

Nested Therapeutics Presents First Preclinical Data for Lead Candidate, NST-628, a RAS/MAPK Pathway Inhibitor at 2023 AACR-NCI-EORTC Conference

NST-628 demonstrates superior anti-cancer activity in animal models for multiple tumor types and potential for daily dosing

NST-628 broadly penetrates the CNS in animal models

NST-628 robustly and durably decreases RAS/MAPK pathway reactivation

IND filing expected in first half of 2024

Cambridge, Mass., October 12, 2023 – Nested Therapeutics, a biotechnology company pioneering a next-generation precision medicine platform to address hard-to-treat cancers, today presented the first preclinical data from its lead candidate, NST-628, a mechanistically novel non-degrading molecular glue that targets multiple nodes in the RAS/MAPK pathway, outlined in three poster presentations at the 2023 AACR-NCI-EORTC International Conference taking place in Boston, Massachusetts from October 11-15, 2023.

NST-628 outperformed other MAPK-targeted compounds administered as either single agents or combinations in anti-tumor activity and tolerability. Additionally, NST-628 effectively crossed the blood-brain barrier, suggesting a potential advantage for the treatment of brain metastases and primary CNS malignancies with MAPK pathway alterations.

“Taken together, these superior preclinical data suggest that NST-628 could offer a potential first-in-class treatment in the current RAS/MAPK inhibitor space, supporting its advancement into first-in-human clinical trials,” said Darrin Miles, Chief Executive Officer of Nested Therapeutics. “We understand the need to bring more effective treatment options that have the ability to overcome the intrinsic mechanisms that tumor cells evolve to become resistant to cancer therapies, and we look forward to initiating our Phase 1 study in patients in the first half of 2024.”

NST-628 is being developed through a robust biophysical and cellular characterization to leverage proprietary structural insights of how signaling complexes form and function in cancer. The compound acts through a defined mechanism of action that could address common pitfalls of other MAPK-targeted compounds, which remain unable to circumvent the risk of intrinsic resistance via signaling pathway reactivation.

Key takeaways from the posters are as follows:

NST-628 is a novel molecular glue that inhibits signaling and pathway reactivation in oncogenic RAS-MAPK cancers (Abstract Number: A086)

- NST-628 bound to CRAF-MEK, BRAF-MEK, ARAF-MEK complexes were structurally characterized using x-ray crystallography and cryogenic electron microscopy (cryo-EM). Increased stabilization of the CRAF-MEK complex by NST-628 was observed and may contribute to the decreased pathway reactivation in specific biomarker-driven tumors.

NST-628 is a potent, best-in-class MAPK pathway molecular glue that inhibits RAS- and RAF-driven cancers (Abstract Number: A088)

- NST-628 demonstrated strong efficacy and tolerability across multiple tumor types with RAS-MAPK alterations, including melanoma, lung, and pancreatic animal models.
- The predicted effective human half-life is amenable to daily dosing in the clinic, supporting best-in-class potential for NST-628.

NST-628 is a potent, fully brain-penetrant, RAS/MAPK pathway molecular glue inhibitor with efficacy in CNS tumor models (Abstract Number: A089)

- Currently approved inhibitors of the RAS-MAPK pathway have limited CNS exposure, and NST-628 demonstrates full CNS permeability far higher than trametinib or VS-6766.
- NST-628 leads to dose-dependent inhibition of the MAPK pathway in murine brain tissue, along with tumor regressions observed with a daily dosing regimen.

Nested Therapeutics plans to submit an IND for NST-628 following completion of ongoing preclinical and IND-enabling studies, to support first-in-human studies to start in the first half of 2024.

About DeCRYPTion Platform

Nested Therapeutics' DeCRYPTion Platform is a purpose-built, insightful drug discovery platform that enables Nested to identify new, overlooked areas of opportunity in the form of high value targets and design therapeutics for a perfect fit. The platform includes three critical components: (1) mapping mutational clusters onto the structural proteome, (2) identifying druggable pockets and cancer-driving mechanisms, and (3) designing novel drugs optimized for the druggable pocket.

About Nested Therapeutics

Nested Therapeutics is a biotechnology company focused on discovering and developing novel, targeted, small molecule precision medicine therapies for patients with cancer by using mutation clusters to identify druggable pockets. With a platform that utilizes insights from genomics, computational chemistry, proteomics, and AI, Nested is working to reach untapped mutations with the potential to improve outcomes for millions of patients. To learn more, visit www.nestedtx.com and follow Nested Therapeutics on Twitter (@Nestedtx) and LinkedIn.



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