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NST-628 is a Novel, Potent, Fully Brain-Penetrant MAPK Pathway Molecular Glue that Inhibits RAS- and RAF-Driven Cancers

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NESTED THERAPEUTICS

Disclosure Information

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Klaus Hoeflich

I have the following relevant financial relationships to disclose:

Co-Founder, employee: Nested Therapeutics

Stockholder: Nested Therapeutics

My additional financial relationship disclosures are:

Advisor and stockholder: Turbine AI

RAS/MAPK Pathway Is the Heartland of Cancer Research, but a High Degree of Unmet Need Persists

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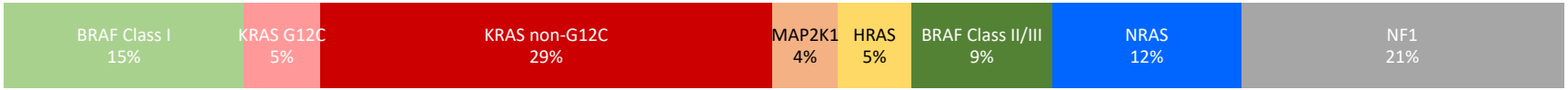
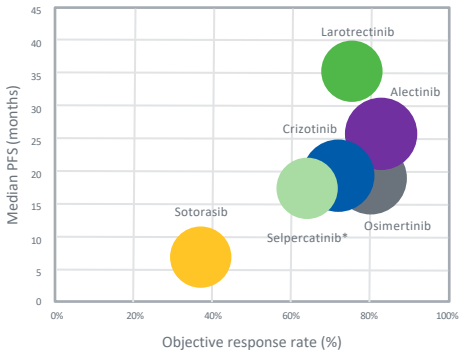
PATIENTS BY MUTATION CLASS



>80% of RAS mutations not addressed by current or research-stage precision treatments

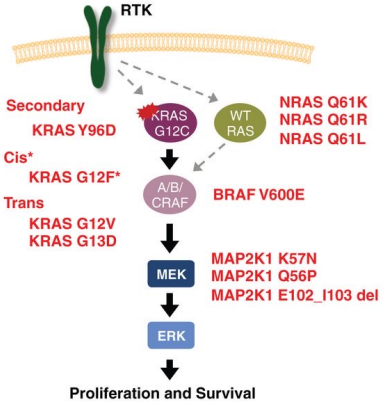
RAS INHIBITORS HAVE LIMITATIONS



Mutant-specific KRAS inhibitors have reduced ORR and PFS compared to other targeted therapies in the same tumor types

Polyclonal resistance observed for KRAS inhibitors in the clinic.

NST-628 MOI is effective for these mutant tumors.



Drs. Jessica Lin and Ryan Corcoran (MGH)

Current Therapies Are Vulnerable to Reactivation

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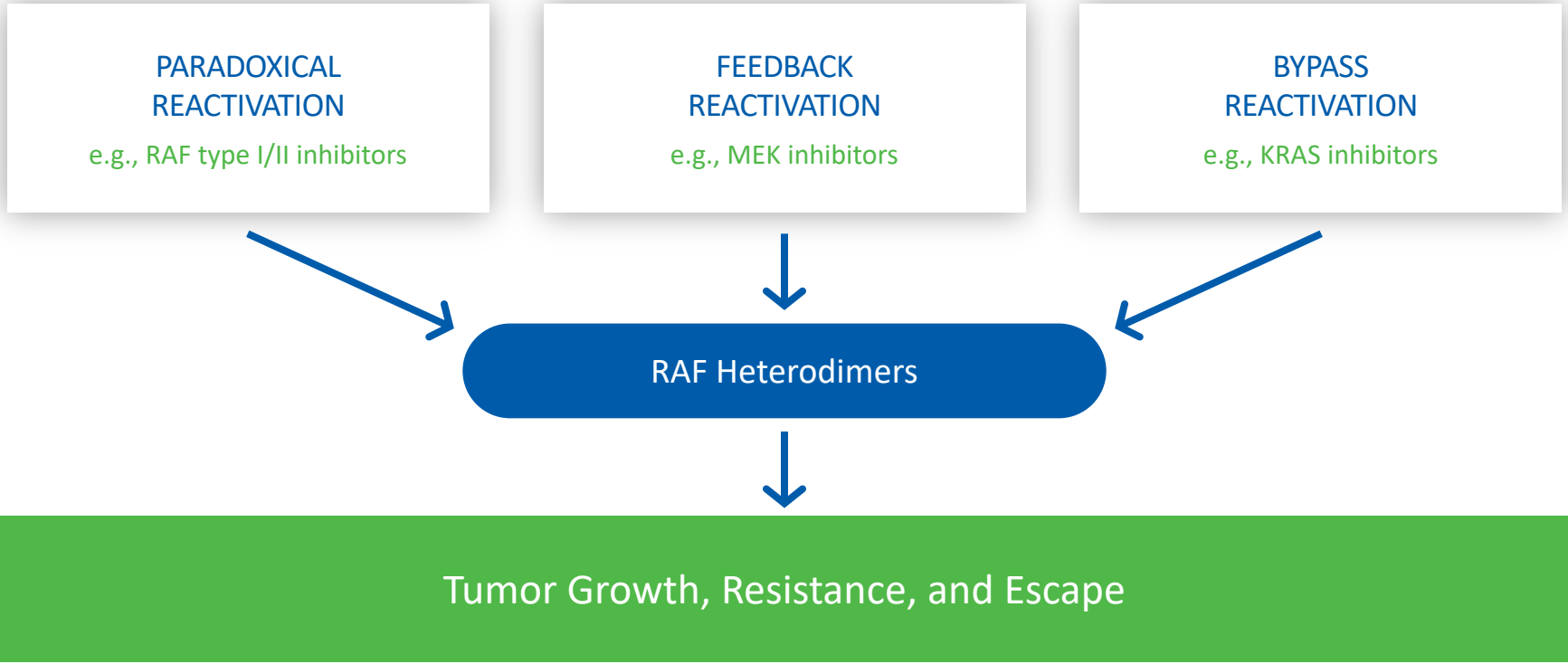

NST-628 Addresses Paradoxical Reactivation of MAPK Pathway by Preventing RAF Heterodimers

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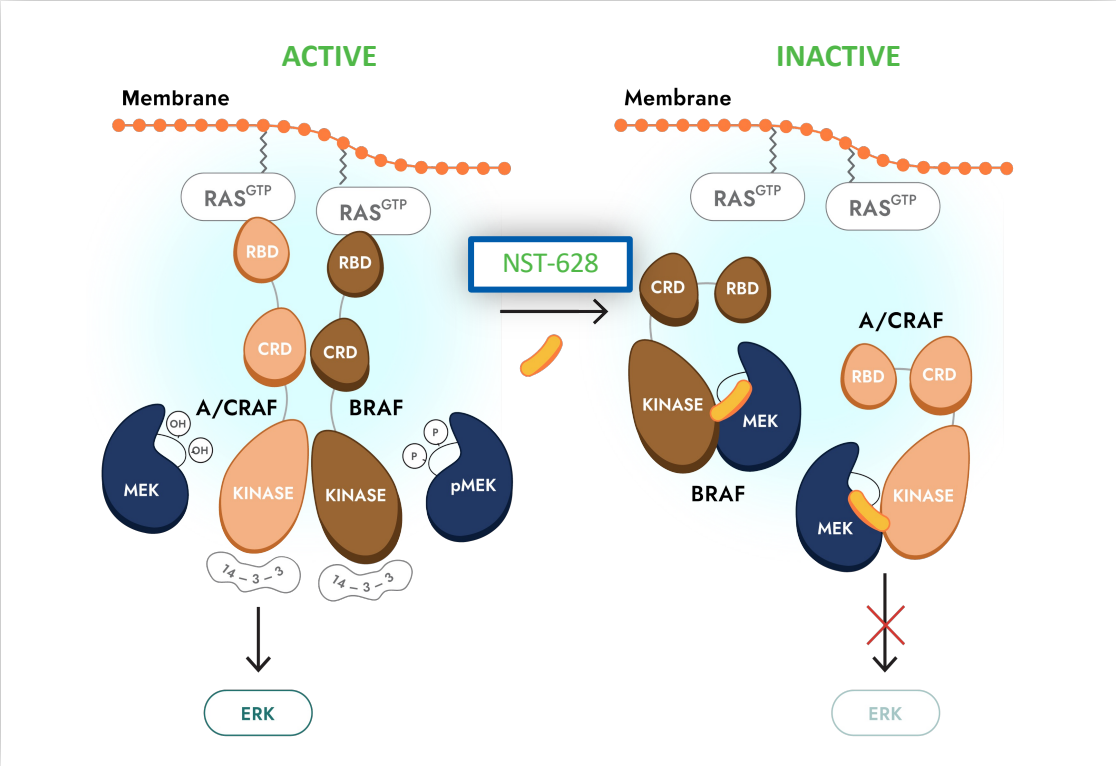

Prevents RAF paralog heterodimerization by stabilization and inactivation of CRAF-MEK, BRAF-MEK and ARAF-MEK complexes

Fully brain penetrant MEK/pan-RAF molecular glue shuts down MEK and ERK phosphorylation

NST-628 Modulates pan-RAF-MEK Complexes by Engaging Paralog-Specific Pocket Features

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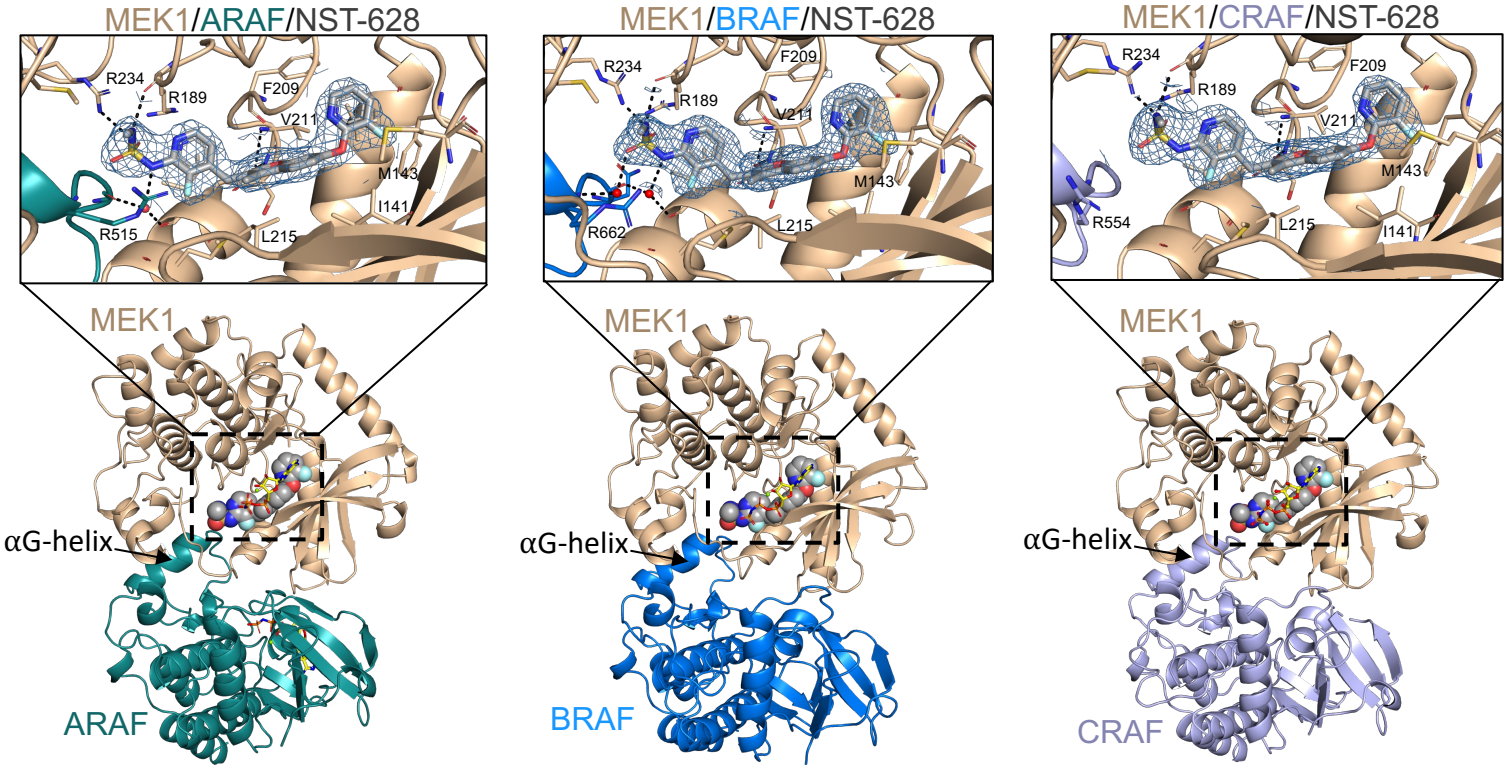

NST-628 is a Highly Potent and Selective pan-RAF-MEK Molecular Glue

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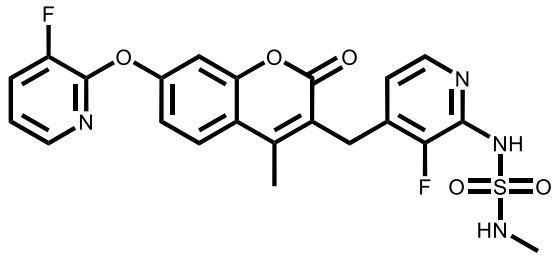
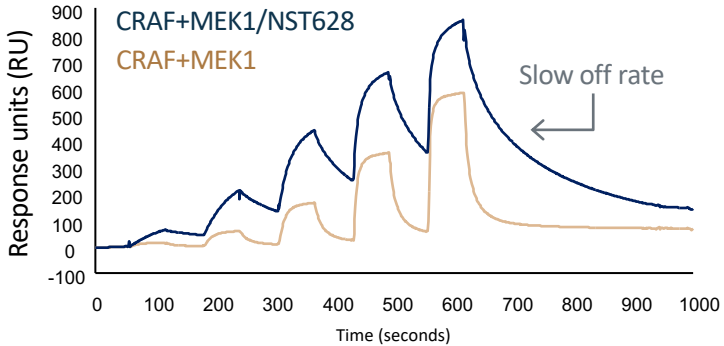
NST-628



SPR-based ternary complex assay quantifies increase in affinity between RAF and MEK by NST-628



GST-CRAF immobilized and MEK1 titrated in presence/absence of NST-628

Properties	NST-628
Phospho-MEK, HCT116^{KRASG13D} (IC_{50})	0.3 nM
Cell TiterGlo, HCT116^{KRASG13D} (IC_{50})	20 nM
Selectivity (proteomics, kinase panel)	Only MEK/RAF
hERG inhibition to 30 uM	Clean
Off target panel to 10 uM (n=44)	Clean
Cardiac ion channel to 30 uM	Clean
CYP DDIs (7 isoforms), TDI	>19 uM, Clean
Oral bioavailability (all species)	>50%
Predicted clinical CL (mK/min/Kg), $t_{1/2}$ (h)	0.33 / 10-12h
Rat $K_{p,uu}$	1.3
Phototoxicity potential	Low

NST-628 Prevents Formation of RAF Heterodimers, Thereby Suppressing Pathway Reactivation

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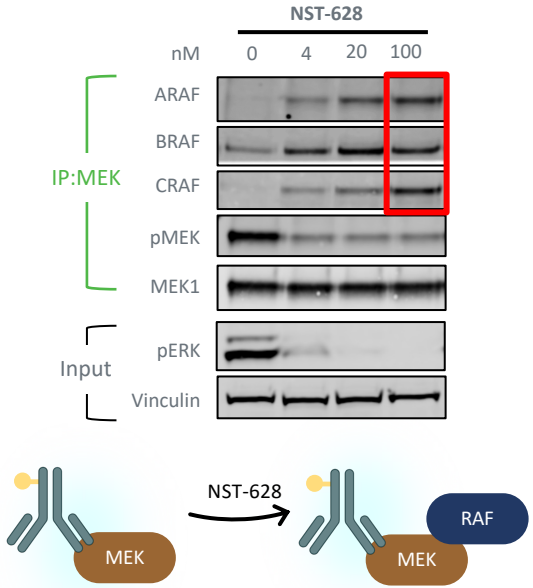
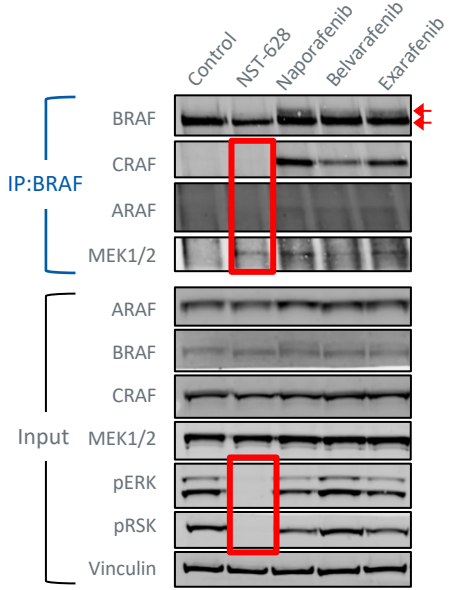
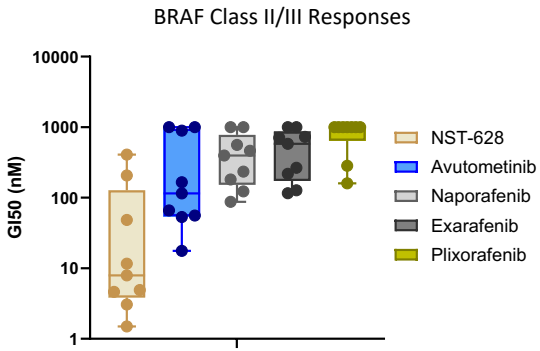
NEST-628 pan-RAF-MEK endogenous ternary complexes



NST-628 does not induce RAF heterodimer formation



NST-628 Superior Efficacy in RAF Dimer-Dependent Cancer Cells



* NST-628 potency also broadly observed across RAS pathway biomarkers in 550 cell line panel

HCT-116 (KRAS G13D), BRAF or MEK IP (endogenous), 100 nM, 2 h treatment
Similar ternary complexes observed for BRAF, CRAF and ARAF IPs

Significant Anti-Tumor Activity & Prolonged Survival in RAS or RAF mutant PDX models by NST-628

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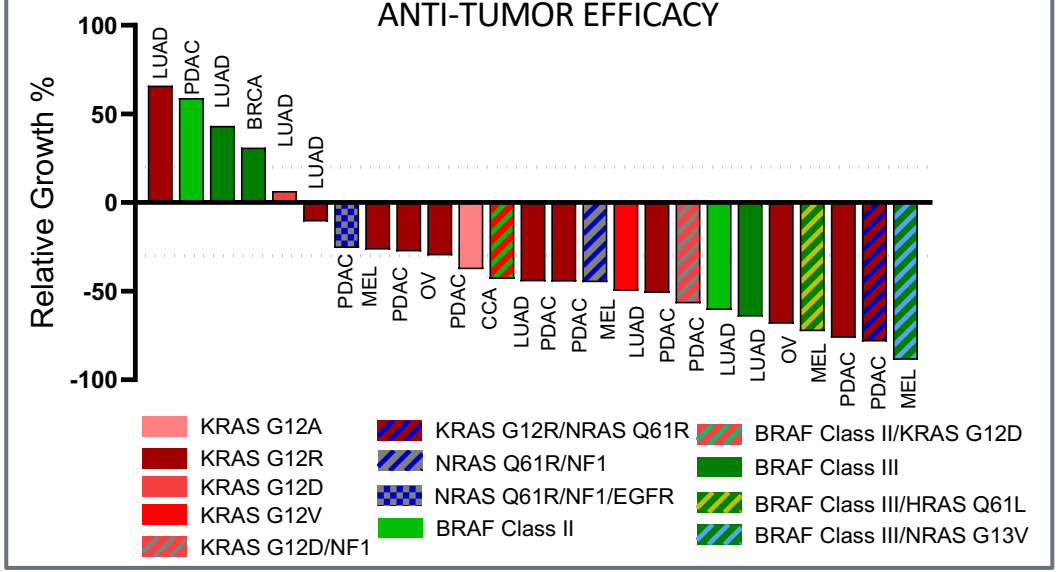
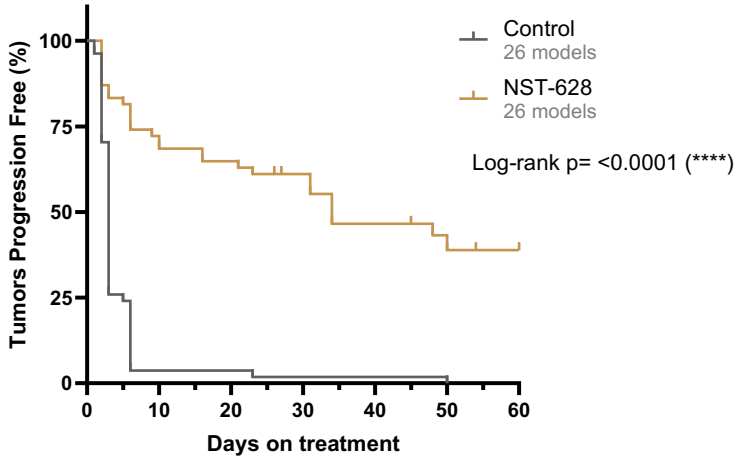
RAS/RAF-MUTANT ANTI-TUMOR EFFICACY



RAS/RAF-MUTANT PROGRESSION FREE SURVIVAL



- 3 mg/kg QD NST-628 dose matches start of projected clinical efficacy
- Each tumor normalized to D0 starting size
- ORR: 16/26 models (61.5%) ≤ -30% tumor regression
- DCR: 22/26 models (84.6%) ≤ 20% tumor outgrowth

NST-628 ADME/PK Properties Optimized for Anti-Tumor Activity and Therapeutic Index in Patients

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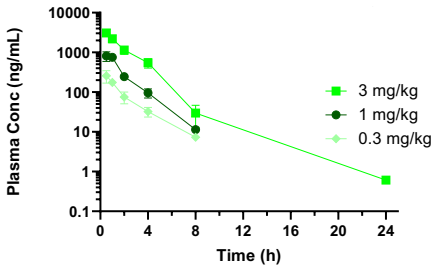
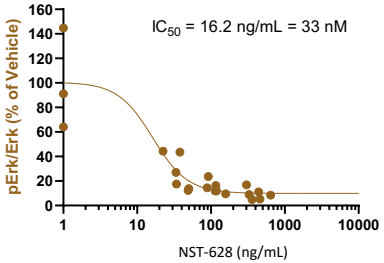
INTEGRATED EXPERIMENTAL DATA

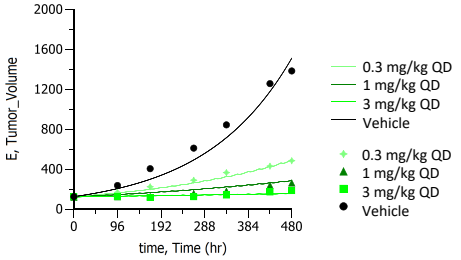
PK Profiles of NTX-628 on Day 7



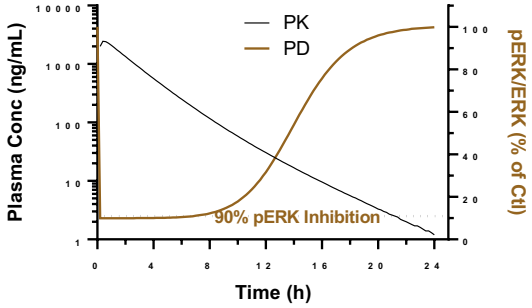
Plasma PK vs phospho-ERK Inhibition



Tumor Growth Inhibition



PK/PD MODELING



- 90% of pERK inhibition for 10-12 hours by NST-628 led to tumor regression in preclinical tumor models
- QD oral doses >2 mg predicted to be clinically efficacious with steady-state C_{min} achieving efficacious concentrations (20-30 ng/mL)
- NST-628 is amenable to flexible dosing schedules to optimize anti-tumor activity and therapeutic index

NST-628 has Broad Efficacy without Sacrificing Tolerability at Clinically Achievable Exposures

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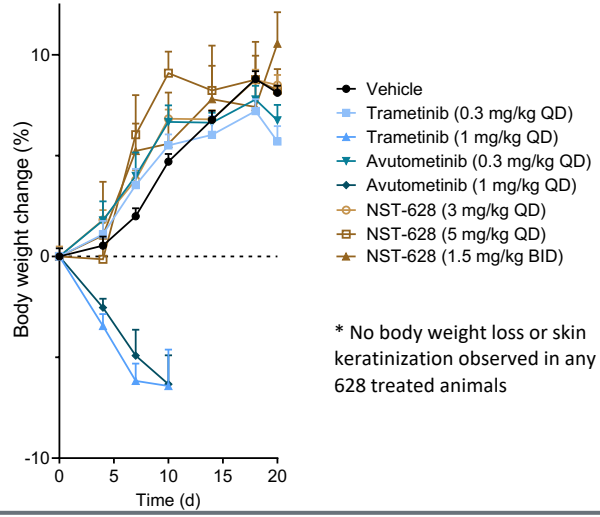
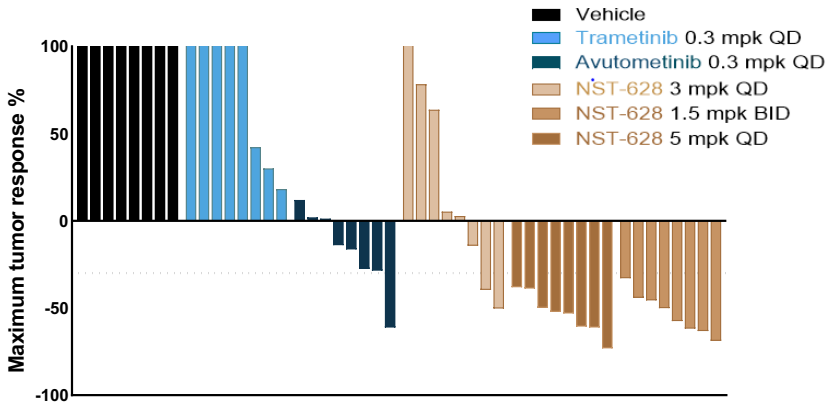
TOLERABILITY



* No body weight loss or skin keratinization observed in any NST-628 treated animals

ANTI-TUMOR ACTIVITY



HTC-116 (KRAS G13D) tumor xenograft model

- NST-628 treatment results in higher response rate and is better tolerated than trametinib or Avutometinib
- Trametinib and Avutometinib doses selected based on clinically achievable drug exposures

NST-628 has Superior Pathway Inhibition and Anti-Tumor Efficacy in Intracranial Tumors

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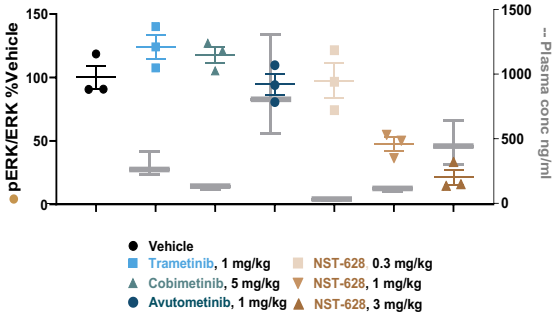
NST-628 Demonstrates Superior CNS PK/PD

Non-tumor bearing mice (fully intact blood-brain barrier)

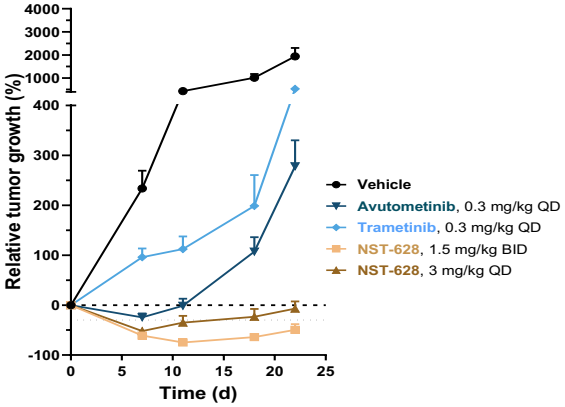


Plasma concentration and phospho-ERK in mouse brain tissue measured 4 h after single dose

Only NST-628 inhibits phospho-ERK in mouse brain tissue at comparable plasma concentration

NST-628 Reduces the Size of NRAS-mutant Brain Tumors In Mice

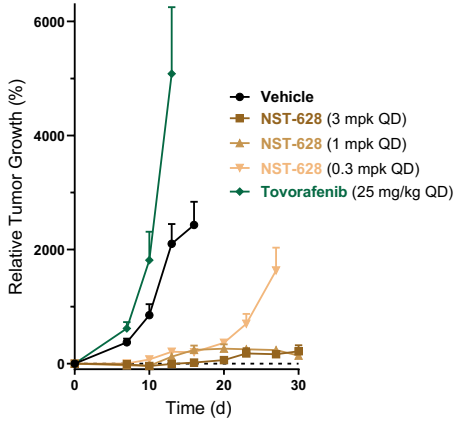
SK-MEL-2-Luc, NRAS Q61R, Melanoma



SK-MEL-2-Luc intracranial tumors treated with indicated inhibitors and tumor volume measured by bioluminescence (BLI)

NST-628 Inhibits the RAS MAPK Pathway and Growth of NF1-mutant Brain Tumors in Mice

MeWo-Luc, NF1 Q1336* Melanoma



MeWo-Luc intracranial tumors implanted in NOD SCID mice treated with indicated inhibitors and tumor volume measured by bioluminescence (BLI)

Tovorafenib accelerates tumor growth due to paradoxical RAF reactivation in RAS-driven cancers

NST-628 Differentiation (Broad Efficacy, Superior Drug Properties) Warrants Clinical Exploration

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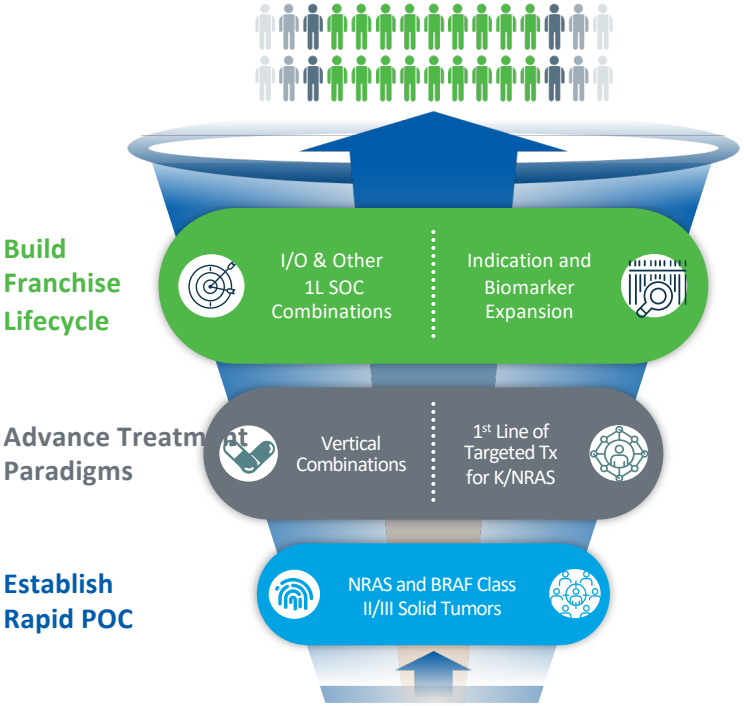
CLINICAL DEVELOPMENT FOCUS

- RAS: Robust pre-clinical data across tumor histologies with KRAS and NRAS codon mutations
- BRAF: Superior activity in select Class II and III mutant malignancies
- High CNS exposure offers efficacy for patients with primary CNS malignancies and CNS metastases
- Optimal half-life (10-12 h) offers superior therapeutic index and dosing optionality



DEVELOPMENT STRATEGY

NST-628 Summary

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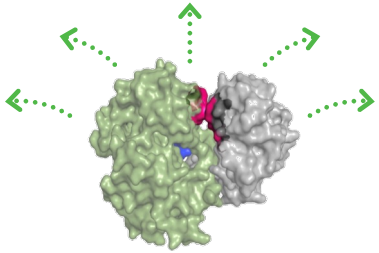
MEK/PAN-RAF Glue

- High potency and selectivity
- Potent stabilization of CRAF-MEK, BRAF-MEK and ARAF-MEK complexes
- Lack of paradoxical pathway activation through prevention of RAF paralog heterodimerization
- Balanced metabolic profile to maximize therapeutic index and provide dosing flexibility in clinic



Fully Brain Penetrant

Allows treatment of brain metastases;

only RAS/MAPK inhibitor with full intrinsic brain penetration

Superior Risk/ Benefit Profile vs. Other Pathway Combination Therapy

Potential for monotherapy and to become backbone for various combination approaches

Broad Addressable Biomarker Populations that Have No Targeted Treatment Options as of Today

BRAF class II and III, NRAS, KRAS, NF-1, MAP2K1, HRAS

GLP toxicology studies demonstrate improved exposure margins vs. MEKi's in both non-clinical species

Phase 1 clinical studies initiated (NCT06326411)

Acknowledgements

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