Phase 3 Study of CG0070 in Patients With Non-Muscular Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus-Calmette-Guerin (BCG)

E. Uchio, MD, FACS, CPI[1], D. Lamm, MD, FACS[2], Neal Shore MD, FACS[3], Paul D. Anderson MBBS FRACS[4], Tran Ben MBBS, FRACP[5], Nicholas Gaspar PhD[6], Paola Grandi Ph.D[6], James Burke, MD[6]

[1]The University of California, Irvine, CA; [2]University of Arizona College of Medicine, Phoenix, AZ; [3]Atlantic Urology Clinics, Myrtle Beach, SC; [4]Royal Melbourne Hospital, Melbourne, Australia; [5]Peter MacCallum Cancer Centre, Melbourne, Australia; [6]CG Oncology, Inc. 400 Spectrum Center Drive, Suite 2040, Irvine, CA

Abstract

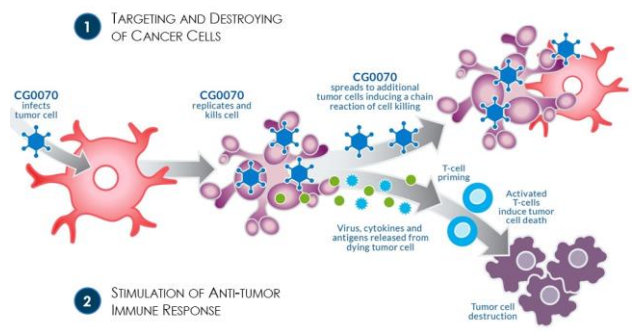
CG0070 is a serotype 5 adenovirus engineered to express GM-CSF and replicate in cells with mutated or deficient RB. A complete response rate (CR) at anytime of 62% has been observed for monotherapy in NMIBC after BCG failure (ref. 1, 2). This single arm phase 3 study was launched to confirm the clinical activity of monotherapy CG0070 in patients with NMIBC unresponsive to BCG.

110 patients with BCG-unresponsive CIS with or without concurrent Ta or T1 disease will be treated with intravesical (IVE) CG0070 at a dose of $1x10^{12}$ vp. CG0070 will be administered weekly x 6 as induction followed by weekly x 3 maintenance instillations at months 3, 6, 9, 12, and 18. Patients with persistent CIS or HG Ta at 3 months (m) may receive re-induction with weekly x 6 CG0070. Assessment of response will include q 3 m cystoscopy with biopsy of areas suspicious for disease, urine cytology, CTU/MRU, and mandatory bladder mapping at 12 m. Detection of high-grade disease within the bladder will be enumerated as recurrence or non-response.

The primary endpoint of the study is CR at anytime on study. Secondary endpoints will include CR at 12 m, duration of response, progression free survival, cystectomy free survival and safety. Correlative assessments will include changes in the tumor immune microenvironment, systemic immune induction as reflected in the peripheral blood and urine, as well as viral replication and transgene expression. Baseline expression of coxsackie adenovirus receptor, E2F transcription factor as well as anti-adenovirus antibody titer will be correlated with tumor response. The study is being conducted in the US, Japan, and APAC region.

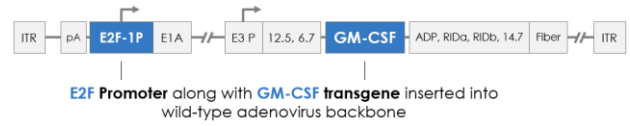
Oncolytic Immunotherapy

(1) Tumor-selective infection and replication of the virus, followed by cell killing, inducing local inflammation and trafficking of immune cells to the infected tumor site **(2)** Priming and amplification of systemic antitumor immunity, resulting in Induction of tumor-antigen-specific T cells that can eliminate uninfected tumor cells, including distant metastases.



CG0070

In CG0070, the human E2F-1 promoter drives expression of the essential viral genes and restricts viral replication to retinoblastoma (Rb) gene pathway defective tumor cells, selectively killing these cells with minimal damage to normal tissues. In addition, CG0070 encodes the cDNA for human GM-CSF expressed and secreted by tumor cells transduced with CG0070.



Gene / Protein	Function
E2F	In retinoblastoma (RB) pathway-defective cells, consistently found in human cancers, RB does not bind to E2F, leading to selective CG0070 viral replication in tumor cells, but not normal cells
E1A	Viral gene retains wild-type adenovirus lytic ability
GM-CSF	Instigates production of GM-CSF cytokines, danger signals that activate and matures antigen-presenting cells (the immune system) to fight cancer

Phase 1 Study for NMIBC (V0046)

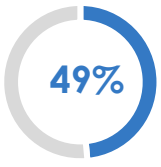
N = 35 NMIBC CIS or CIS with Ta/T1, and Ta or T1

Multi-dose (MD): $1x10^{12}$, $3x10^{12}$, $1x10^{13}$, $3x10^{13}$ viral particles/ml

Multi-schedule: Single dose (SD), Every 28 days, Weekly x 6

Objective: Dose-escalation trial of intravesical CG0070 for superficial transitional cell carcinoma of the bladder after BCG failure

3-Month Response



Overall CR: 17/35
Median Duration: 10.4 months

CR by Schedule

Schedule	CR
SD	23%
Every 28 Days	54%
Weekly x 6	78%
MD	64%
Total	49%

CR by Dose

Dose	CR
1×10^{12}	62%
3×10^{12}	44%
1×10^{13}	50%
3×10^{13}	0%

Phase 2 Study for NMIBC (BOND2)

N = 65 evaluable NMIBC CIS or CIS with Ta/T1, and Ta, or T1

Design: Single-arm, intravesical administration of CG0070

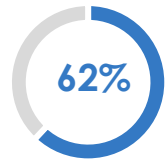
Regimen: Induction course = Weekly x 6 (1×10^{12} vp/mL)

Second induction course = Weekly x 6 at Month 3

Maintenance courses = Weekly x 6 at Month 6, every 6 months

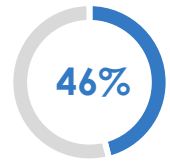
Primary Endpoint: Complete Response (CR)

CR at Any Time



Complete Response at any time

Duration of Response



CR Maintained in 46% of Responders at 12m

Adverse Event

Adverse Event
Most AEs: Transient Grade 1-2 urinary tract symptoms
Two related Grade 3 AEs, patients were able to complete treatment course
No related Grade 4 or 5 AEs

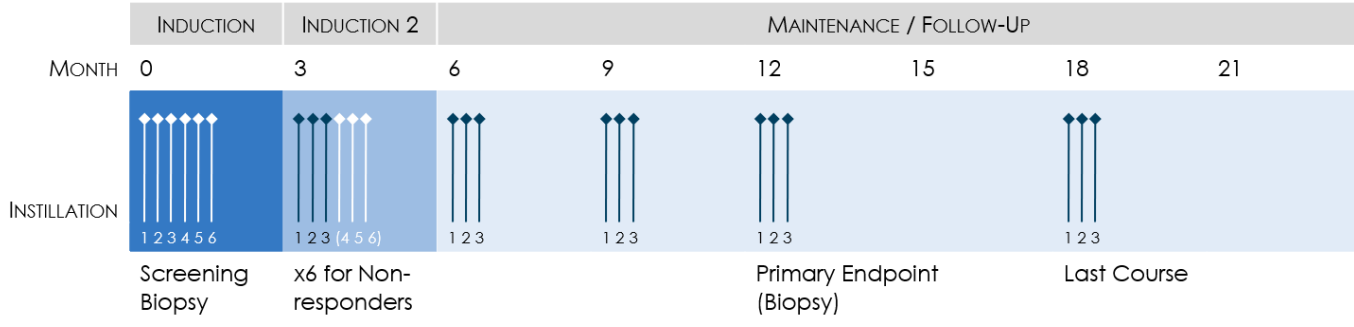
Phase 3 Study for NMIBC (BOND3)

N = 110 NMIBC CIS-containing **Trial Type**: Open Label **Design**: Single-arm, Intravesical Administration of CG0070

Regimen: Induction course = Weekly x 6 (1×10^{12} vp/mL) **Primary Endpoint**: Complete Response (CR) at any time

Second induction course[1] = Weekly x 6 (1×10^{12} vp/mL) for non-responders

Maintenance courses[2] = Weekly x 3 (1×10^{12} vp/mL) for complete responders



[1] Second induction course of weekly x 6 for non-responders at month 3

[2] Maintenance course for complete responders starts at month 3 every 3 months for 1st year, and every 6 months for 2nd year

Note: Patients undergo urine cytology and cystoscopy every 3 months for first 2 years; mandatory, site-directed biopsy at month 12

References. 1. Burke JM et al. *J Urol*. 2012;188:2391–7; 2. Packiam VT et al. *Urol. Oncol*. 2018;36(10):440–7)

CG ONCOLOGY