SECN-15: A neuropilin-1-targeting antisense oligonucleotide overcomes checkpoint inhibitor resistance through remodeling of the tumor microenvironment

Julia Festag1 , Anne Sadewasser1 , Sven Michel1 , Monika Schell1 , Janani Sekar1 , Stefanie Raith1 , Konstantin Petropoulos1 , Frank Jaschinski1 , Richard Klar1 1Secarna Pharmaceuticals GmbH & Co. KG, Planegg, Germany Background: SECN-15 is a high-affinity locked nucleic acid-modified antisense oligonucleotide designed to selectively downregulate Neuropilin-1 (NRP1), a multifunctional co-receptor promoting tumor progression through immune suppression and neoangiogenesis. High NRP1 expression and activation of NRP1-dependent pathways correlate with poor prognosis and immune checkpoint inhibitor resistance in gastric cancer and other solid tumors, supporting NRP1 as a therapeutic target to overcome resistance to immune checkpoint blockade. Method: NRP1-specific ASOs were identified using Secarna's OligoCreator platform and characterized for efficacy and safety in vitro and in vivo. Anti-tumor efficacy was assessed as monotherapy and in combination with PD-1 blockade in syngeneic mouse tumor models. Single-nucleus and bulk RNA sequencing were used to assess NRP1 knockdown and treatment-induced remodeling of the tumor microenvironment. Soluble NRP1 was monitored as a pharmacodynamic biomarker. Public single-cell and bulk RNA-seq datasets from solid tumors were analyzed to validate indications for NRP1-targeted therapy. Results: The SECN-15 mouse surrogate achieved sustained NRP1 knockdown in tumors across multiple tested dosing schedules. As monotherapy, SECN-15 mouse surrogate induced complete tumor regressions in ~20% of animals, while combination therapy with anti-PD-1 achieved complete responses in ~70% of animals. Single-nucleus RNA sequencing revealed that NRP1 knockdown reprograms tumor endothelial cells from an angiogenic to an immune-permissive, interferonresponsive state, accompanied by markedly reduced vascularization and increased intratumoral T cell and B cell infiltration. Soluble NRP1 in plasma served as a robust target-engagement biomarker, with sustained reduction for over six weeks. NRP1 expression correlates with immunosuppressive and tumor-promoting pathways across multiple solid tumors beyond gastric cancer, supporting broad clinical development. Conclusion: SECN-15 represents a promising immunotherapeutic strategy that overcomes checkpoint inhibitor resistance through NRP1-knockdown-mediated remodeling of the tumor microenvironment. These findings support clinical evaluation of SECN-15 as monotherapy and in combination with PD-1 blockade in gastric cancer and other solid tumors, with IND-enabling studies underway.