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Clinical Trials Corner

Dear Readers,

In this issue, we highlight two recent trials that have reported phase II results and have initiated plans for phase III trials. These agents are among the furthest developed and studied for BCG unresponsive high grade non-muscle invasive bladder cancer (NMIBC). Mechanistically, both are forms of gene therapy delivered with modified adenoviruses. In the future, if you feel that you would like to draw attention to a specific trial, please feel free to email us at: piyush.agarwal@nih.gov or cns9006@med.cornell.edu and/or at BLC@iospress.com.

Sincerely,

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Study Title: An Open Label, Single Arm, Phase II, Multicenter Study of the Safety and Efficacy of CG0070 Oncolytic Vector Regimen in Patients With Non-Muscle Invasive Bladder Carcinoma Who Have Failed BCG Therapy and Refused Cystectomy

Clinicaltrials.gov identifier: NCT02365818

Sponsor: Cold Genesys, Inc.

Enrollment: 66

Rationale: CG0070 is a replication-competent oncolytic adenovirus that selectively replicates in retinoblastoma (Rb) pathway-defective cells that are often present in bladder cancer. The adenovirus also contains a transgene for granulocyte-macrophage colony-stimulating factor (GM-CSF), a cytokine that can active the immune system. CG0070 works by 2 major mechanisms: 1) induction of tumor lysis by selective replication in Rb-deficient tumor cells and 2) local GM-CSF production that augments immunogenic cell death.

Study Design: The Phase II single-arm multicenter trial targeted BCG unresponsive high-grade NMIBC patients who refused radical cystectomy. In the reported trial, interim results were published in 45 patients treated on the trial with at least 6 months of follow-up.

Endpoints: The primary endpoint was 6-month complete response (CR) rate defined by absence of disease on cystoscopy, cytology, and random biopsies.

Results: The disease characteristics of the 45 patients consisted of 24 pure CIS, 8 CIS + Ta, 4 CIS + T1, 6 Ta, and 3 T1. The overall 6-month complete response (CR) rate was 47% for all patients. CR was highest in pure CIS patients at 58% and lowest in pure Ta/T1 patients at 33%. Of note, none of the 3 pure T1 patients had a CR at 6 months and one patient (with Ta and T1 disease) progressed to muscle invasion. The most common

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treatment-related adverse events (AEs) were bladder spasms (36%), hematuria (28%), and dysuria (25%). However, none of the patients experienced grade 4-5 AEs.

Comments: This trial is limited for many reasons including small numbers of patients, an interim analysis, and no comparison a control group given the heterogeneity of this disease and the multiple pathologic cohorts. Nevertheless, important takeaways from this interim analysis are that 1) CIS tumor respond best to this therapy and 2) pure T1 patients should be followed closely and counseled extensively on the need for early cystectomy. Finally, with an explosion of clinical trials in BCG unresponsive high grade NMIBC, it is important to remember that there is a real, albeit low risk of progression to muscle invasion.

Study Title: A Phase 2, Randomized, Open Label, Parallel Arm Study to Evaluate the Safety and Efficacy of rAd-IFN/Syn3 Following Intravesical Administration in Subjects With High Grade, BCG Refractory or Relapsed Superficial Bladder Cancer

Clinicaltrials.gov identifier: NCT01687244

Sponsor: FKD Therapies Oy

Enrollment: 40

Rationale: Instiladrin is a non-replicating recombinant adenovirus vector containing the human interferon alpha-2b gene. It is administered intravesically and serves as a gene transfer vector and is formulated with Syn3, a polyamide surfactant that enhances the adenoviral transduction of the bladder lining. This allows for more reliable viral transduction of the IFNα-2b gene and ultimately production of IFNα-2b in the bladder. IFNα-2b is believed to be a key early cytokine in the immune response initiated by BCG and Instiladrin allows for more reliable production of this cytokine.

Study Design: This was a Phase II multicenter study targeting BCG unresponsive high grade NMIBC patients and refused to undergo radical cystectomy were randomized to one of two different Instiladrin viral particle dosages for their disease. The patients received treatments every 3 months for a total of 4 treatments if they continued to respond to therapy without a recurrence.

Endpoints: The primary endpoint was freedom from high grade recurrence-free survival (RFS) at 12 months defined by negative bladder biopsies.

Results: The disease states of the 40 patients consisted of 21 pure CIS, 4 CIS + Ta, 5 CIS + T1, 4 Ta, and 6 T1. Overall, the 12-month high grade RFS was 35% and was comparable between the two groups that only differed in the number of viral particles received. RFS at 12 months was highest in Ta or T1 patients at 50% and lowest in pure CIS patients at 29%. On long-term follow-up, seven patients who recurred with disease on the trial died within a median of 16 months. Although none of the deaths was thought to be treatment-related, at least two of the deaths were due to disease progression. The most common treated-related adverse events (AEs) were urgency (40%), dysuria (40%), and fatigue (33%). However, none of the patients experienced grade 4-5 AEs.

Comments: This trial is limited for many reasons including the small number of patients and the lack of a comparison control group given the heterogeneity of this disease and the multiple pathologic cohorts. Interestingly, the RFS was least in the pure CIS patients at 12 months which is unfortunate since CIS that no longer responds to BCG some is among the most difficult to treat.. Furthermore, without a comparison control group, it is unknown if the high RFS seen at 12 months in Ta or T1 disease was due to the Instiladrin or to the resection of disease. However, it was tolerable and the phase III trial has already been completed and so results are eagerly anticipated.

CONFLICTS OF INTEREST

Conflicts of interest can be found under Board Disclosures on the website: https://www.bladdercancerjournal.com/board-disclosures.