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First-in-Human Study of RAG-01, a Novel Small Activating RNA Therapeutic in BCG Failure Non-Muscle Invasive Bladder Cancer (NMIBC) Patients

Topic: Urothelial Cancer
Sub topic: NMIBC
Clinical step: Treatment
Management tool: Intravesical Therapy

Presentation mode
Abstract presentation

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Introduction & Objectives

Targeting the $p21^{WAF1/CIP1}$ (p21) gene represents a promising yet challenging therapeutic strategy in cancer treatment. p21, a critical cell cycle inhibitor with significant tumor suppressive potential, has remained largely "undruggable" for conventional modalities. RAG-01 introduces a novel approach using small activating RNA (saRNA) technology to directly upregulate p21 gene expression at the transcriptional level via the RNAa mechanism. This is a first-in-human clinical trial of a saRNA targeting p21, in patients with NMIBC to establish a potential novel therapeutic paradigm in cancer treatment by activating tumor suppressor genes. This open-label, multicenter, phase I study (NCT06351904) is designed to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of intravesical RAG-01 in patients with NMIBC who have failed Bacillus Calmette Guérin (BCG) therapy.

Materials & Methods

BCG failure patients will receive RAG-01 at escalating doses (30 mg, 100 mg, 300 mg, and 600 mg). For dose expansion, BCG-unresponsive patients will be randomized in a 1:1 ratio into 2 groups to receive 2 dose levels selected based on the data from dose escalation. RAG-01 treatment consists of a 6-week induction course (weekly instillations) followed by maintenance of 3 weekly instillations at weeks 12, 24, 36, 48, and 72. Patients with persistent carcinoma in situ (CIS) or high-grade Ta at 12 weeks may receive a 6-week re-induction. Assessments of response include cystoscopy every 12 weeks with biopsy of suspicious lesions or mandatory bladder mapping for CIS, urine cytology, and imaging. p21 protein induction will be assessed via IHC in urothelial cells and tumor tissues.

Results

As of Dec 15, 2024, 9 patients were enrolled across 3 dose-escalation cohorts (30-300 mg). Dose escalation is ongoing, and no dose-limiting toxicities (DLTs) have occurred. Adverse events (AEs), all grade ≤2, were reported in 8 patients (88.9%, 8/9). The most frequently reported AEs included urinary urgency (11.1%, 1/9), increased urinary frequency (11.1%), urinary tract infection (11.1%), dyspnea (11.1%), lethargy (11.1%), nausea (11.1%), and decreased appetite (11.1%). RAG-01 showed minimal systemic exposure with a dose-dependent maximum urine concentration (83.3-1,820 µg/ml at 2 hours) and urine $AUC_{0\text{-}24h}$. A dose-dependent increase in p21-positive urothelial cells was observed. Preliminary efficacy analysis revealed a 66.7% (2/3) complete response rate for CIS at any time and a 66.7% (2/3) disease-free survival rate for papillary tumors at 3 months.

Conclusions

Intravesical RAG-01 demonstrated a favorable safety profile. Dose-dependent p21 protein induction in urothelial cells confirmed target engagement. Preliminary anti-tumor efficacy supports further clinical investigation of this saRNA as a novel therapeutic approach for NMIBC.