Nested Therapeutics Announces Oral Presentation of Preclinical Data for NST-628, a Novel, Fully Brain-Penetrant, Pan-RAF/MEK Molecular Glue, at the 2024 AACR Annual Meeting

Concurrent publication in the journal Cancer Discovery *highlights NST-628's differentiated mechanism and preclinical activity across diverse KRAS-, NRAS-, and BRAF-driven tumors*

Phase 1 study of NST-628 open and enrolling patients with advanced solid tumors; Company expects to initiate dosing imminently

San Diego, Calif., April 8, 2024 – Nested Therapeutics, a biotechnology company pioneering a next-generation precision medicine platform to address hard-to-treat cancers, today announced that preclinical data for the company's lead program, NST-628, were featured in an oral presentation in the "New Drugs on the Horizon" series at the American Association for Cancer Research (AACR) Annual Meeting. The presentation, titled "NST-628 is a Novel, Potent, Fully Brain-Penetrant MAPK Pathway Molecular Glue that Inhibits RAS- and RAF-Driven Cancers," was given by Klaus Hoeflich, Ph.D., chief scientific officer and co-founder of Nested. The data were published concurrently online in the journal *Cancer Discovery*.

"Dysregulation of RAS-MAPK pathway signaling is one of the most frequently occurring events in tumor development, impacting one in three newly diagnosed patients in the U.S. every year, the vast majority having no approved targeted treatment alternatives. While therapies have been developed for every node of the pathway, tolerability and durability of response continue to be challenging for patients with these difficult-to-treat cancers," said Dr. Hoeflich. "NST-628 was developed as a fully brain-penetrant, non-degrading molecular glue targeting the RAF and MEK nodes of the RAS-MAPK pathway. The preclinical data presented at AACR show that NST-628 induces broad efficacy in tumor models and demonstrated the potential to overcome limitations of existing MEK and RAF inhibitors and RAS inhibitors in development. With a half-life and metabolic profile optimized to achieve a superior therapeutic index on a daily dosing schedule, as well as full intrinsic blood brain barrier penetrance, these data support NST-628's potential as a best-in-class treatment for RAS- and RAF-driven cancers."

Preclinical data presented at AACR and published in *Cancer Discovery* highlight the differentiated mechanism and drug-like properties of NST-628. Specifically:

- In cellular and patient-derived tumor models harboring diverse KRAS, NRAS and BRAF alterations, NST-628 induced potent, deep and durable inhibition of the RAF-MEK signaling complex with broad efficacy without sacrificing tolerability at clinically achievable exposures over other MAPK-targeted compounds administered as either single agents or combinations.
- With a predicted clinical half-life of 10-12 hours, the pharmacokinetic and metabolic profile of NST-628 has been optimized to broaden the therapeutic window and be clinically efficacious with once-daily oral dosing.
- In mouse models with an intact blood brain barrier as well as central nervous system (CNS) models with RAS-MAPK alterations, NST-628 demonstrated full intrinsic CNS permeability. These data suggest NST-628 has the potential to treat brain metastases and primary CNS malignancies with MAPK pathway alterations. Approximately 40% of

patients with metastatic cancer will develop symptomatic brain metastases, in particular in RAS-MAPK pathway dysregulated tumors such as lung, breast and melanoma.
- Good laboratory practices (GLP) toxicology studies demonstrate significantly improved exposure margins when compared to other MEK inhibitors in non-clinical species.
- Preclinical data support NST-628 as an ideal combination partner for upstream inhibitors including KRAS inhibitors by effectively *preventing pathway reactivation*.
- In totality, the data validate NST-628's potential to provide transformative clinical benefit as both a monotherapy or vertical combination anchor.

About the Phase 1 Study of NST-628
The ongoing Phase 1 open-label, single-arm, two-part study (NCT06326411) is intended to investigate the safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary efficacy of single agent NST-628 in adult patients with RAS-MAPK pathway mutated/dependent advanced solid tumors, especially diverse KRAS, NRAS and BRAF alternations, who have exhausted standard treatment options. The study includes two parts: dose escalation (Part A) followed by dose expansion (Part B). The primary objectives for Part A, which recently initiated, are delineating NST-628's safety profile and establishing the recommended dose for Part B. For more information, visit clinicaltrials.gov.

About NST-628
NST-628 is a fully brain-penetrant, mechanistically novel non-degrading molecular glue that targets multiple nodes in the RAS/MAPK pathway. NST-628 was developed based on Nested's proprietary structural insights of how signaling complexes form and function in cancer and addresses common pitfalls of other MAPK-targeted compounds, which remain unable to circumvent the risk of intrinsic resistance via signaling pathway reactivation. Preclinical data evaluating oncology biomarkers relevant to RAS/MAPK-driven cell and patient-derived models collectively demonstrate superior anti-tumor activity, including in RAS and central nervous system-implanted tumor models, and tolerability of NST-628 compared to other MAPK-targeted compounds administered as either single agents or in combination. With a half-life and metabolic profile optimized to achieve a superior therapeutic index on a daily dosing schedule, as well as full intrinsic blood brain barrier penetrance, these data support NST-628's potential as a best-in-class treatment especially for KRAS, NRAS and BRAF-driven cancers.

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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