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Abstract CT203: Fc-optimized anti-CD40 agonist antibody 2141-V11 for BCG-unresponsive non-muscle invasive bladder cancer: Updates on phase 1 study clinical outcomes and biological correlatives FREE

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Abstract

Introduction and Objectives:

2141-V11 is a novel anti-CD40 antibody developed by our group, with enhanced binding to FcγRIIB that results in effective tumor-specific T-cell responses *in vivo* and in a recent first-in-human phase I clinical trial (NCT04059588). In several preclinical bladder cancer models, including BCG-unresponsive disease, intravesical administration of 2141-V11 results in durable anti-tumor immunity without systemic toxicity. Based on these findings, we initiated a first in human Phase I/II study of intravesical 2141-V11 for the treatment of BCG-unresponsive NMIBC.

Methods:

This is an investigator-initiated Phase I, open-label, dose-escalation study to evaluate the safety and tolerability of intravesical 2141-V11 in patients with BCG-unresponsive NMIBC who are ineligible for or decline radical cystectomy (NCT05126472) (N=25). Following complete transurethral resection, intravesical 2141-V11 is administered once weekly for three doses with re-treatment eligibility at week 13 and 25, depending on disease status. Dose escalation follows an MCRM design (5 dose levels from 0.7 to 70 mg). The primary endpoints are safety and dose tolerability to determine maximal tolerated dose (MTD) and/or RP2D. Secondary endpoints include pharmacokinetic profiling and preliminary evaluation of clinical activity. Exploratory objectives include investigation biological markers of drug activity in tissue and urine biospecimens.

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Results:

Full enrollment (n= 25) was achieved by the data cutoff of December 28th, 2024. Patients included had carcinoma in situ (CIS) with or without TA/T1 (N=18) or TA/T1 without CIS (N=7). Intravesical 2141-V11 was well tolerated (no grade ≥3 events) with no dose-limiting toxicities up to the highest tested dose of 70mg of drug. MTD was not reached. Complete response (CR) was achieved in 10 (41.7%) out of 25 patients. Among 19 evaluable patients at six months, 7 (37%) achieved CR at 6 months, with final therapeutic analysis pending completion of follow up. At baseline, no significant differences were observed in the absolute counts of major immune cell populations (CD8+ T cells, CD4+ T cell, B cells, dendritic cells[DC], Tregs) between responders and non-responders. Post-treatment, responders exhibited increased interactions between DCs and specific CD8+ T cell subsets, including activated, cytotoxic, and CXCL13+ CD8+ T cells. In contrast, these interactions significantly decreased in non-responders. Tertiary lymphoid structures (TLS) were present in both responders and non-responders at baseline. However, responders showed an increase in TLS upon treatment with 2141-V11, while TLS numbers decreased in non-responders.

Conclusions:

In patients with BCG-unresponsive NMIBC, intravesical administration of 2141-V11 is safe and leads to CR in a subset of patients. 2141-V11 promotes immune interactions among dendritic cells and distinct subsets of CD8+ T cells and is associated with increased presence of TLS in clinical responders. These findings provide biological rationale for further evaluation of this agent in the treatment of NMIBC.

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