CORE1: Phase 2, Single Arm Study of CG0070 Combined with Pembrolizumab in Patients with Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG)

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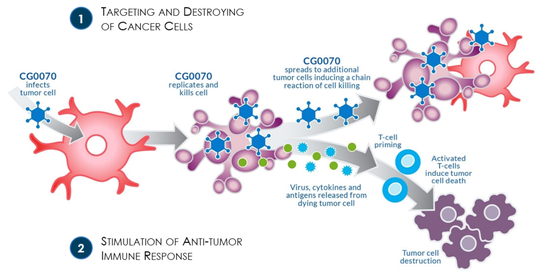
Overview

CG0070, an oncolytic vaccine available as an intravesical therapy, is a serotype 5 adenovirus engineered to express GM-CSF and replicate in tumor cells with mutated or deficient RB (which results in increased free levels of the transcription factor E2F). The CG0070 mechanism of action includes direct cell lysis in conjunction with immune mediated cell death which is enhanced in the presence of GM-CSF. In an initial phase 1 study as well as a subsequent open label phase 2 study, an overall CR rate of ~62% and a CR at 12 months (m) of 29% have been observed in patients with high risk NMIBC previously treated with BCG. Intravenous Pembrolizumab, a PD-1 checkpoint inhibitor, was recently approved by the FDA for patients with BCG-unresponsive CIS (with or without papillary tumors) with an overall complete RR of 41% and a 12 m CR rate of ~20%. This phase 2 study (NCT04387461) will assess the potential synergy of the two agents in the treatment of BCG-unresponsive NMIBC.

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

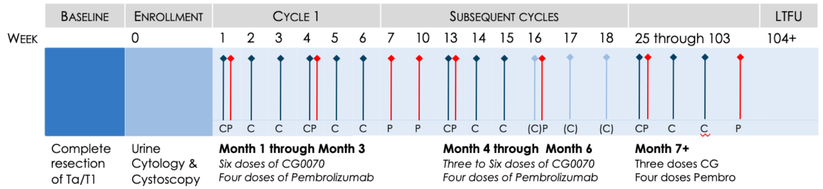
In CG0070, the human E2F-1 promoter drives expression of the essential viral genes and restricts viral replication to retinoblastoma (Rb) gene pathway defective tumor cells, selectively killing these cells with minimal damage to normal tissues. In addition, CG0070 encodes the cDNA for human GM-CSF expressed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

E2F Promoter along with **GM-CSF transgene** inserted into wild-type adenovirus backbone

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**

Phase 2 Study for NMIBC (CORE1)

Study Administration Schedule:



- 35 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 in combination with pembrolizumab at a dose of 400 mg IV q6 weeks.
- 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 m may receive re-induction with weekly x 6 CG0070.
- Pembrolizumab will be administered up to 24 m.
- Assessment of response will include q 3 m cystoscopy with biopsy of areas suspicious for disease, urine cytology, CTU/MRU, and mandatory bladder mapping biopsies at 12 m. Recurrence of HG disease will be enumerated as disease recurrence.

Study Endpoints

- The primary endpoint of the study is CR at 12 m.
- Secondary endpoints will include CR at any time, progression free survival, duration of response, cystectomy free survival and the safety of the combination.
- Exploratory endpoints will include:
  - Assessment of immune induction in the tumor, blood and urine
  - Investigation of viral infection, replication, and transgene expression
  - Baseline assessment of PD-L1, CAR, E2F transcription factor and anti-Ad5 antibody titers vs response

RESULTS

Efficacy

Patient	3-Mo Eval	6-Mo Eval	9-Mo Eval
1	**CR**	**CR**	**CR**
2	**CR**	**CR**	**CR**
3	**CR**	**CR**	**Not Yet Reached**
4	**CR**	**CR**	**Not Yet Reached**
5	**CR**	**CR**	**Not Yet Reached**
6	**CR**	**CR**	**Not Yet Reached**
7	**CR**	**Not yet Reached**	**Not yet Reached**

To date, all 7 (100%) patients evaluable for efficacy have achieved CR at the initial 3 month timepoint. Six of these 7 have also maintained a CR through 6 months and 2 at the 9 month assessment.

Treatment related AE were limited to transient grade 1-2 local genitourinary symptoms and irAE including urinary frequency (4 patients), bladder spasm (2), fatigue (2), chills, autoimmune thyroiditis, blood discharge, dysuria, and flu-like symptoms (1 patient each). No treatment-related grade 3 or higher AE or SAE have been observed.

Safety

Adverse Event	GRADE 1	GRADE 2	Total
Urinary frequency	3	1	4
Fatigue	2	-	2
Bladder spasm	1	1	2
Autoimmune thyroiditis	1	-	1
Bloody discharge	1	-	1
Catheter leakage	1	-	1
Chills	1	-	1
Flu like symptoms	1	-	1
Headache	1	-	1
Hematuria	1	-	1
Hypothyroidism	-	1	1
Joint Aches	1	-	1
Malaise	1	-	1
Nocturia	-	1	1
Painful urination	-	1	1
Urinary Tract Infection	-	1	1
Urinary urgency	1	-	1

Data Cut off Sept 30, 2021

CONCLUSIONS & FUTURE

Based on preliminary data, the combination of CG0070 and pembrolizumab for BCG unresponsive NMIBC has been well tolerated with encouraging early efficacy data. Patient enrollment and follow-up is ongoing with future data readout expected to include more mature safety and efficacy data as well as clinical correlates.

CG ONCOLOGY

This study was in collaboration with Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA