21-11060

CORE-001: 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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INTRODUCTION AND OBJECTIVE: CG0070, an oncolytic vaccine available as an intravesical therapy, is a serotype 5 adenovirus engineered to express GM-CSF and replicate selectively in tumor cells with mutated or deficient RB. 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 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 will assess the potential synergy of the two agents in the treatment of BCG-unresponsive NMIBC.

METHODS: 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 of 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.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. Correlate assessments will include changes in the tumor immune microenvironment, systemic immune induction reflected in the peripheral blood and urine, as well as viral replication and transgene expression. Baseline expression of PD-L1, coxsackie adenovirus receptor, E2F transcription factor as well as anti-adenovirus antibody titer will be correlated with tumor response.

RESULTS: At this time there have been 6 patients accrued to this study, of whom 5 are evaluable for 3 m CR and 6 for safety. Assessment of these 5 patients demonstrates 100% 3 m CR. Thus far, treatment related AE have been limited to transient grade 1-2 urinary frequency (3 patients) and grade 1 bladder spasm, hematuria, painful urination, thyroiditis, and flu-like symptoms (one patient each). No grade 3, 4, or 5 AE or SAE were observed.

CONCLUSIONS: Based on preliminary data, the combination of CG0070 and pembrolizumab for BCG unresponsive NMIBC has been well tolerated with encouraging early efficacy at 3 m. At the time of presentation, safety and efficacy results will be further updated.

Source of Funding: CG Oncology