A Phase 1, first-in-human, dose escalation and expansion study of oral pan-RAF/MEK molecular glue NST-628 in subjects with solid tumors harboring RAS-MAPK pathway alterations

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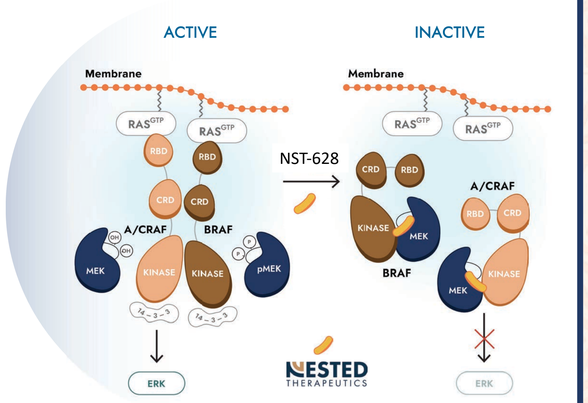
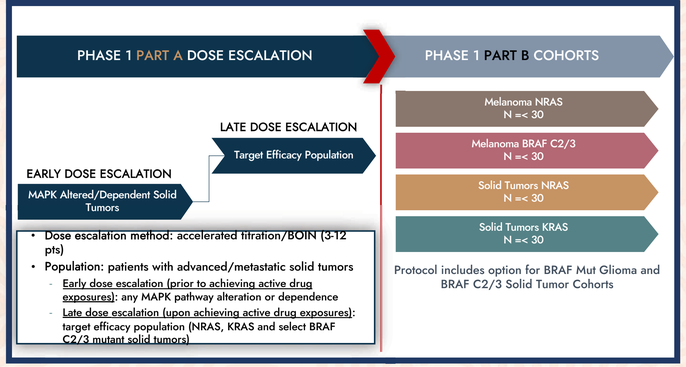
Background

- RAS-MAPK (RAS-RAF-MEK-ERK) signaling pathway is frequently mutated in malignancy [1].
- Tumor cell proliferation and viability are driven by activation of mutations in RAS-MAPK pathway.
- Current RAS–MAPK targeted therapies are limited by tolerability, depth and durability of response d/t pathway reactivation, limited CNS exposure.
- **NST 628 is an oral, CNS-penetrant non-degrading, pan-RAF/MEK molecular glue.**
- **NST-628 inhibits RAS/MAPK pathway while not inducing RAF dimerization: this may prevent pathway reactivation (Fig. 1)**
- NST-628 demonstrated robust activity in cell lines and xenograft/patient-derived models, including intracranially implanted, with a broad spectrum of RAS-MAPK pathway mutations [2].

Figure 1 Mode of Action for NST-628 Non-degrading Pan-RAF/MEK Molecular Glue



Study Design



Part A - Dose Escalation

Objective: Estimate NST-628 maximum tolerated dose (MTD) using Bayesian Optimal Interval method (BOIN) [3]; establish the recommended dose for expansion (RDE).

- Patients with any solid tumor with dependence on RAS-MAPK pathway
- Standard DLT definitions
- Upon evidence of target engagement study will enroll only patients with defined set of mutations:
  - NRAS, select KRAS, Class 2 and 3 BRAF mutations (ex. CRC); CRC with BRAF/RAS double hit; glioma with BRAF mutations
- Backfill allowed up to 15 patients per cohort

Part B – Dose Expansion

Objective: Evaluate NST-628 anti-tumor activity in cohorts (N = 30 each) of subjects with one of the following solid tumors harboring specified genetic alterations:

- Melanoma: NRAS; BRAF class 2 or 3 mutation
- Solid tumor: NRAS; KRAS mutation
- Measurable disease defined by RECIST v1.1 or other assessment tool standard for tumor type.

Key Study Participation Criteria

Key Inclusion Criteria

- Age ≥18 years
- Histologically or cytologically documented metastatic or locally advanced solid tumor.
  - Standard of care (SoC) therapy does not exist, no longer provides benefit, or is not tolerated by subject; or subject is not suitable for SoC therapy per Investigator.
- Performance status
  - Solid tumors other than glioma: ECOG 0 or 1
  - Glioma: Karnofsky ≥ 70 and ECOG 0 or 1
- Adequate organ function.
- Life expectancy ≥12 weeks.

Key Exclusion Criteria

- Conditions interfering with oral intake of NST-628.
- History or current evidence of significant retinal pathology leading to increased risk of RVO.
- History or evidence of cardiovascular risk.
- Current or history ≤6 months of planned Cycle 1 Day1 of pneumonitis or interstitial lung disease.
- Prior treatment with any MEK or BRAF inhibitor (Part B only).
- Untreated or symptomatic central nervous system metastases.
- Chemotherapy, radiation, gene therapy, vaccine therapy, or anti-cancer antibodies/ADCs within 28 days of Cycle 1 Day 1.
- Targeted small molecule agents within 14 days or 5 half-lives of Cycle 1 Day 1.

Study Endpoints

Part A - Dose Escalation

- Primary: dose-limiting toxicity of NST-628 and adverse events (AEs).
- Secondary: Objective response per RECIST v1.1 or other assessment tool standard for tumor type; NST-628 plasma concentration; progression-free survival (PFS), overall survival (OS)
- Exploratory: tumor/blood pERK level, circulating tumor DNA levels

Part B – Dose Expansion

- Primary endpoints: radiographic objective response and adverse events
- Secondary endpoints: PK, AEs, PFS, and OS
- Exploratory endpoints: circulating tumor DNA levels, serum tumor markers, and tumor/blood pERK

Trial Status

- Enrollment began in April 2024.
- Subjects have been treated and the trial is currently recruiting patients in the United States and Australia.

References

1. Ryan MB, Corcoran RB. Therapeutic strategies to target RAS-mutant cancers. Nat Rev Clin Oncol. 2018;15(11):709-720.
2. Ryan MB, et al. The Pan-RAF-MEK Nondegrading Molecular Glue NST-628 Is a Potent and Brain-Penetrant Inhibitor of the RAS-MAPK Pathway With Activity Across Diverse RAS- and RAF-Driven Cancers. Cancer Discov. 2024;14(7):1190-1205.
3. Liu and Yuan. Bayesian Optimal Interval Designs for Phase I Clinical Trials. Appl. Statist. 2015;64(3):507–523.

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