Nested Therapeutics Reports Initial Encouraging Clinical Activity and Favorable Tolerability of NST-628, a Brain-Penetrant Pan-RAF/MEK Molecular Glue, at AACR 2026

38% response rate and 85% disease control rate at recommended dose in advanced/metastatic NRAS and BRAF Class II/III melanoma following failure of standard therapy

Responses observed across multiple RAS/MAPK-driven tumors with early evidence of CNS activity

Approximately 8,000 NRAS and BRAF Class II/III melanoma patients diagnosed each year in the U.S. with no approved targeted therapies following treatment with immune checkpoint inhibitors

Cambridge, Mass., April 17, 2026 – Nested Therapeutics, a clinical-stage oncology company developing transformative therapies for RAS/MAPK-driven disorders, today reported initial clinical results from its ongoing Phase 1 study evaluating NST-628, a brain-penetrant non-degrading pan-RAF/MEK molecular glue, in patients with advanced solid tumors. Data presented at the AACR Annual Meeting 2026 demonstrate encouraging single-agent anti-tumor activity and a favorable tolerability profile in a range of RAF and RAS-mutant tumors, including a 38% response rate and 85% disease control rate at the recommended dose in heavily pretreated NRAS and BRAF Class II/III melanoma, a population that represents approximately 33% of cutaneous melanoma patients, for whom no approved targeted therapies are available.

"These initial data support our hypothesis that targeting RAF/MEK signaling with a single-agent, fully brain-penetrant pan-RAF/MEK molecular glue can deliver meaningful clinical benefit with a tolerability profile that supports sustained dosing even in comparison to what may be expected from combination regimens," said Darrin Miles, Chief Executive Officer of Nested Therapeutics. "We are particularly encouraged by the durable responses in NRAS and BRAF Class II/III melanoma – large patient populations with historically poorer outcomes and for whom there are no approved targeted therapy options – as well as early signals of clinical activity beyond melanoma, including in KRAS-mutant solid tumors and evidence of brain penetrance. Together, these clinical findings, in addition to robust preclinical evidence and favorable drug properties, support the potential for NST-628 to address significant unmet need across RAS/MAPK-driven cancers and to serve as a foundational therapy in both monotherapy and combination settings."

Key Data Highlights

As of the data cutoff date of February 1, 2026, NST-628 has been administered to 69 patients: 64 patients in dose-escalation and 5 patients in the expansion phase. Key findings are summarized below.

Monotherapy Clinical Activity in evaluable patients (with at least one tumor assessment or who discontinued the study) at Recommended Dose for Expansion (RDE)

- NST-628 monotherapy demonstrated a 38% response rate in BRAF Class II/III and NRAS-mutant melanoma (N=13) and 33% response rate overall (N=18); response rates include one unconfirmed partial response
- Disease control rate was 85% in the melanoma subgroup and 72% overall
- With a median follow-up of 6.4 months, the median duration of response in melanoma was not yet reached

Anti-Tumor Activity Beyond Melanoma

- Responses to NST-628 were observed across multiple tumor types and genotypes, including KRAS-mutant ovarian and cervical cancers – highlighted by an ongoing partial response in a KRAS G12V-mutant cervical cancer patient with a treatment duration exceeding one year – as well as NRAS/BRAF Class III-mutant colorectal cancer and BRAF Class II-mutant thymic cancer
- A patient with high-grade astrocytoma (BRAF V600E), previously treated with multiple lines of RAF/MEK-targeted therapy, demonstrated 70% tumor shrinkage on NST-628 monotherapy, consistent with NST-628's preclinical brain penetration profile
- Reductions in ctDNA correlated with radiographic response

Safety and Tolerability

- Adverse events were consistent with the mechanism of action and predominantly Grade 1-2
- Most common treatment-related adverse events included dermatologic, gastrointestinal, CK elevation, constitutional, and ocular events
- Grade ≥3 TRAEs were infrequent; most common was CK elevation
- No Grade 5 events reported
- At the RDE:
    - Discontinuation rate: 9%
    - Dose intensity (actual dose delivered vs. intended): 82%

"The anti-tumor activity observed with NST-628 monotherapy is encouraging," said Philip Komarnitsky, MD, PhD, Chief Medical Officer of Nested Therapeutics. "A safety profile that supports continuous dosing at 82% dose intensity with a 9% discontinuation rate, combined with the response rate of 38% and disease control rate of 85% in NRAS and BRAF Class II/III melanoma patients at the recommended dose, is promising for this patient population with no approved targeted therapies. The clinical evidence of activity in malignancies with BRAF class III mutations, an emerging resistance mechanism to RAS inhibitors, and of brain penetrance

consistent with preclinical findings is particularly noteworthy. These data support the continued development of NST-628 as monotherapy and its evaluation in rational combinations."

Nested plans to continue enrollment in the ongoing Phase 1 expansion cohort and evaluate NST-628 in additional malignant and non-malignant MAPK-driven diseases and combination settings, including mutant-selective RAS and other inhibitors.

Poster Presentation Details

Title: Preliminary results from a Phase 1a/b dose-escalation and expansion trial of the pan-RAF-MEK molecular glue NST-628 in patients (pts) with advanced or refractory RAF, KRAS, and NRAS-mutant solid tumors

Presenter: Ahmad A. Tarhini, MD, PhD, Moffitt Cancer Center

Presentation Date and Time: Monday, April 20, 2026, 2:00 PM-5:00 PM PT

Session: PO.CT01.01 - Phase 0 and First-in-Human Phase I Clinical Trials

Location: Section 51

About the Phase 1 Study of NST-628, NST-628-001

The ongoing Phase 1 open-label, single-arm, two-part study (NCT06326411) is investigating 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 alterations, who have exhausted standard treatment options. The study includes two parts: dose escalation (Part A), which enrolled 64 patients across seven dose regimens, followed by dose expansion (Part B) at the recommended dose for expansion. Part B is currently enrolling. For more information, visit clinicaltrials.gov.

About NST-628

NST-628 is a brain-penetrant, non-degrading molecular glue designed to inhibit RAF and MEK signaling by stabilizing RAF-MEK complexes in a catalytically inactive form. This mechanism is intended to prevent pathway reactivation, a common liability of existing RAS/MAPK-targeted therapies, and enable more durable pathway suppression across RAS/MAPK-driven cancers.

About Nested Therapeutics

Nested Therapeutics is a clinical-stage biotechnology company dedicated to developing transformative therapies for RAS/MAPK-driven disorders. The company is advancing NST-628, a fully brain-penetrant, non-degrading pan-RAF/MEK molecular glue with a differentiated tolerability and efficacy profile in genetically defined patient populations. NST-628 is currently being evaluated in the expansion portion of a Phase 1 clinical trial, NST-628-001

(NCT06326411). By applying a precision medicine approach, Nested aims to deliver better options for patients. To learn more, visit www.nestedtx.com and follow Nested Therapeutics on X (@Nestedtx) and LinkedIn.

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