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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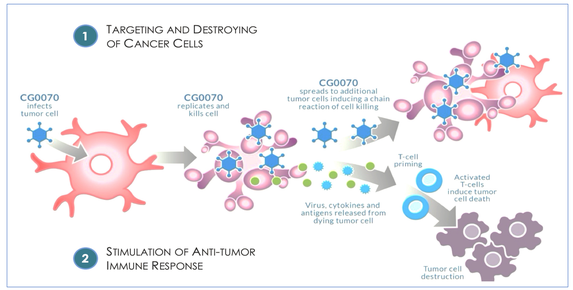
Overview

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

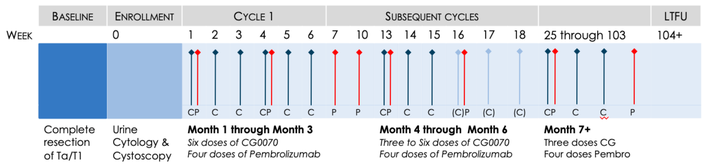
CG0070

Replication and transgene expression is controlled by the E2F promoter which has been inserted in place of the wild type E1a promoter sequence. In cells which have an aberrant retinoblastoma pathway, the E2F transcription factor is free to bind the promoter sequence and drive expression of the essential viral genes and restricts viral replication to retinoblastoma (RB1) 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.

E2F1	In Rib-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:



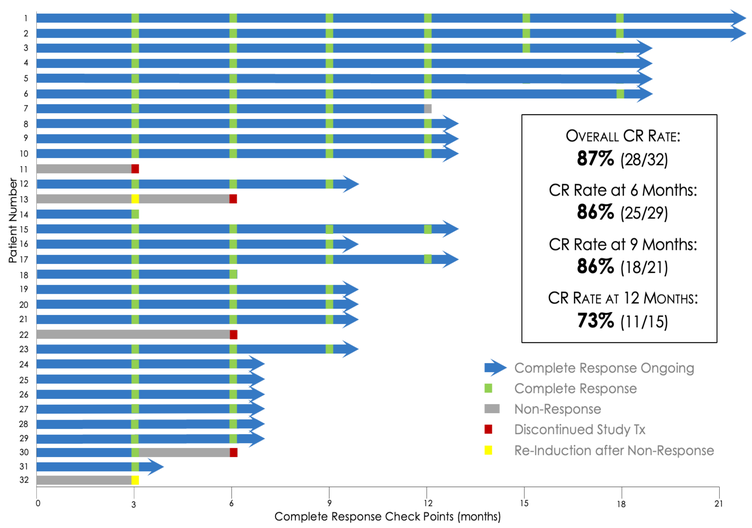
- 35 patients with BCG-unresponsive CIS with or without concurrent Ta or T1 disease will be treated with intravesical (IVE) CG0070 at a dose of $1x10^{12}$ up in combination with pembrolizumab at a dose of 400 mg IV q6 weeks.
- CG0070 will be administered weekly x 6 as induction followed by weekly x 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.

Key Objectives:

- 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.

RESULTS

EFFICACY: Preliminary Summary of Response



SAFETY: Adverse Events Related to Treatment *

Preferred Term	GRADE 1	GRADE 2	GRADE 3	Total
Bladder spasm	9	4		13
Fatigue	10	1		11
Pollakiuria	8	1		9
Dysuria	5	1		6
Urinary tract infection	4	1		5
Haematuria	3	1		4
Micturition urgency	2	2		4
Nocturia	4			4
Abdominal pain	3			3
Alanine aminotransferase increased	2	1		3
Aspartate aminotransferase increased	1	2		3
Diarrhoea	3			3
Headache	3			3
Hypothyroidism		3		3
Arthralgia	1	1		2
Blood creatinine increased	1	1		2
Chills	2			2
Joint stiffness	2			2
Myalgia	2			2
Polyuria	2			2
Pruritus	1	1		2
Urinary tract pain	2			2
Ejection fraction decreased			1	1
Immune-mediated hepatitis			1	1
Neutrophil count decreased			1	1
Data cut off. 03 Oct 2022				

*Most frequent grade 1-2 AE and all grade 3 or higher AE related to treatment

CONCLUSIONS

➢ The combination of CG0070 and pembrolizumab appears promising to date based on preliminary data showing efficacy beyond that observed in past studies for either agent alone in conjunction with a tolerable safety profile in line with the prior the adverse event profile reported for each agent as monotherapy. The enrollment has been completed. Data readout on all patients through a minimum of 12 months is expected in 2023 (clinical trial: NCT04387461).

This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

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