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

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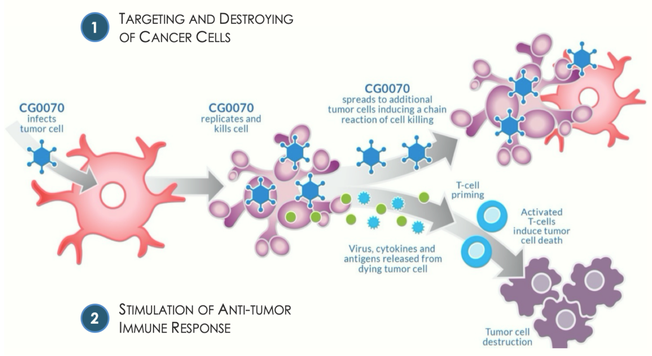
Overview

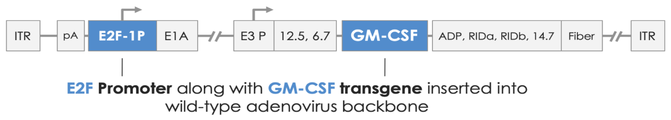
CG0070 is a serotype 5 adenovirus engineered to express GM-CSF and replicate in cells with mutated or deficient RB. A complete response rate (CR) at anytime of 62% has been observed for monotherapy in NMIBC after BCG failure. This single arm phase 3 study was launched to confirm the clinical activity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

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



E2F1	In Rb-pathway defective cells, Rb doesn't bind to E2F, leading to select replication of CG0070 in cancer cells
E1A	Essential viral gene
GM-CSF	Activator of Antigen Presenting Cells

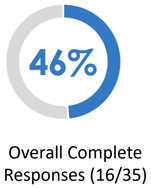
In CG0070, the human E2F-1 promoter drives expression of the essential viral genes and restricts viral replication to retinoblastoma (Rb) gene pathway defective tumor cells, selectively killing these cells with minimal damage to normal tissues. In addition, CG0070 encodes the cDNA for human GM-CSF expressed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

CG0070 in the Clinic

Phase 1 Study for NMIBC (V0046)

N = 35 NMIBC CIS or CIS with Ta/T1, and Ta or T1
Multi-dose: $1x10^{12}$, $3x10^{12}$, $1x10^{13}$, $3x10^{13}$ viral particles/ml
Multi-schedule: Single dose (SD), Every 28 days, Weekly x 6
Objective: Dose-escalation of intravesical CG0070 for superficial transitional cell carcinoma of the bladder after BCG failure

3-month Response



Overall Complete Responses (16/35)

CR by Schedule

Schedule	CR
Single dose	23%
Every 28 Days	54%
Weekly x 6	78%
Multi-dose	64%
Total	49%

CR by Dose

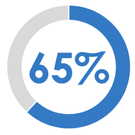
Dose	CR
1×10^{12}	62%
3×10^{12}	44%
1×10^{13}	50%
3×10^{13}	0%

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) rate

Positive CR Rate & Duration of Response (CIS-Containing)

CR Rate



CR at any time (30/46)

12-month response

CR maintained in 13/46 pts

Adverse Events

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

Phase 3 Study for NMIBC (BOND3)

Target population: 110 patients with BCG unresponsive NMIBC CIS with or without concurrent high grade Ta/T1 disease

Trial Type: Open Label, single arm, registration study

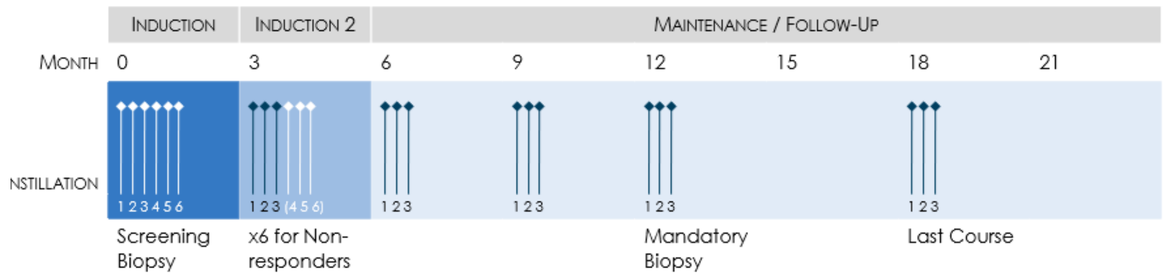
Regimen: Induction = CG0070 IVE Weekly x 6 (1×10^{12} vp/mL)
Second Induction [1] = Weekly x 6 (1×10^{12} vp/mL) for non-responders
Maintenance courses[2] = Weekly x 3 (1×10^{12} vp/mL) for complete responders

Primary Endpoint: CR at Any Time

Secondary Endpoints: CR at 12 m, DoR, PFS, cystectomy free survival and safety.

Correlative assessments: Immune induction (TME and systemic), viral replication, GM-CSF expression; and baseline CAR, E2F, and anti-Ad5 antibody quantification vs response

Study Administration Schedule:



[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

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