Abstract #3084: First-in-Human Dose Escalation Study of NBF-006, a Novel Investigational siRNA Targeting GSTP, in Patients with Non-Small Cell Lung, Pancreatic, or Colorectal Cancer

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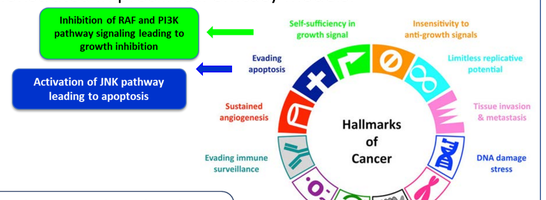
Background

- KRAS mutations occur frequently in pancreatic, colorectal, and lung cancers, making it a desirable target in anticancer drug development.
- Glutathione S-transferase Pi (**GSTP**) is strongly upregulated in many of these cancer types, has an important role in detoxification, and is a significant protein regulating key oncogenic pathways such as the KRAS and JNK pathways.
- NBF-006 is a novel drug product containing a GSTP siRNA encapsulated within a lipid nanoparticle. It has been designed to deliver siRNA to tumors of the lung and common sites of metastatic spread (liver and marrow) which has been demonstrated in preclinical efficacy models.



Glutathione S-Transferase (GSTP)
- Overexpressed in multiple solid tumors, including lung
- Phase II detoxification enzyme
- Chaperone functions (many binding partners)

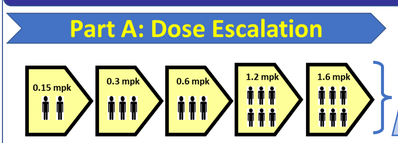
Hanahan and Weinberg, 2011

Study Objectives

Primary	• Determine safety profile, maximum tolerated dose (MTD), and recommended dose for Part B
Secondary	• Evaluate preliminary efficacy • Investigate pharmacokinetics (PK)
Exploratory	• Evaluate biomarkers & clinical outcome • Evaluate KRAS-mutations and clinical outcome

Study Design

Part A: Dose Escalation



- *70-minute IV infusion (step-wise)*
- *Once-a-week dosing for 4 weeks*
- *2-week rest period between cycles*

- This first-in-human (FIH) phase 1 part A dose escalation study enrolled patients with previously treated advanced NSCLC, pancreatic (PANC), or colorectal (CRC) cancer, with or without KRAS mutations.
- Followed traditional 3+3 design, and five dose levels were evaluated.
- The DLT period was the first cycle of therapy (6 weeks), and patients were evaluated for response (CT scan) every 12 weeks (dose levels 0.15 – 1.2 mg/kg) or every 6 weeks (dose level 1.6 mg/kg).

Results: Patient Characteristics

	0.15 mg/kg		0.3 mg/kg			0.6 mg/kg			1.2 mg/kg					
Patient	001-0001	001-0002	002-0003	002-0004	002-0005	002-0006	001-0007	001-0008	001-0009	001-0010	001-0011	002-0012	001-0013	001-0014
Sex, Age	M, 60	M, 65	M, 68	F, 74	F, 51	M, 73	M, 64	M, 64	M, 75	M, 69	F, 58	M, 61	M, 65	F, 63
Diagnosis	Panc	Panc	NSCLC	CRC	CRC	CRC	Panc	Panc	Panc	CRC	Panc	CRC	NSCLC	NSCLC
Number of prior lines of Tx	2	3	5	5	3	5	4	3	1	4	3	3	3	3
Cycles in study	0.5 (PD)	1	3	1.5	2	4	2	4	6	2	1.25	2	1	6

	1.6 mg/kg						
Patient	001-0015	011-0021	011-0029	011-0038	011-0043	012-0044	011-0045
Sex, Age	M, 75	M, 78	M, 68	M, 75	F, 58	F, 50	M, 74
Diagnosis	KRAS-NSCLC	KRAS-NSCLC	KRAS-NSCLC	KRAS-NSCLC	KRAS-NSCLC	KRAS-NSCLC	KRAS-NSCLC
Number of prior lines of Tx	6	5	7	6	1	3	3
Cycles in study	10.75	1	1	1	1	0.5 (SAE/PD)	1.25

Note:
- *Patients 001-0001 and 012-0044 did not complete a full cycle of treatment in cycle 1 and were replaced per protocol*

Results: Safety

≥Possibly Related AEs (21 treated patients)

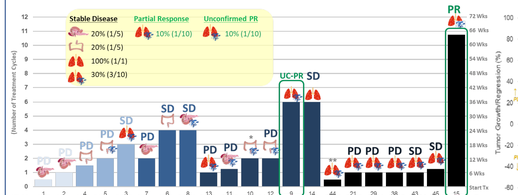
Adverse Event	# of Patients	Grade 1	Grade 2	Grade 3	Observed at Dose 0.15	0.3	0.6	1.2	1.6
Arthralgia	2	2	0	0			X	X	
Diarrhea	2	1	1	0		X	X		
Fatigue	2	1	1	0	X			X	
Vomiting	2	1	1	0		X		X	
Dry Skin	1	1	0	0				X	
Edema Limbs	1	0	1	0					X
Fever	1	1	0	0		X			
Hives	1	1	0	0		X			
Hypokalemia	1	0	1	0					X
Infusion related reaction	1	1	1	0		X			
Myalgia	1	1	0	0			X		
Nausea	1	1	0	0				X	
Peripheral Motor Neuropathy	1	0	1	0				X	
White Blood Cell Decreased	1	0	0	1			X		

- Treatment was well tolerated, with no treatment related SAEs.
- Adverse events assessed as possibly related to study drug were mostly grades 1-2 and with no apparent dose-response relationship.
- No DLTs nor clinically meaningful cytokines, complements, or anti-drug antibodies (ADAs) were observed.

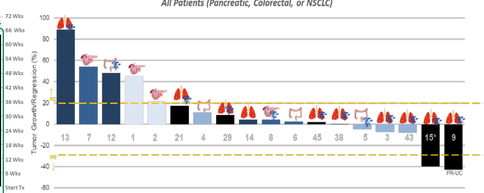
- *One patient had 2 infusion-related reactions (grades 1 and 2).*
- *Unrelated SAEs (most attributed to underlying disease) included Ascites and Cerebrovascular accident (0.15 mg/kg), Chest pain, and Disease progression (0.30 mg/kg), Sepsis and Bile duct stenosis (0.60 mg/kg), Pleural effusion, Pain, Disease progression and Muscular weakness (1.6 mg/kg).*

Results: Efficacy

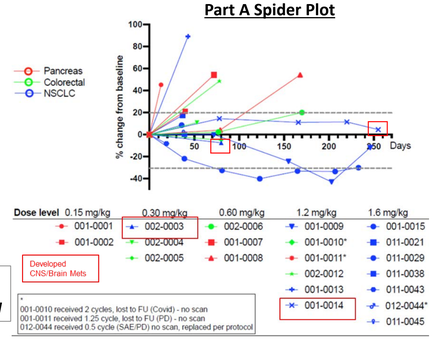
Part A Overall Treatment Duration and Best Response of Target Lesions



Part A (All Patients) Waterfall Plot – Best Overall Response of Target Lesions



Part A Spider Plot



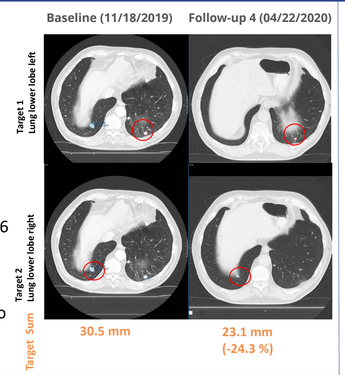
Dose Levels:
0.15 mg/kg | 0.3 mg/kg | 0.6 mg/kg | 1.2 mg/kg | 1.6 mg/kg

**= No scans due to lost to follow-up due to Covid-19*
*** = No scans as patient did not complete cycle 1 prior to disease progression and was replaced per protocol*

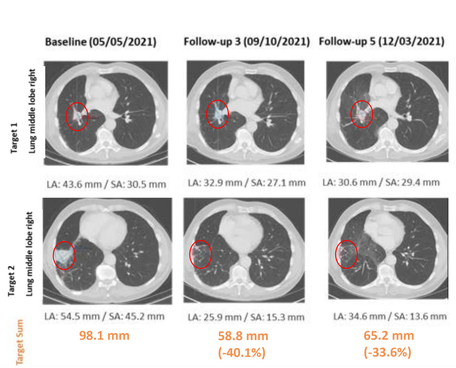
*NBF-006, a **novel lyophilized siRNA-lipid nanoparticle (LNP)**, for the inhibition of glutathione S-transferase P (**GSTP**), is **well tolerated up to 1.6 mg/kg dose level for up to 64 weeks with early signs of efficacy** in NSCLC cancer patients.*

Results: Case Studies

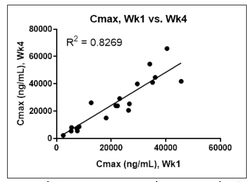
Patient 001-0009
- Cohort 4 (1.2 mg/kg)
- 1 prior line of systemic treatment (chemoimmunotherapy)
- Good durable SD, with -24.3% after 4 cycles (24 weeks), and an unconfirmed partial response (-43.0 %) after 5 cycles.
- Patient received 6 cycles of treatment (36 weeks) before PD in July 2020 (new lung lesion and targets increasing 9 mm).
- Tolerated treatment well, no SAEs and no treatment related AEs.

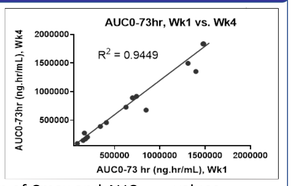


Patient 001-0015
- Cohort 5 (1.6 mg/kg)
- 6 prior lines of systemic treatment
- Good durable PR; continued through end of cycle 6 scan (29-DEC-2021).
- Radiotherapy to treat hemoptysis in January 2022 (Target lesion 1).
- Continued treatment until June 2022 (PD; new lesions).
- Tolerated treatment well, no SAE and only one possibly related AE (G2 hypokalemia June 2022).

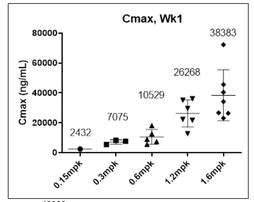


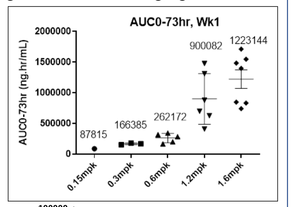
Results: Pharmacokinetics (PK)

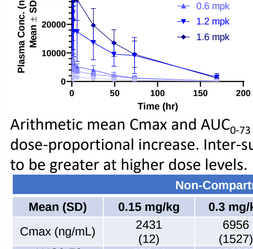


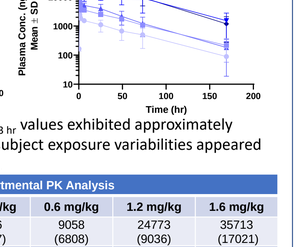


Week 1 versus Week 4 correlation of Cmax and $AUC_{0\text{-}73hr}$ values suggest no apparent exposure accumulation and no reduction in exposure following multiple dosing from 0.15 to 1.6 mg/kg levels.









Arithmetic mean Cmax and $AUC_{0\text{-}73\ hr}$ values exhibited approximately dose-proportional increase. Inter-subject exposure variabilities appeared to be greater at higher dose levels.

Non-Compartmental PK Analysis

Mean (SD)	0.15 mg/kg	0.3 mg/kg	0.6 mg/kg	1.2 mg/kg	1.6 mg/kg
Cmax (ng/mL)	2431 (12)	6956 (1527)	9058 (6808)	24773 (9036)	35713 (17021)
AUC0-73 (ng.hr/mL)	67944 (24922)	166025 (13336)	225142 (93893)	820131 (414707)	1162762 (401638)
CL (L/hr)	0.1294 (0.0577)	0.0799 (0.0197)	0.1449 (0.0286)	0.0614 (0.0245)	0.2064 (0.3284)
V_{ss} (L)	5.84 (1.12)	4.18 (1.22)	5.87 (0.37)	3.60 (1.04)	10.17 (19.90)
$T_{1/2}$ (hr)	32 (9)	38 (14)	31 (6)	41 (13)	34 (6)

Conclusions

- This FIH study with NBF-006, a novel RNA-based therapeutic, demonstrated a favorable safety profile
  - No DLTs or treatment-related SAEs were observed
  - Only 1 patient with infusion-related reactions, which was clinically well managed
- NSCLC disease control rate of 55% (6/11) was observed in heavily pre-treated patient population
- NSCLC partial response and unconfirmed partial response rate of 18% (2/11) was observed
- NBF-006 demonstrated dose-proportional increases with no accumulation or exposure reduction from 0.15 – 1.6 mg/kg
- Due to favorable safety profiles with early signs of efficacy, NBF-006 dose expansion in KRAS-mutant NSCLC patients, is ongoing