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Development and Clinical Progress of RAG-01, a Novel saRNA Targeting p21 for Non-Muscle Invasive Bladder Cancer Treatment

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Abstract

Background: Bladder cancer ranks as the ninth leading cause of cancer-related deaths globally, with approximately 75% of all new diagnoses classified as non-muscle invasive bladder cancer (NMIBC). Standard-of-care includes transurethral resection of bladder tumors followed by intravesical installation of Bacillus Calmette-Guerin (BCG); yet 50-70% of these cases fail within five years. The loss of tumor suppressor genes, particularly disruptions in the p53-p21WAF1/CIP1 (p21) pathway, is a primary driver of tumorigenesis. Small activating RNA (saRNA) offers an innovative therapeutic approach that targets and activates endogenous genes via RNA activation. RAG-01, an saRNA conjugated to a lipid, is designed to restore p21 expression, thereby reactivating the p53-p21 axis and inhibiting tumor growth.

In vitro analyses demonstrated that RAG-01 activated p21 expression approximately 6-fold and inhibited bladder cancer cell growth via arresting cell cycle, inducing apoptosis and senescence in a dose-dependent manner with low nanomolar potency. Intravesical administration of RAG-01 (3 times per week for 2 weeks) inhibited the growth of orthotopic tumors by 73% in mouse bladder models. Single-dose pharmacokinetic study of RAG-01 revealed it has a half-life (t1/2) of ~115 hours with minimal systemic exposure (approximately 0.5% relative to bladder tissue). These data provide a preclinical proof-of-concept for saRNA as a novel p21-targeting modality in the treatment of bladder cancer.

Encouraged by these preclinical results, a first-in-human study of RAG-01 (NCT06351904) was initiated. This open-label, dose-escalation, multi-center Phase I study evaluates the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of RAG-01 in NMIBC patients who have failed BCG therapy. The trial employs a 3+3 dose-escalation protocol with doses ranging from 30-600 mg. As of July 31, 2024, six patients across two cohorts have been enrolled without reporting any dose-limiting toxicities or severe adverse events.

Conclusions: The development and clinical progress of RAG-01 suggest it could be a promising therapeutic option for NMIBC, supported by strong preclinical evidence. Further clinical evaluation is needed to confirm its potential impact on treatment outcomes for this condition.