomy or alternative treatment. Patients who refused cystectomy could elect to continue to be followed at the established study follow-up intervals.

The 6-month evaluation also included mandatory biopsies. Patients with CR at 6 months who did not already receive AM received maintenance treatment (weekly treatments for 6 weeks). Cystoscopy, bladder biopsy for visual positive lesions, and urine cytology were subsequently performed at 9, 12, 15, 18, 21, and 24 months. Maintenance treatments were given for patients with CR at 6, 12, and 18 months from the date of first intravesical treatment. Patients with PD or recurrence (after achieving CR) were not eligible for further treatments, advised to reconsider cystectomy, and encouraged to remain under study follow-up for adverse events and long-term follow-up.

Local and systemic toxicity was recorded by measuring all adverse events (AEs) occurring to study participants after the first instillation of CG0070 and within 4 weeks after the last treatment. Grading was according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.0 https://ctep.cancer.gov/). Relationship of the AE to CG0070 and DDM was determined by the Principal Investigator at each site.

Blood and urine samples for pharmacokinetic analysis were obtained before and 2 hours postinstillation of CG0070 administered as the first and last treatments in

each 6-week course (first induction, sixth induction, first maintenance, sixth maintenance, etc.), as well as 24 hours following the first and sixth induction treatments. The concentration of CG0070 genomes within blood was measured using previously described methods [7].

3. Results

3.1. Patient characteristics

The distribution of all patients enrolled at the time of interim analysis is shown in Fig. 1. There were 45 patients who were evaluable for 6-month follow-up. Considering all patients accrued ($n = 67$, Table 1), median patient age was 72 years (interquartile range: 64–80). There were 54 (81%) men and 13 (19%) women. Forty-seven (70%) patients had CIS-containing tumors and 31 (46%) patients had pure CIS. Of those with a papillary component, there were 10 CIS + Ta (15%), 6 CIS + T1 (9%), 11 Ta without CIS (16%), and 9 T1 without CIS (12%). Considering patients who were evaluable for 6-month follow-up, there were 36 CIS-containing tumors, 24 pure CIS, 8 CIS + Ta, 4 CIS + T1, 6 Ta, and 3 T1 (Table 2).

3.2. Efficacy

At 3 months, 2 patients progressed to muscle-invasive disease, 1 patient had baseline CIS, and the other had T1 disease. Efficacy was assessed for the 45 patients with evaluable 6-month follow-up (Table 2). Overall 6-month CR rate in addition to the 95% CI was 47% (95% CI: 32%–62%). Considering 6-month CR for pathologic subsets, pure CIS was 58% (95% CI: 37%–78%), CIS ± Ta/T1 50% (95% CI: 33%–67%), CIS + Ta/T1 33% (95% CI: 10%–65%), and pure Ta/T1 33% (95% CI: 8%–70%) (Fig. 2). There was an improved response observed in patients with pure CIS compared to those with papillary with or without CIS. Patients with pure T1 had the lowest response rates and highest progression to muscle-invasive disease.

At 6 months, no patients with CIS-containing tumors progressed to muscle-invasive disease. All of the 9 patients with CIS-containing tumors who had PD were due to initial 3-month CR and subsequent non–muscle-invasive recurrence.

Twenty-five patients (38%) of the 66 patients underwent AM. Twenty of 34 patients with 3-month SD received AM. In addition, 5 patients with CR received off protocol AM. At 6 months, of the 20 patients with 3-month SD who received AM, 8 were CR, 8 were SD, 4 had not yet reached the month 6 time point.

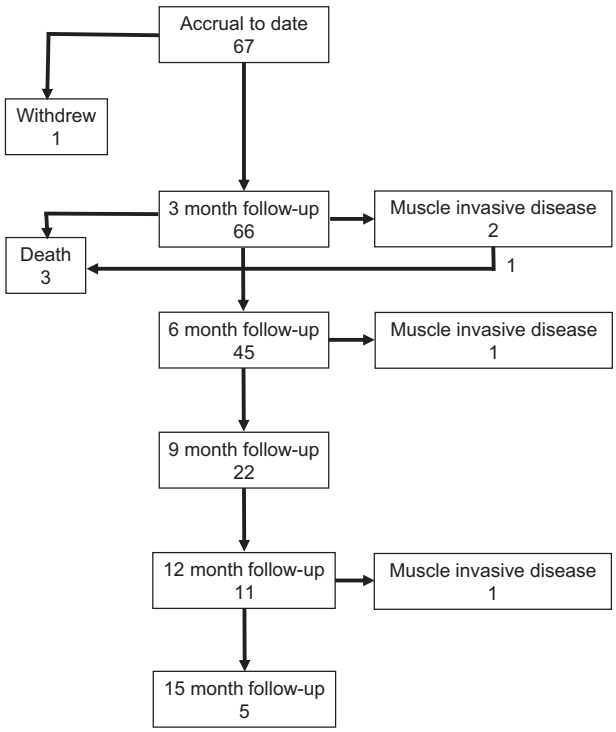

Fig. 1. Accrual diagram of all patients at the time of interim analysis.

Table 1
Baseline characteristics of patients

Number of patients[a]	67
Age, y (median, IQR)	72 [64,80]
Sex, male (%)	54 (81%)
Caucasian race, *n* (%)	61 (91%)
Stage, *n* (%)	
CIS containing	47 (70%)
Pure CIS	31 (46%)
CIS + Ta	10 (15%)
CIS + T1[b]	6 (9%)
Ta/T1 only	19 (28%)
Ta	11 (16%)
T1[c]	8 (12%)
Unknown	1 (1.5%)

IQR = interquartile range.
[a]Patients with 6-month follow-up presented.
[b]Two patients with CIS + T1 + Ta.
[c]Two patients with T1 + Ta.

Table 2
CR rates by stage

	6-month CR (%)	6-month SD (%)	6-month PD (%)
Overall	47% (21/45)	27% (12/45)	27% (12/45)[a]
CIS containing	50% (18/36)	25% (9/36)	15% (9/36)
Pure CIS	58% (14/24)	13% (3/24)	29% (7/24)
CIS + Ta	38% (3/8)	50% (4/8)	12% (1/8)
CIS + T1[b]	25% (1/4)	50% (2/4)	25% (1/4)
Ta/T1 only	33% (3/9)	33% (3/9)	33% (3/9)
Ta	50% (3/6)	33% (2/6)	17% (1/6)
T1[c]	0% (0/3)	33% (1/3)	67% (2/3)

Responses expressed as percentage (number/total number evaluable).
[a]One patient developed T2 disease, in a patient with baseline Ta + T1 disease.
[b]Two patients had CIS + T1 + Ta.
[c]Two patients had T1 + Ta.

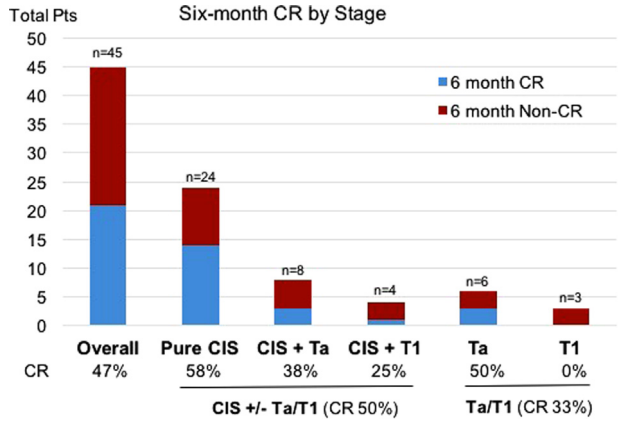

Fig. 2. Six-month clinical response (CR) by stage in patients with 6-month follow-up. (Color version of the figure available online.)

3.3. Adverse events

Fifty-eight patients (87%) reported at least 1 AE during the course of the study. All AEs are shown in Supplementary Table 1. Treatment–related AEs (related to CG0070 or DDM) are summarized in Table 3. A total of 38 patients (66%) reported at least 1 treatment–related AE during the course of the study. All treatment–related AEs were grade I to III. The most common treatment–related events were lower urinary tract symptoms: bladder spasms (36%), hematuria (28%), dysuria (25%), and urgency (22%). Treatment–related infectious events included urinary tract infection (16%). The most plausibly immunologic treatment–related AEs included flu-like symptoms (12%), fatigue (6%), and hypotension (3%). Three grade III treatment–related AEs included dysuria (3%) and hypotension (1.5%). No patients had grade IV or V AEs related to treatment in this study.

There were 3 nontreatment–related deaths. One death secondary to a cardiac event occurred before the 3-month evaluation. A second death from esophageal adenocarcinoma occurred in a patient with CIS before the 6-month evaluation. A third death occurred in the patient with T1 who progressed at month 3 to muscle-invasive disease before the month 9 evaluation.

3.4. Pharmacokinetic data

Urine CG0070 genomes generally peaked at 2 hours posttreatment and remained higher than baseline at 24 hours posttreatment. For example, considering the first induction treatment, mean urine CG0070 was 4.9×10^2 genomes/mL before treatment, 1.6×10^7 genomes/mL 2 hours after treatment, and 4.3×10^5 genomes/mL 24 hours after treatment (Supplementary Table 2). The serum CG0070 was low throughout the study duration. When analyzing all patients accrued to date, there was a range between 2.5×10^2 and 3.1×10^2 genomes/mL for time first and last induction, AM, and 6-month maintenance treatments (Supplementary Table 3).

4. Discussion

BCG-unresponsive high-risk NMIBC is a prevalent and serious problem because of high rates of disease recurrence and progression [10]. Radical cystectomy is currently the most preferable treatment to limit mortality in this setting [1–3]. However, there is an unmet need for effective therapy for patients who require or seek bladder-sparing management [5,11]. The interim results from this phase II study reveal a 47% overall CR rate at 6 months in the high-risk BCG-unresponsive setting.

At the time of this interim analysis, there have been several promising intravesical agents recently evaluated for BCG-unresponsive patients [6]. Although Valrubicin is the only FDA-approved agent for these patients, it has been shown to only yield CR of 8% at 2 years [12,13]. The multicenter SWOG study of intravesical gemcitabine by Skinner et al in 2013 showed 47% initial CR rate at 3 months, but ultimately only 21% at 2 years [14]. Unique agents with notably high, albeit short-term, responses for BCG-unresponsive enriched cohorts include adenovirus-mediated interferon (43% CR at 3 months in 17 patients) and nanoparticle albumin bound (nab)-paclitaxel (36% CR at 3 months in 28 patients) [15,16]. Longer-term follow-up for nab-paclitaxel shows 18% disease-free survival at median follow-up of 41 months [17]. The heterogeneous nature of cohorts in trials for intravesical agents makes direct comparison of results difficult. The large 1007 patient trial of interferon by Joudi et al showed 45% CR at 2 years; however, only 16% of these patients were BCG unresponsive [18]. Our trial is fairly unique in being composed of 100% high-risk BCG-unresponsive patients, optimizing its applicability in practice [6,8]. However, data regarding specific BCG-refractory status were not able to be assessed, precluding subset analysis within these distinct populations [9].

Overall and CIS-containing 6-month CR rates in this study (47% and 50%, respectively) are comparable to those in other recently published trials with short follow-up [15,16,19–22]. The 58% 6-month CR for pure CIS is higher than for most other published series, to our knowledge. Contrasted with the poor response in Ta/T1 containing tumors, these findings are clinically meaningful, suggesting that CIS may be the pathologic subset with the most favorable response to CG0070. Additionally, patients with pure CIS in this study experienced limited disease progression, with only 1 patient progressing to muscle-invasive disease at 3 months, giving reassurance within the short-term follow-up of this study regarding the risk of PD and a missed opportunity for cure in patients with pure CIS.

There was a poor response in all subsets of Ta/T1 containing tumors. Given the small number of patients with

Table 3
BOND2 study treatment–related adverse events (highest grade per subject) ($n = 67$)[a,b,c]

System organ class	CG0070-related AEs			DDM-related AEs		
	Grade (*n*)			Grade (*n*)		
Preferred term	1	2	3	1	2	3
Ear and labyrinth disorders						
Ear pain	1 (1.5)			1 (1.5)		
Hearing impaired	1 (1.5)			1 (1.5)		
Gastrointestinal disorders						
Nausea	1 (1.5)					
Vomiting	1 (1.5)			1 (1.5)		
General disorders and administration site conditions						
Fatigue	2 (3)	1 (1.5)		1 (1.5)		
Flu-like symptoms	5 (7.5)			3 (4.5)		
Infections and infestations						
Urinary tract infection	3 (4.5)	3 (4.5)		3 (4.5)	2 (3)	
Metabolism and nutrition disorders						
Dehydration		1 (1.5)			1 (1.5)	
Musculoskeletal and connective tissue disorders						
Flank pain	1 (1.5)					
Nervous system disorders						
Dizziness	1 (1.5)			1 (1.5)		
Dysgeusia	1 (1.5)			1 (1.5)		
Paresthesia		1 (1.5)			1 (1.5)	
Tremor	1 (1.5)	1 (1.5)		1 (1.5)	1 (1.5)	
Renal and urinary disorders						
Bladder spasm	10 (15)	4 (6)		7 (10.4)	3 (4.5)	
Hematuria	9 (13.4)	2 (3)		6 (9)	2 (3)	
Renal colic	1 (1.5)			1 (1.5)		
Urinary frequency	6 (9)			5		
Urinary incontinence	1 (1.5)			1 (1.5)		
Urinary tract pain	4 (6)	5 (7.5)	1 (1.5)	3 (4.5)	3 (4.5)	1 (1.5)
Urinary urgency	5 (7.5)	4 (6)		4 (6)	2 (3)	
Other, specify: burning in bladder	2 (3)			2 (3)		
Reproductive system and breast disorders						
Penile erythema	1 (1.5)			1 (1.5)		
Penile pain	1 (1.5)			1 (1.5)		
Respiratory, thoracic, and mediastinal disorders						
Other, specify: nasal discharge	1 (1.5)			1 (1.5)		
Vascular disorders						
Hot flashes	1 (1.5)					
Hypertension		1 (1.5)				
Hypotension		1 (1.5)	1 (1.5)			

[a]Unaudited data as of April 18, 2017.
[b]Toxicity graded according to the NCI Common Terminology Criteria for Adverse Events.
[c]Responses expressed as *n* (%).

Ta and T1 disease (with or without CIS), we were unable to detect differences in response rates between these subsets. This is especially likely given the known increased progression to muscle-invasive disease in patients with T1 vs. Ta containing tumors [23]. Furthermore, intravesical therapy is considered prophylactic for papillary disease and treatment for CIS. More complete resection of papillary tumors with aggressive TURBT and improved detection with blue light cystoscopy could affect results, as these are known to influence progression [24,25]. Extent of TURBT and the use of enhanced cystoscopy was not assessed in this study. Finally, an issue for any intravesical therapy, including CG0070, is unknown differences in drug absorption in papillary vs. CIS tumors.

CG0070 was well tolerated in this study, with 94% of patients tolerating all induction and maintenance doses. There was no occurrence of grade IV or V treatment–related AEs in this study. The phase 1 study for CG0070 similarly demonstrated no Grade III to V treatment–related AEs [7]. Pharmacokinetic data demonstrated far higher levels of CG0070 genomes/mL in urine vs. serum, suggesting minimal systemic absorption. GM-CSF levels were previously demonstrated to similarly have far higher urine vs. serum expression [7]. The nontreatment–related toxicities (grade III/IV AEs and deaths) reported in this series reflect the significant comorbidities of the high-risk NMIBC population.

There were several limitations worth noting. First, as this is an interim analysis, the strength of the study was limited by relatively small sample size and short follow-up. Other trials for NMIBC have shown promising results at 3 to 6 months with more limited durability at 1 to 2 years. Owing to short follow-up, there was minimal data from cystectomy in patients with PD. Tissue staining was not available to assess for Rb status and PDL-1 expression, which would have further elucidated both mechanism of action of CG0070 and potential immune activation. AM was frequently administered off protocol in the trial, confounding assessment of an ideal instillation regimen. Finally, although the single-arm trial design was intentionally and carefully chosen, there is nevertheless no control arm in this trial for a notoriously heterogeneous population.

5. Conclusions

In summary, 6-month interim results from this phase II study reveal an overall CR rate of 47% in patients with high-risk BCG-unresponsive NMIBC. There was impressive 58% CR in patients with pure CIS and 50% CR for patients with CIS-containing tumors. Overall toxicity was acceptably low. Ongoing follow-up in this and other intravesical trials will be valuable for patients with BCG-unresponsive NMIBC.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.urolonc.2017.07.005.

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