Preliminary results from a Phase 1a/b dose-escalation and expansion trial of the pan-RAF-MEK molecular glue NST-628 in patients with advanced or refractory RAF, KRAS, and NRAS-mutant solid tumors (NCT06326411)

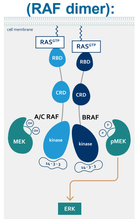
Ahmad A. Tarhini[1], Monica F. Chen[2], Jia Liu[3], Varun Monga[4], Victoria Atkinson[5] Sarina A. Piha-Paul[6], Bartosz Chmielowski[7], Benjamin Herzberg[8], Charlotte Lemech[9], Prachi Bhave[10], Ganessan Kichenadasse[11], Gerald Falchook[12], Janice Mehnert[13], Andrae Vandross[14], Mohamad Salkeni[15], Meredith McKean[16], David Wages[17], Ann Marie Kennedy[17], Meagan Ryan[17], John Clark[17], Abdulaziz Nanah[18], Michael Fossler[18], Philip Komarnitsky[17], Igor Puzanov[19]

[1]H. Lee Moffit Cancer Center and Research Institute, Tampa, FL,[2]Memorial Sloan Kettering Cancer Center, New York, NY,[3]The Kinghorn Cancer Centre, St Vincent's Health Network Sydney, Darlinghurst, NSW, Australia,[4]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA,[5]Princess Alexandra Hospital, Gallipoli Medical Research Foundation, University of Queensland, Woolloongabba, Qld, Australia,[6]University of Texas, M. D. Anderson Cancer Center, Houston, TX,[7]UCLA Medical Center, Los Angeles, CA,[8]Columbia University, New York, NY,[9]Scientia Clinical Research, Sydney, NSW, Australia,[10]Cabrini Health, Melbourne, Vic, Australia,[11]Southern Oncology, Bedford Park, SA, Australia,[12]Sarah Cannon Research Institute at Health ONE, Denver, CO,[13]NYU Langone, New York, NY,[14]Next Oncology Austin, Austin, TX,[15]Next Oncology Virginia, Fairfax, VA,[16]Sarah Cannon Research Institute, Nashville, TN,[17]Nested Therapeutics, Cambridge, MA,[18]Cytel, Inc, Waltham, MA,[19]Roswell Park Comprehensive Cancer Center, Buffalo, NY

Background

- The RAS-MAPK pathway is altered in ~40% of all human cancers, yet its therapeutic inhibition has been limited by adaptive resistance, paradoxical activation, and poor CNS penetration
- NST-628 is a potent non-degrading fully brain penetrant pan-RAF-MEK molecular glue with broad preclinical anti-tumor activity.
- NST-628 prevents RAF paralog heterodimerization by promoting potent stabilization of CRAF-MEK, BRAF-MEK and ARAF-MEK complexes in inactive confirmations, blocking downstream signaling through ERK and bypassing the RAF heterodimer driven feedback loops that cause pathway reactivation with BRAF or MEK inhibitors

Active conformation (RAF dimer):



Inactive conformation (Stabilized RAF/MEK complex):

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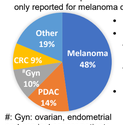
- NRAS & non-V600 BRAF (Class II/III) mutant melanoma represents ~1/3rd (~8K patients in the US) of incident melanoma population with no effective treatment options following immune checkpoint inhibitors (ICIs)
- Treatment outcomes remain modest with ~15% response rates for binimetinib and <15% for ICI retreatment or chemotherapy
- **We report preliminary findings from the first-in-human Phase 1a/b study of NST-628 in patients with RAS–MAPK–altered cancers**
- **Clinical data from Phase 1 provides evidence of single agent anti-tumor activity with continuous pathway inhibition in RAS/MAPK mutant solid tumors with emerging best-in-class profile in NRAS- & BRAF Class II/III-mutant melanoma**

Disposition/Demographics

Tumor \ Dose	Part A: All Doses	Part A: RDE	Part B: RDE	Study Overall: N
All Patients	64	18	5	69
Melanoma	28	13	5	33

	Overall	Melanoma	RDE Melanoma
Age			
Median	65	72	74
Range	18-89	33 - 88	33 - 88
Mutation			
KRAS	11	-	-
NRAS	34	28	16
BRAF C1	2	-	-
BRAF C2 or 3	14	3	-
CRAF	1	-	-
BRAF&RAS	7	2	2
ECOG			
0	34	17	9
1	35	16	9
Prior Systemic Tx			
Median	2	2	2
Range	1 - 8	1 - 6	1 - 6
LDH*			
>ULN	NR	17	9
≤ULN	NR	15	8

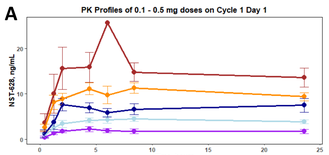
* One melanoma patient LDH not available at data cut-off. LDH only reported for melanoma due to prognostic relevance

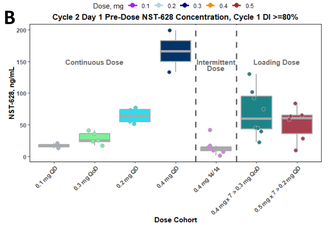


#: Gyn: ovarian, endometrial and cervical cancer patients

- 69 patients dosed
- Melanoma most frequent tumor
  - All patients had prior immune checkpoint therapy
  - Approximately equal Ns of ECOG PS 0/1 and LDH >< ULN
- NRAS most frequent mutation, followed by non-V600 (Class II/III) BRAF

NST-628 Pharmacokinetics

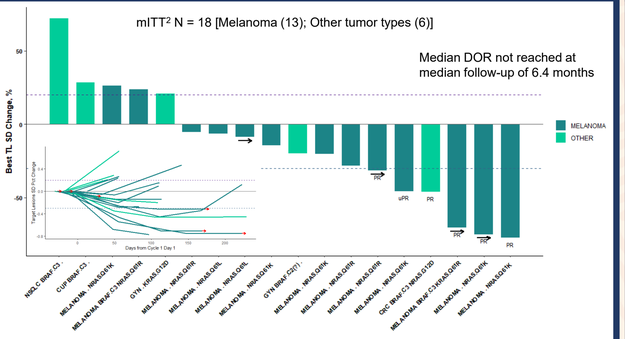




A: NST-628 blood levels 0-24 hours following single dose of the drug. Terminal $t_{1/2}$ ~9 days. Exposure is dose-dependent with no evidence of saturation

B: NST-628 blood levels at Cycle 2 Day 1. Levels at MTD (0.4 mg, ~180 ng/mL median) significantly higher than at RDE (0.4 mg QDx7 → 0.3 mg QoD, ~60 ng/mL). Loading doses implemented to rapidly reach steady state NST-628 levels. Note: C2D1 NST-628 levels with intermittent schedule are following 14 days dose holiday.

33% Single Agent Response Rate at RDE | 38% in Melanoma



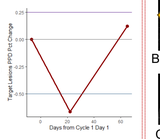
Responses	RDE: Overall	RDE: Melanoma Subgroup	Melanoma (all dose levels)
Best observed response (%; 95% CI)	N=18	N=13	N=28 (mITT[2])
Partial Response	33%[1]; 13% - 59%	38%[1]; 14%- 68%	29%[1]; 13%-49%
Stable Disease	39%; 17% - 64%	46%; 19% - 75%	46%; 28%- 66%
Disease control rate (%; 95% CI)	72%; 47% - 90%	85%; 55% - 98%	75%; 55%-89%

(1) Includes one unconfirmed PR; (2) mITT: patients with ≥1 assessment or who discontinued study

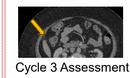
Activity in CNS & Beyond Melanoma

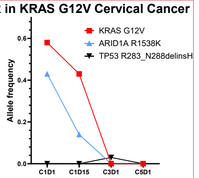
Preliminary Evidence of Activity in CNS

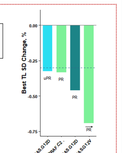
- High grade astrocytoma (BRAF V600E)
- Regimen: 0.2 mg QD
- Treatment history: Trametinib/dabrafenib (CR → PD); Tovorafenib (PD)
- NST-628: baseline PrPDi 690; 1st scan 223; last scan 775



Ongoing durable PR in KRAS G12V Cervical Cancer

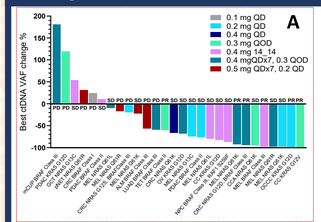


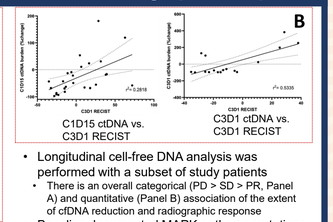




- KRAS G12V-mutant cervical patient with a deep and durable RECIST response and corresponding clearance of ctDNA
- Four non-melanoma responders on study across 3 dosing cohorts and 4 histologies, including 2 KRAS-mutant gynecologic cancers, 1 NRAS/BRAF-Class III double mutant colorectal cancer, and 1 BRAF Class II thymic cancer

Changes in ctDNA Levels Associated with Radiographic Response





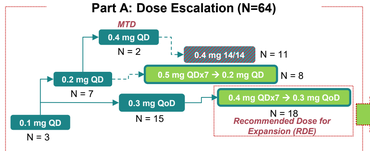
C1D15 ctDNA vs. C3D1 RECIST

C3D1 ctDNA vs. C3D1 RECIST

- Longitudinal cell-free DNA analysis was performed with a subset of study patients
  - There is an overall categorical (PD > SD > PR, Panel A) and quantitative (Panel B) association of the extent of cfDNA reduction and radiographic response
- Baseline documented MAPK pathway mutations were detected in pre-treatment cfDNA in 86% of tested patients (data not shown)

NST-628-001 Study Design & Conduct

Part A: Dose Escalation (N=64)



- Continuous (QD or QoD) schedule
- Loading Dose: 7 x QD load, then continuous QD/QoD maintenance
- Intermittent schedule (14 days on / 14 days off)

Part B: Expansion

Melanoma Cohort @ RDE

N = up to 30, ongoing

- Alternate schedules were chosen based on the emergent PK profile
- Loading doses enable rapid attainment of steady state plasma levels considering NST-628 PK properties
- 0.4 mg QD → 0.3 mg QoD regimen was selected as RDE based on the balance of anti-tumor activity and tolerability

METHODS

- BOIN-guided dose escalation with accelerated titration
  - MTD determined with isotonic regression for DLTs across all dose levels
  - RDE selection: dose level(s) under consideration could be expanded to up to 15 DLT-evaluable patients per level

PATIENTS

- Patients with MAPK pathway-mutant advanced solid tumors
  - Type of mutations and tumor types allowed could be adjusted during dose escalation
  - Enrollment was restricted to patients with documented NRAS, CRAF and BRAF Class II/III (non-V600) mutant solid tumors or KRAS mutant gynecologic malignancies (ovarian, endometrial or cervical cancer) once anti-tumor activity/on-target toxicity was observed
- No existing/beneficial standard of care therapy; no limits on the number of prior lines of therapy
- ECOG PS 0-1 and normal organ function
- Primary CNS malignancies allowed; treated and stable CNS metastases

NST-628 Safety: 82% Dose Intensity, Low Discontinuation Rate

Any Grade TRAE Reported in ≥ 15% of Patients

	RDE		All Patients	
N	23		69	
Any Grade TRAEs	N	%	N	%
Diarrhea	3	13%	21	30%
Nausea	4	17%	11	16%
Vomiting	3	13%	11	16%
Fatigue	8	35%	21	30%
Peripheral edema	5	22%	15	22%
Blood CK increased	8	35%	25	36%
Acneiform dermatitis	8	35%	27	39%
Rash	7	30%	23	33%
Total	**18**	**78%**	**60**	**87%**

Grade ≥ 3 TRAEs Reported in ≥ 2 Patients

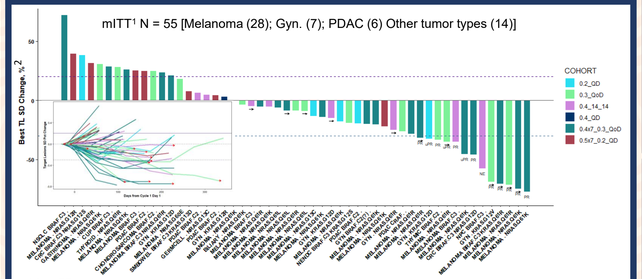
	RDE		All Patients	
N	23		69	
Grade ≥ 3 TRAEs	N	%	N	%
Anaemia	2	9%	3	4%
Diarrhea	-	0%	3	4%
Blood CK increased	-	0%	6	9%
Decreased LVEF	2	9%	2	3%
Muscular weakness	2	9%	2	3%
Acneiform dermatitis	1	4%	2	3%
Total	**7**	**30%**	**23**	**33%**

Dose Modifications

	RDE		All Patients	
N	23		69	
Dose Interruptions	9	39%	30	43%
Dose Reductions	2	9%	16	23%
Dose Withdrawals	2	9%	5	7%

- Overall safety profile: most frequent TRAEs are skin, GI, CK elevation, constitutional and ocular
  - Grade 1-2 visual impairment 10%, blurred vision 9% (no Grade ≥ 3 ocular events)
- Most frequent Grade ≥ 3TRAE is CK elevation
- A total of 4 patients with Grade 4 TRAEs: CK (3) and thrombocytopenia (1)
- No Grade 5 TRAEs were observed
- 57% of patients experienced dose modifications at RDE
  - Majority of dose modifications are dose interruptions, with less frequent dose reductions
  - 9% of patients discontinued NST-628 d/t AEs
- Dose intensity at RDE 82%

Anti-Tumor Activity in KRAS GYN and NRAS or BRAF Class II/III Tumors[3]



(1) mITT: patients with ≥1 assessment or who discontinued study
(2) CNS malignancies best responses not included in the waterfall plot
(3) Patients with tumor types and driver mutations allowed following enrollment restriction in Part A of the study

Anti-tumor activity observed in KRAS-mutant gynecologic cancers and NRAS/BRAF Class II/III solid tumors

- Responses in KRAS-mutant ovarian (non–low grade) and cervical cancers
- Activity across dose levels; durable responses and stable disease observed
- Notable activity in BRAF Class III-mutant tumors, a setting with no/very infrequent responses to targeted therapy: 4/11 patients achieved >30% tumor reduction (3 PRs (27%), one NE due to RTx) across melanoma, CRC, and nasopharyngeal carcinoma

Conclusions and Acknowledgements

- NST-628 shows promising single agent anti-tumor activity in heavily pre-treated NRAS and BRAF Class II/III (non-V600) melanoma patients with no available effective treatment options
  - 38% response rate at RDE; with median follow-up of 6.4 months median DOR not reached
- Single agent anti-tumor activity is observed beyond melanoma, including KRAS mutant tumors
  - Responses in CRC, ovarian (KRAS G12D), cervical (KRAS G12V), and thymic malignancies
  - Potential to explore combinations with KRAS inhibitors considering pre-clinical synergy[a,b]
- Safety profile consistent with MoA; on-target AEs (mainly Grades 1 & 2) show target engagement; dose intensity of 82% and low discontinuation rates indicate acceptable tolerability
- Clinical evidence of brain penetrance consistent with preclinical data
- Further investigation in melanoma is ongoing; study beyond melanoma warranted

Nested team and study investigators are deeply grateful to patients who participated in the study and their families and to all past and current members of Nested R&D team who contributed to the NST-628 program

[a]Ryan MB et al. The pan-RAF-MEK non degrading 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.
[b]Ryan M et al 516LBA (PB-519) LBA Posters: The novel pan-RAF-MEK glue NST-628 is highly efficacious as monotherapy and as an anchor for vertical inhibition of the RAS-MAPK pathway in KRAS-mutant cancers. European Journal of Cancer, 211

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