Nitto BioPharma Inc.

Clinical Study Protocol

NBF-006-001: A Phase I/Ib Open-Label, Multi-Center, Dose-Escalation Study to Investigate the Safety, Pharmacokinetics and Preliminary Efficacy of Intravenous NBF-006 in Patients with Non-Small Cell Lung, Pancreatic, or Colorectal Cancer Followed by a Dose Expansion Study in Patients with KRAS-Mutated Non-Small Cell Lung Cancer

Investigational Product: NBF-006

NCT03819387

06 June 2022

A Phase I/Ib Open-Label, Multi-Center, Dose-Escalation Study to Investigate the Safety, Pharmacokinetics and Preliminary Efficacy of Intravenous NBF-006 in Patients with Non-Small Cell Lung, Pancreatic, or Colorectal Cancer Followed by a Dose Expansion Study in Patients with KRAS-Mutated Non-Small Cell Lung Cancer

Protocol No.:	NBF-006-001
IND No.:	139860
Sponsor:	Nitto BioPharma, Inc. 10618 Science Center Drive San Diego, California, 92121 (858) 255-3010
Medical Monitor:	Theradex Oncology 4365 Route 1 South, Suite 101 Princeton, New Jersey, 08540 (609) 799-7580
Protocol Version:	Amendment 4
Date:	06 June 2022
Replaces:	Amendment 3, 08 February 2021

CONFIDENTIAL

INVESTIGATOR'S STATEMENT

1. I have carefully read this protocol entitled "A Phase I/Ib Open-Label, Multi-Center, Dose-Escalation Study to Investigate the Safety, Pharmacokinetics and Preliminary Efficacy of Intravenous NBF-006 in Patients with Non-Small Cell Lung, Pancreatic, or Colorectal Cancer Followed by a Dose Expansion Study in Patients with KRAS-Mutated Non-Small Cell Lung Cancer" and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.
2. I understand that this study will not be initiated without approval of the appropriate Institutional Review Committee/Independent Ethics Committee (IRB/IEC), and that all administrative requirements of the governing body of the Institution will be complied with fully.
3. Informed written consent will be obtained from all participating patients in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union Good Clinical Practice (GCP) Directive 2005/28/EC, the International Council for Harmonization (ICH) Guideline for GCP, Section 4.8, and the terms of the Declaration of Helsinki (2013).
4. I will enroll patients who meet the protocol criteria for entry.
5. I understand that my signature on each completed electronic Case Report Form (eCRF) indicates that I have carefully reviewed the complete set of eCRFs and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the Food and Drug Administration, a Competent Authority of the European Union or another Regulatory Authority.

Amendment 4 – 06 June 2022

Investigator:

Name: _____ Telephone: _____

Address: _____

_____

Signature: _____ Date: _____

Sponsor Representative:

Signature: _____ Date: _____

Joachim Gullbo, MD PhD
Medical Monitor, Theradex Oncology

Sponsor Contact:

Signature: _____ Date: _____

Sonya Zabludoff PhD
Vice-President, Clinical Operations (GCP Clinical Director), Nitto BioPharma, Inc.

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CLINICAL STUDY SYNOPSIS

Name of Sponsor: Nitto BioPharma, Inc. 10618 Science Center Drive San Diego, California, 92121 (858) 255-3010	**Name of Monitor:** Theradex Oncology 4365 Route 1 South, Suite 101 Princeton, New Jersey, 08540 (609) 799-7580
Name of finished product: NBF-006	
Name of active ingredient: NDT-05-1040	
Title of the study: A Phase I/Ib Open-Label, Multi-Center, Dose-Escalation Study to Investigate the Safety, Pharmacokinetics, and Preliminary Efficacy of Intravenous NBF-006 in Patients with Non-Small Cell Lung, Pancreatic, or Colorectal Cancer Followed by a Dose Expansion Study in Patients with KRAS-Mutated Non-Small Cell Lung Cancer	
Protocol number: NBF-006-001	
Clinical phase: Phase I/Ib	

Objectives:

Part A (Dose escalation)

Primary:

- To determine the safety profile, maximum tolerated dose (MTD), and recommended dose of NBF-006 for Part B in patients with advanced non-small cell lung cancer (NSCLC), pancreatic, or colorectal cancer for dose levels 1-4 (0.15, 0.3, 0.6, and 1.2 mg/kg) and in patients with Kirsten rat sarcoma (KRAS)-mutated NSCLC for dose level 5 (1.6 mg/kg).

Secondary:

- To evaluate preliminary efficacy of NBF-006 in patients with advanced NSCLC, pancreatic, or colorectal cancer for dose levels 1-4 (0.15, 0.3, 0.6, and 1.2 mg/kg) and in patients with KRAS-mutated NSCLC for dose level 5 (1.6 mg/kg).
- To investigate the pharmacokinetics (PK) of NBF-006.

Exploratory:

- To evaluate correlation between biomarkers and clinical outcome.
- To evaluate correlation between KRAS mutations and clinical outcome.

Part B (Dose expansion)

Primary:

- To evaluate preliminary efficacy and safety profile of NBF-006 in patients with KRAS-mutated NSCLC.

Secondary:

- To investigate the PK of NBF-006.

Exploratory:

- To evaluate correlation between glutathione S-transferase pi (GSTP) messenger ribonucleic acid (mRNA) knockdown (KD) in surrogate tissue (peripheral blood mononuclear cells [PBMCs]), biomarkers, and clinical outcome.

Study Overview:
This is an open-label, non-placebo-controlled study conducted in two parts: Part A (dose escalation) and Part B (dose expansion). In both parts, NBF-006 will be administered via intravenous (IV) infusion over approximately 70 minutes, once a week (QW) for 4 weeks followed by a 2-week rest period. The length of each cycle is 6 weeks.

Part A (Dose escalation):
Patients in Part A will have previously treated progressive or metastatic NSCLC, pancreatic, or colorectal cancer, with or without KRAS mutation.

The first dose level (0.15 mg/kg) will be a single patient cohort. If any Grade 2 or greater drug-related event occurs during the first cycle of treatment, the cohort will be expanded up to 3 patients. If a dose-limiting toxicity (DLT) occurs during the first cycle, the cohort will be expanded up to 6 patients before proceeding with dose escalation.

Subsequent cohorts in the dose escalation phase will enroll patients following the standard 3+3 design. If 1 out of 3 patients experience a DLT during the first cycle of treatment, the dose cohort will be expanded up to 6 patients. If no DLT is observed in the first 3 patients enrolled at the highest dose, this cohort will be expanded to 6 patients. If 2 or more out of 6 patients experience DLTs, the MTD has been exceeded, and dose escalation will cease. Up to 3 additional patients will be enrolled at a lower dose if only 3 patients were treated at that dose level, to confirm safety of that dose. MTD will be defined as a dose where 0 or 1 out of 6 patients have DLTs. To collect clinically important information in the target population, and prepare for Part B, the 6-patient cohort(s) must each include at least 3 patients with histologically or cytologically confirmed progressive or metastatic NSCLC, up to dose level 4 (1.2 mg/kg). In dose level 5 (1.6 mg/kg), only patients with previously-treated NSCLC with KRAS mutation will be included. Once safety has been confirmed in Part A at 1.6 mg/kg (i.e., 0-1 DLT in 6 patients), an additional 4 patients with KRAS-mutated NSCLC will be enrolled in Part B of the study at this dose level. Stratification for GSTT1-null genotype patients will not occur in Part A.

Part A NBF-006 Dose Levels

Dose level	NBF-006 dose	Number of patients
1	0.15 mg/kg	1-6
2	0.3 mg/kg	3-6
3	0.6 mg/kg	3-6
4	1.2 mg/kg	3-6
5	1.6 mg/kg	3-6

Part B (Dose expansion):
Patients in Part B must have previously treated NSCLC with confirmed KRAS mutation. Two dose levels will be explored further in Part B: 0.6 mg/kg and 1.2 mg/kg. Twenty (20) patients will be enrolled in Part B, with 10 patients enrolled in each of the two cohorts. Both cohorts will be stratified for GSTT1-null genotype patients. Once dose level 5 (1.6 mg/kg) has been confirmed to be safe in Part A, an additional 4 patients will then be enrolled at 1.6 mg/kg, for a planned total of 24 patients in Part B. The proportion of GSTT1-null patients treated at the highest dose level (1.6 mg/kg) will be balanced with the previous two expansion cohorts as much as possible by

applying stratification rules in Part B (depending on the distribution of patients enrolled in Part A, unstratified).

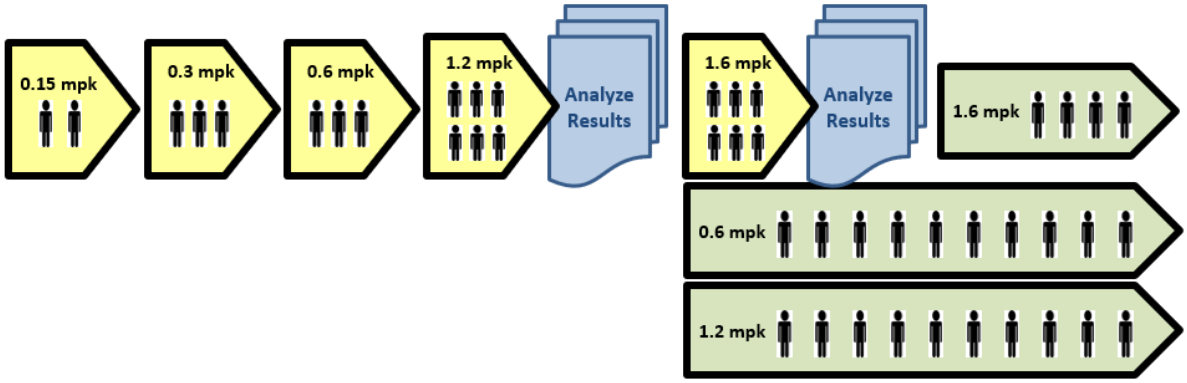
Part B NBF-006 Dose Levels

Dose level	NBF-006 dose	Number of patients
3	0.6 mg/kg	10
4	1.2 mg/kg	10
5	1.6 mg/kg	4*

*Dose level 5 pending confirmation of safety in Part A

Visits and study examinations will be performed per the Study Calendar. In both Part A and Part B, patients will be monitored regularly with physical examinations and laboratory tests. Concomitant measures and adverse events (AEs) will be monitored throughout the study. AEs will be assessed per National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Tumor measurement by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will be conducted at baseline and after every second cycle in Part A dose levels 1-4, and at the end of every cycle for dose level 5 in Part A and all patients in Part B. A post-treatment safety visit will be conducted approximately 30 days following the last dose.

Part A and B Schematic of Study Design



Number of patients: Part A: Up to 20 patients anticipated
Part B: 20 or 24 patients (depending on outcome of 1.6 mg/kg dose level in Part A)

Diagnosis and main criteria for inclusion:

Inclusion Criteria:

1. Part A: Patients with histologically or cytologically confirmed progressive or metastatic NSCLC, pancreatic, or colorectal cancer that have failed standard treatment and for which no other effective treatment is available or appropriate for the patient up to dose level 4. In dose level 5 (1.6 mg/kg), patients with histologically or cytologically confirmed progressive or metastatic NSCLC with documented KRAS-mutant genotype, who have failed standard treatment and have no other effective treatment available or appropriate for the patient.

Part B: Patients with histologically or cytologically confirmed progressive or metastatic NSCLC with documented KRAS-mutant genotype, who have failed standard treatment and have no other effective treatment available or appropriate for the patient.

2. Eastern Cooperative Oncology Group performance status of 0-2.
3. Men and women ≥ 18 years of age.
4. Patients must have recovered from all acute adverse effects (excluding alopecia) of prior therapies to baseline or ≤ Grade 1 prior to study entry.
5. Adequate bone marrow function, defined as an absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and a platelet count ≥ 100 x 10^9/L.
6. Adequate renal function, defined as serum creatinine ≤ 1.5 x upper limit of normal (ULN) for the institution or calculated creatinine clearance [Cockcroft-Gault method] must be ≥ 60 mL/min/1.73 m^2. If serum creatinine is >1.5 x ULN, then creatinine clearance can be calculated from a 24-hour urine collection.
7. Adequate hepatic function, defined as total bilirubin ≤ 1.5 mg/dL and alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5 x ULN, or ≤ 5 x ULN if known liver metastases.
8. Female patients of childbearing potential must have a negative serum or urine pregnancy test result at time of pre-treatment screening.
9. Patients with reproductive potential must agree to use at least one form of highly effective contraception (APPENDIX III) prior to study entry and for up to 30 days beyond the last administration of study drug.
10. Patients must be capable of providing informed consent and must be willing to provide written informed consent prior to the start of any study-specific procedures.
11. All patients must have measurable tumor per RECIST 1.1.
12. Agree to adhere to all study protocol requirements.

Exclusion Criteria:

1. Prior radiation therapy within 2 weeks; or prior chemotherapy or non-cytotoxic therapy within 4 weeks or 5 drug half-lives, whichever is shorter (exception: 6 weeks for nitrosoureas or mitomycin C); or monoclonal antibodies within 4 weeks prior to the first dose of study treatment.
2. Concurrent use of any other investigational agent.
3. Known or clinically suspected central nervous system or leptomeningeal metastases, unless irradiated or treated a minimum of 4 weeks prior to first study treatment and stable without requirement of corticosteroids for > 1 week.
4. Pregnant or breast feeding. A negative pregnancy test must be documented at baseline for women of childbearing potential. Patients may not breast-feed infants while on this study.
5. Significant cardiovascular disease or condition, including:
   a. Congestive heart failure currently requiring therapy
   b. Need for antiarrhythmic medical therapy for ventricular arrhythmia
   c. Severe conduction disturbance
   d. Angina pectoris requiring therapy
   e. QTc interval > 450 msec (males) or > 470 msec (females) Fridericia's correction.
      Note: QTc values up to 500 ms will be acceptable where patient's medical history e.g., bundle branch block, is known to cause mild QTc prolongation and the condition is well controlled.
   f. History of congenital long QT syndrome or congenital short QT syndrome
   g. Uncontrolled hypertension (per the Investigator's discretion)

h. Class III or IV cardiovascular disease according to the New York Heart Association's Functional Criteria
i. Myocardial infarction within 6 months prior to first study drug administration

6. Known history of human immunodeficiency virus or active infection with hepatitis B virus or hepatitis C virus.
7. Known uncontrolled intercurrent illnesses, including uncontrolled viral influenza and COVID-19, systemic bacterial infections, and fungal infections.
8. Psychiatric disorder or altered mental status that would preclude understanding of the informed consent process and/or completion of the necessary studies.
9. Known allergic reactions to H1/H2 antagonists.

Test product, dose and mode of administration:

NBF-006 (10 mg of active ingredient per vial) will be reconstituted with 5.6 mL of the 60 mM sodium acetate diluent (provided by Sponsor) and then diluted with normal saline to 300 mL (or to 320 mL for the 1.6 mg/kg dose level) and administered to the patient via IV infusion.

The infusion will be implemented as a stepwise infusion:

(1) 0.5 mL/min for 10 minutes,
(2) then 1.5 mL/min for 10 minutes, and
(3) finally 6 mL/min for the remaining volume

Total infusion duration of approximately 70 minutes (± 20 minutes).

Doses ranging from 0.15 to 1.6 mg/kg will be evaluated. The drug will be administered weekly for 4 weeks, followed by a 2-week rest period. The length of each cycle is 6 weeks.

For detailed instructions on vial concentration, preparation and dispensing, please refer to the Pharmacy Manual.

In the case of an infusion reaction, the infusion should be temporarily interrupted. If symptoms resolve, then resume and complete the stepwise infusion as outlined above. If the symptoms have not resolved by 15 minutes, wait until the symptoms have resolved before resuming the infusion or the patient should receive symptomatic treatment. Recommencing the infusion should only be attempted after reactions have resolved completely. If the infusion reaction does not resolve within one hour after administration of symptomatic treatment (e.g., acetaminophen and/or antihistamines) the dosing should not be resumed the same day. Rechallenge should be discussed with the Medical Monitor, and premedication must be given if the patient receives any further doses.

Dose-limiting toxicity:

AEs will be assessed per NCI CTCAE version 5.0. DLT is defined as any treatment related toxicity (i.e., not attributable to the underlying active disease or intercurrent illness) during the first 42 days (Cycle 1) of study treatment meeting any of the criteria below. Ongoing safety events beyond Cycle 1 will be reviewed across all cohorts during the study to help inform dose escalation decisions.

DLT includes:

1. Treatment-related hematological toxicities as follows:
   - Grade 4 neutropenia.
   - Any grade neutropenic fever.
   - ≥ Grade 3 thrombocytopenia lasting longer than 3 consecutive days.
   - ≥ Grade 3 thrombocytopenia with bleeding.
   - Any other confirmed hematological toxicity ≥ Grade 4 (a repeat test may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value).

2. Treatment-related non-hematological toxicity ≥ Grade 3 including:
   - Electrolyte abnormalities that do not resolve within 48 hours of intervention (a repeat test may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value).
   - ≥ Grade 3 infusion-related reactions.
   - ≥ Grade 3 cytokine release syndrome.
   - Any hepatic toxicity meeting Hy's Law criteria.
   - Grade 3 nausea/vomiting or diarrhea or other self-limited or medically controllable toxicities that last > 72 hours regardless of medical intervention.

3. Any other treatment-related toxicity i.e., greater than at baseline, which is clinically significant and/or unacceptable, does not respond to supportive care and results in a disruption of the dosing schedule of more than 14 days.

4. Any death not clearly due to the underlying disease or extraneous causes.

DLT excludes:
- Alopecia of any grade.

Duration of treatment:

Upon completion of Cycle 1, in the absence of disease progression or unacceptable toxicity, patients may continue to be treated with NBF-006 at the same dose and schedule until disease progression, death, withdrawal of consent, Investigator decision to remove patient, or intolerable toxicity, whichever occurs first. A patient may continue on study (even if one or more criterion meets Disease Progression per RECIST 1.1) at the Investigator's discretion if deemed that the drug is well-tolerated and that the patient may continue to receive benefit from continuing treatment.

Reference therapy, dose and mode of administration: Not applicable.

Criteria for evaluation:

Study assessments are summarized in the Study Calendar. All screening procedures will be performed within 28 days prior to the first dose, unless otherwise specified.

Safety: All patients who have received any component of study treatment will be considered evaluable for safety.

Safety will be assessed by means of physical examination, weight, vital signs, performance status, laboratory evaluations (hematology, biochemistry), electrocardiogram (ECG), pain assessment, and

recording of concurrent illness/therapy and AEs. NCI CTCAE version 5.0 will be used to grade all toxicities. All related AEs will be monitored until resolution.

Patients will be monitored for safety and concomitant medications throughout the study.

Efficacy: Response to treatment will be assessed according to RECIST 1.1. For Part A (dose levels 1-4), the objective evaluation will be performed at baseline and at the end of every even numbered cycle. For Part A (dose level 5) and Part B, the objective evaluation will be performed at baseline and at the end of every cycle. A patient may continue on-study (even if one or more criterion meets Disease Progression per RECIST 1.1) at the Investigator's discretion if deemed that the drug is well-tolerated and that the patient may continue to receive benefit from continuing treatment.

Pharmacokinetics:
Plasma concentrations of NDT-05-1040 will be measured from blood samples collected at the following timepoints for Part A:

- Cycle 1, Day 1:
  - Before start of infusion (SOI),
  - During the infusion: 20 m (±5m) after the start of the last infusion step implemented at 6 mL/min rate
  - End of Infusion (EOI); after EOI: 0.5 hr (±5m), 2 hr (±10m), 6 hr (±15m), 24 hr (±1hr), 48 hr (±2hr), 72 hr (±3hr)
- Cycle 1, Day 8: pre-dose
- Cycle 1, Day 22:
  - Before SOI
  - During the infusion: 20 m (±5m) after the start of the last infusion step implemented at 6 mL/min rate
  - EOI; after EOI: 0.5 hr (±5m), 2 hr (±10m), 6 hr (±15m), 24 hr (±1hr), 48 hr (±2hr), 72 hr (±3hr)
- Cycle 2, Day 1: pre-dose

Plasma concentrations of NDT-05-1040 will be measured from blood samples collected at the following timepoints for Part B. (Note: timepoints are the same as the Part A PK sample collection with the exception of the 48 and 72 hr timepoint collections, which will not be measured in Part B):

- Cycle 1, Day 1:
  - Before SOI,
  - During the infusion: 20 m (±5m) after the start of the last infusion step implemented at 6 mL/min rate
  - EOI; after EOI: 0.5 hr (±5m), 2 hr (±10m), 6 hr (±15m), 24 hr (±1hr)
- Cycle 1, Day 8: pre-dose
- Cycle 1, Day 22:
  - Before SOI
  - During the infusion: 20 m (±5m) after the start of the last infusion step implemented at 6 mL/min rate
  - EOI; after EOI: 0.5 hr (±5m), 2 hr (±10m), 6 hr (±15m), 24 hr (±1hr)
- Cycle 2, Day 1: pre-dose

Anti-drug antibody (ADA) assay:

- Cycle 1, Day 1: pre-dose
- Cycle 1, Day 15: pre-dose
- Cycle 2, Cycle 4, Cycle 6, Cycle 8, etc. (i.e., every even numbered cycle), up to one year: Day 1 pre-dose
- Year 2 and beyond: every 6 months
- End of treatment (EOT)
- 30-day safety follow-up visit

KRAS genotyping:

Depending upon availability and patient consent, we may request an archival tumor sample and/or results of a genomic tumor profile, but these are not required to confirm patient eligibility for dose levels 1-4 in Part A.

Confirmation of KRAS mutation is a requirement for dose level 5 (1.6 mg/kg) in Part A and for all patients in Part B. Genomic tumor profile results from either core biopsies or liquid biopsies can be used (outlined in Section 8.5). Fresh biopsy (if needed) may be obtained only if it has minimal risk of complications for the patient. If such type of biopsy is needed but cannot feasibly be collected, the sponsor and Medical Monitor should be consulted.

GSTT1 genotyping and stratification:

In Part A dose level 5 (1.6 mg/kg) of the study, patients will not be stratified for the GSTT1-null genotype, but whole blood samples will still be collected during the screening visit and batch analyzed at a central lab.

Patients enrolled in Part B of the study will be stratified for the GSTT1-null genotype. Analysis will be done at a central lab from blood samples collected during the screening visit.

Immune activation markers (cytokines):

Blood samples will be collected during Cycle 1 (Week 1) for all patients treated in Part A of the study for determination of cytokines (IFN-γ, IL-1β, IL-6, TNF-α):

- Pre-dose
- 10 ± 3 minutes after SOI
- 60 ± 10 minutes after EOI
- 6 hr ± 15 minutes after EOI
- 24 hr ± 1 hr after EOI

For Dose levels 3 (0.6 mg/kg) and 4 (1.2 mg/kg) did not result in immune activation in Part A and therefore, cytokine activity will not be monitored at those two dose levels in Part B. However, if a patient, during or after any infusion of NBF-006, develops IRR symptoms (e.g., backache, fever, nausea, headache, rash, rapid heartbeat, low blood pressure, or trouble breathing), best attempts should be made to collect cytokines as described for Part A with the exception of 10 ± 3 minutes after SOI, which should be collected as close as feasible to the IRR. If there is no meaningful cytokine induction in the 6-patient dose level 5 (1.6 mg/kg) during Part A, then cytokine testing will also not be needed in the remaining 4 patients in Part B at that same dose level (1.6 mg/kg).

Immune activation markers (complement):
Blood samples will be collected during Cycle 1 (Week 1) for all patients in Part A and Part B of the study for determination of complement (CH50, Bb, C3a, C5a):

- Pre-dose
- 10 ± 3 minutes after SOI
- 60 ± 10 minutes after EOI
- 6 hr ± 15 minutes after EOI
- 24 hr ± 1 hr after EOI

Exploratory studies:
PBMCs isolated from patient blood samples (at baseline) and/or tumor tissue (archival samples or those procured for routine medical care during the course of the study) may be retained for biomarker testing. Biomarkers may include (but are not limited to) GSTP or related proteins of the glutathione S-transferase (GST) family.

GSTP mRNA KD:
Blood samples will be collected at the following timepoints for evaluation of GSTP KD in the 6 patients from Part A at 1.6 mg/kg dose level and from all patients in Part B of the study:

- Cycle 1, Day 1:
  - Before SOI
  - After EOI: 6 hr (±15m), 24 hr (±1hr)
- Cycle 1, Day 8: before SOI

Patients who are willing to provide exploratory pre- and on-study biopsies will be sampled prior to the first dose and 24 hours after the fourth dose in Cycle 1, if clinically feasible. If possible, lesions selected as RECIST target lesions should not be biopsied.

Statistical methods:
All analyses will be descriptive. Categorical variables will be presented with numbers and, if meaningful, percentages. Continuous variables will be presented by n, mean, median, standard deviation and range (min and max) as appropriate. Presentations will be by each dose cohort.

The Intent-to-Treat population will include all participants who were enrolled into the study, irrespective of whether study medication was administered or not.

Safety Evaluable Population: All patients who received any component of study treatment.

Efficacy Evaluable Population: Patients with measurable disease by RECIST 1.1 who had a baseline assessment and at least one post-baseline assessment. Responses must be confirmed at a second imaging evaluation that should be performed at 4 weeks but no later than 5 weeks for patients in dose levels 1-4 in Part A after the criteria for response are first met. Response will be confirmed at 4 weeks or at the next scheduled scan at Week 6 of the following cycle for patients in dose level 5 in Part A and all patients in Part B. If a confirmative scan is done after 4 weeks, the next scheduled scan may be omitted. Responders (partial response [PR] and complete response [CR]) with confirmatory imaging will be denoted as PR and CR, respectively. Those with only one evaluation documenting PR or CR will be denoted as partial response-unconfirmed (PR-UC) and complete response unconfirmed (CR-UC). The primary evaluation of efficacy will focus on PR and CR but analyses incorporating PR-UC and CR-UC will also be performed.

ABBREVIATIONS

ADA	anti-drug antibodies
AE	adverse event
Akt	protein kinase B
ALT/SGPT	alanine transaminase / serum glutamic-pyruvic transaminase
ANC	absolute neutrophil count
API	active pharmaceutical ingredient
AST/SGOT	aspartate transaminase / serum glutamic-oxaloacetic transaminase
AUC	area under the curve
CFR	Code of Federal Regulations
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
dL	deciliter
DLT	dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EOI	end of infusion
EOT	end of treatment
ERK	extracellular signal-regulated kinase
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GDP	guanosine diphosphate
GLP	Good Laboratory Practice
GST	glutathione S-transferase
GSTP	glutathione S-transferase pi
GTP	guanosine triphosphate
HED	human equivalent dose
HNSTD	highest non-severely toxic dose
hr	hour
IB	Investigator's Brochure
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IFN-γ	interferon-gamma
IL	interleukin
IL-1ra	interleukin-1 receptor antagonist
IND	Investigational New Drug (application)
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	intravenous
JNK	c-JUN N-terminal kinase
KD	knockdown

kg	kilogram
KRAS	Kirsten rat sarcoma
LD	longest diameter
LNP	lipid nanoparticle
MAPK	mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated extracellular signal-regulated kinase
m	minute
mL	milliliter
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
msec	millisecond
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
NCI	National Cancer Institute
NE	not evaluable
nM	nanomolar
NSCLC	non-small cell lung cancer
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PEG	polyethylene glycol
PEG-DSPE	poly(ethylene glycol)–distearoylphosphatidylethanolamine
PET	positron emission tomography
PI3K	phosphatidylinositol-3-kinase
PK	pharmacokinetic
PR	partial response
PTEN	phosphatase and tensin homolog
qRT-PCR	quantitative reverse transcriptase polymerase chain reaction
QT/QTc	time between start of the Q wave and end of the T wave/corrected
QW	once a week
RAF	rapidly accelerated fibrosarcoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
RSI	Reference Safety Information
SAE	serious adverse event
SD	stable disease
siRNA	small interfering ribonucleic acid
SOC	standard of care
SOI	start of infusion
TGI	tumor growth inhibition
TNF-α	tumor necrosis factor-alpha
UC	unconfirmed
ULN	upper limit of normal
US	ultrasound

1.0 GENERAL INFORMATION

1.1 Protocol Number and Title of the Study

Protocol No. NBF-006-001, "A Phase I/Ib Open-Label, Multi-Center, Dose-Escalation Study to Investigate the Safety, Pharmacokinetics and Preliminary Efficacy of Intravenous NBF-006 in Patients with Non-Small Cell Lung, Pancreatic, or Colorectal Cancer Followed by a Dose Expansion Study in Patients with KRAS-Mutated Non-Small Cell Lung Cancer"

1.2 Sponsor

Nitto BioPharma, Inc.
10618 Science Center Drive
San Diego, California, 92121
(858) 255-3010

1.3 Monitor

Theradex Oncology
4365 Route 1 South, Suite 101
Princeton, New Jersey, 08540
(609) 799-7580

1.4 Signature Authorization

Theradex Oncology will act as the Sponsor Representative.

2.0 BACKGROUND INFORMATION

2.1 Introduction

Mutations of genes encoding protein kinases in the mitogen-activated protein kinase (MAPK) (KRAS/RAF/MEK/ERK) and phosphatidylinositol-3-kinase (PI3K) (PI3K/Akt/mTOR) signal-transduction pathways can alter the normal cellular kinase cascade regulatory function, resulting in the dysregulation of cellular proliferation, apoptosis, survival and cell migration common to tumor cell development and tumor progression (Figure 1). In the MAPK pathway, oncogenic Kirsten rat sarcoma (KRAS) drives the activation of the subsequent signaling proteins (RAF/MEK/ERK) and is known to be mutated frequently in pancreatic, colorectal, lung and gastric adenocarcinomas, as well as multiple myeloma and endometrioid carcinoma.[1] The PI3K pathway is regulated by the phosphatase and tensin homolog (PTEN) tumor suppressor and activated by guanosine triphosphate-RAS (GTP-RAS). Mutations of PTEN and KRAS thus alter the control of this important signaling pathway and multiple effector components of the PI3K pathway are known to be frequently mutated or altered in

a large variety of cancers.[2,3]

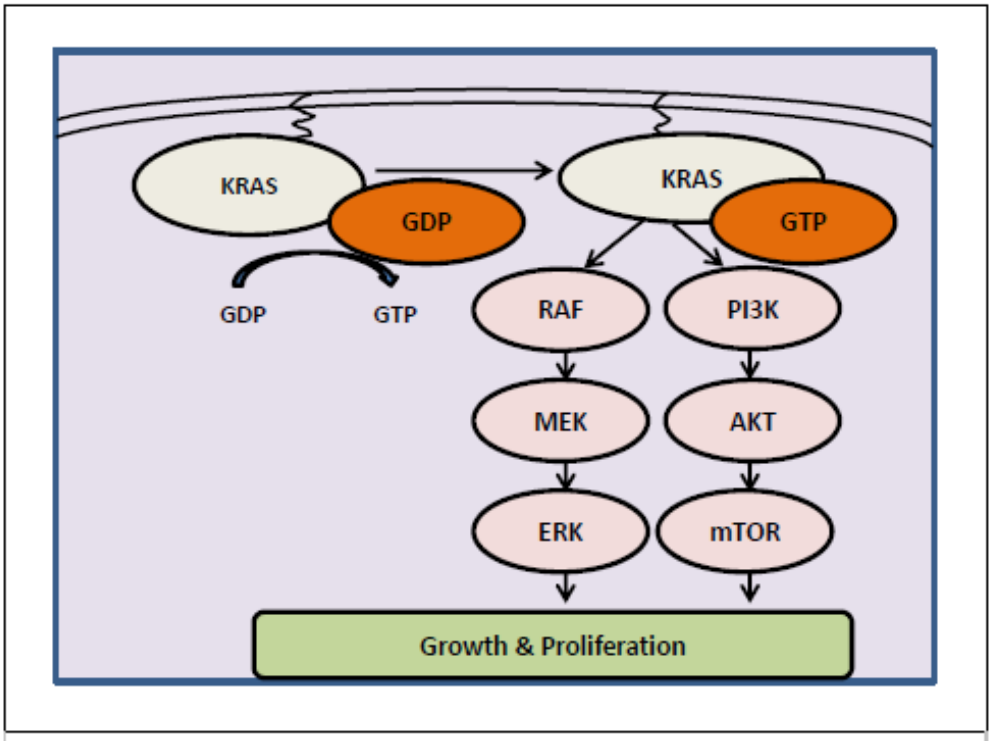


Figure 1: Interactions Among Several Key Components Involved in the MAPK and PI3K Pathways

KRAS is a member of the GTPase family of proteins, which switches to active mode when bound to GTP and inactive mode when bound to guanosine diphosphate. In pathological condition, KRAS mutation results in KRAS-GTP driving oncogenesis. Activation of KRAS phosphorylates and activates downstream targets, such as MEK/ERK in the MAPK pathway and Akt/mTOR in the PI3K pathway. This activation results in increased growth and proliferation.

With the central role of these two signaling pathways in cancer, the inhibition of KRAS and the signaling pathway effector proteins has been a major focus of cancer pharmaceutical research. The mutated KRAS oncoprotein itself has been difficult to target for inhibition due to difficulties in overcoming the impaired GTP hydrolysis of mutant KRAS, similarities of mutant and wild-type KRAS, and the availability of alternate mechanisms for required KRAS membrane association in the face of farnesyl transferase inhibition.[1,4] As a result, while KRAS inhibition remains an ongoing research undertaking, therapies inhibiting specific downstream effector signaling proteins along both pathways comprise the majority of targeted agents currently available or in development.

Nitto BioPharma, Inc. has targeted glutathione S-transferase pi (GSTP), one of a multigene

family of glutathione S-transferases (GST) isoenzymes that exist as mitochondrial, microsomal, or cytosolic enzymes involved in catalyzing thioether bonds between glutathione and electrophilic toxins and protecting cells from cellular oxidative stress.[5] Importantly, GSTP is also a significant protein in cancer cells and is implicated in the modulation of multiple signaling proteins in the RAS and PI3K pathways. GSTP has been detected at high levels in many tumors including ovarian, non-small cell lung, breast, colon, pancreas and lymphomas and has been associated with cancer disease progression as well as chemotherapy drug resistance.[5,6] GSTs have been recognized for their ability to bind structurally to diverse non-substrate ligands. In this non-enzymatic role, GSTs function to sequester the kinase in a complex, thus preventing it from acting on downstream targets.

GSTs are involved in detoxification of many potentially carcinogenic compounds. The homozygous deletions or null genotypes of GSTT1 (theta class) can be found in varying frequency in the normal population and may be associated with cancer incidence and drug effects. The frequency of GSTT1-null varies widely in different populations: approximately 50-60% in Asians, 15% in White populations, 15-20% in Blacks or African Americans, and less than 10% in Hispanic populations.[7]

GSTP has been implicated in regulation of cell signaling in response to intra- and extracellular stimuli in many pathways involving MAPKs. The result of this action is a regulation of pathways that control cell proliferation and apoptotic cell death. For example, GSTP was among the first isoenzymes found to inhibit c-JUN N-terminal kinase (JNK) through direct protein–protein interaction. JNK is a MAP kinase involved in stress response, apoptosis, inflammation, and cellular differentiation and proliferation. Thus, elevated expression of GSTP also has an anti-apoptotic role in tumor cells by interacting directly with MAPK/JNK through binding of the C-terminus of JNK.[8]

2.2 The Investigational Product

The drug product, NBF-006 contains a novel active pharmaceutical ingredient (API), NDT-05-1040, a small interfering ribonucleic acid (siRNA) encapsulated within lipid nanoparticles (LNPs). The LNP is composed of 5 key lipids, designed to inhibit the expression of GSTP messenger ribonucleic acid (mRNA) and protein in tumors and lung tissue. Before use, NBF-006 is reconstituted with 60 mM Sodium Acetate Diluent (Acetate Diluent), which will also be provided by the sponsor.

The significant technological achievement of this program is to provide effective extrahepatic delivery of siRNA. Historically, LNPs have tended to deliver cargo exclusively to the liver. NBF-006 was designed to distribute the siRNA cargo primarily to tumors and the lung. The current preclinical development of NBF-006 has been focused on KRAS-mutant non-small cell lung cancer (NSCLC) given the unmet medical need and the ability to deliver siRNA to lung tumors in preclinical models.

Importantly, NBF-006 delivery is also achieved in other organ locations and the pleiotropic effects of GSTP on the key pathways of many cancers indicate that the siRNA knockdown (KD) of GSTP protein expression may be effective for other cancer indications. Once the safety profile and preliminary anti-cancer activity of NBF-006 is established with this Phase I/Ib clinical trial, the efficacy of NBF-006 in additional malignancies may be explored.

2.3 Preclinical Studies

Key preclinical findings are summarized below. Please refer to the current Investigator's Brochure (IB) for details of these and other studies.

2.3.1 In Vitro Efficacy of NDT-05-1040 siRNA

As the RAS and PI3K signaling pathways play an important role in NSCLC, development and disease progression, preclinical characterization of the mechanism of action and anti-proliferative activity of GSTP-targeted siRNA NDT-05-1040 (the API) was established using KRAS mutant NSCLC cell lines for in vitro and in vivo experiments.

In cell-based assays, NDT-05-1040 demonstrated dose-dependent downregulation of GSTP and high potency in multiple cell lines, including KRAS-mutant NSCLC cells, while not affecting the survival of normal cells. Maximum reduction (~90%) in GSTP mRNA was achieved 24 hours post transfection and maintained for at least 5 days in A549 tumor cells. Maximum reduction was achieved with 10 nM NDT-05-1040, with minimal protein KD observed at 0.016 nM NDT-05-1040. Potential off-target effects of the siRNA were only observed for the guide strand but at concentrations 100-fold higher than the half maximal inhibitory concentration levels required for potent KD of the target gene.

Studies in cancer cell lines have shown an increase in sensitivity to GSTP KD in cell lines that are GSTT1-null and KRAS-mutant. Specifically, data from cell viability assays showed that 60% of the NSCLC cell lines screened were highly sensitive to NDT-05-1040. Furthermore, 38% of the NSCLC lines were GSTT1-null and within GSTT1-null cell lines, an increased sensitivity (72%) to NDT-05-1040 was observed. In addition, 67% of the KRAS-mutant NSCLC were sensitive to NDT-05-1040 treatment. Interestingly, of the KRAS-mutant cell lines, 44% with GSTT1 wild-type were sensitive to NDT-05-1040 as compared to 89% of GSTT1-null cell lines.

GSTP KD by NDT-05-1040 impacted the RAS/MEK/ERK, Akt, mTOR pathways leading to increased apoptosis and decreased proliferation. NDT-05-1040 triggered cell death through caspase activation (i.e., caspase 3/7). Furthermore, cell cycle analysis suggested that NDT-05-1040 inhibited tumor cell growth by reducing the S-phase population and enhancing the sub-G1 cell population.

2.3.2 In Vivo Efficacy of NBF-005 LNPs containing NDT-05-1040 siRNA

In vivo efficacy studies were performed using NBF-005 (an earlier formulation of the drug product that is identical to NBF-006, except for additional salt content) consisting of NDT-05-1040 siRNA encapsulated in an LNP. The LNP formulation serves as a protector to reduce the likelihood of the active siRNA component being metabolized by nucleases in blood and removed by other elimination systems, primarily through the renal excretion system.

NBF-005 demonstrated potent dose-dependent tumor growth inhibition (TGI) in A549, H23, and H2009 xenograft models in mice. A once a week (QW) dosing schedule of 0.5 to 4.0 mg/kg/week resulted in significant TGI, tumor stasis and tumor regression. Moreover, there were no significant differences on TGI between 8 consecutive weekly dosing (continuous) versus 8 doses broken up by a 4-week rest period in between (QW x 4 doses followed by 4-week rest period followed again by QW x 4 doses).

To better mimic human NSCLC tumors, efficacy in two lung orthotopic models –– tail vein injection and surgically grafted –– was evaluated. In the bioluminescent (A549Luc) tail-vein injection orthotopic lung tumor model, the average luminescent signal response in the NBF-005 treated group was markedly lower than the vehicle control group (14.3 vs 69.6 million photon/second, $P < 0.05$). Additionally, in the surgically implanted orthotopic lung tumor model, the survival of NBF-005 treated mice was significantly prolonged ($P < 0.005$) at a 4 mg/kg dose compared to the vehicle control group.

2.3.3 In Vitro Evaluation of GSTP Knockdown in PBMCs by NBF-006

In vitro studies were performed on healthy human peripheral blood mononuclear cell (PBMC) samples and were utilized for quantitative analysis of the mRNA level of GSTP using quantitative reverse transcriptase polymerase chain reaction (qRT-PCR). The purpose of this study was to examine the kinetic profile of GSTP mRNA in PBMCs after NBF-006 treatment. Timepoints and concentrations of NBF-006 were tested in vitro, which would best mimic the expected clinical exposure (based on pharmacokinetic [PK] data generated during the dose escalation phase of this study (NBF-006-001)).

The rationale for selecting 50 nM and 500 nM concentrations for in vitro PBMC testing is based on a representative, sustained plasma concentration range of patients dosed at 0.6 and 1.2 mg/kg, over the time frame of 6-72 hours, i.e., minimum to mean and median concentration levels, to reflect drug duration in blood circulation for the majority of patients.

As seen in Figure 2, when treated with 500 nM NBF-006, GSTP KD started as early as 6 hours and lasted for at least 72 hours in PBMCs. At 500 nM, maximal KD of ~61% was observed at 6 hours which decreased slightly at 48 and 72 hours. At the lower concentration (50 nM), the maximum KD was observed 6 hours post treatment and returned to baseline by 48 hours.

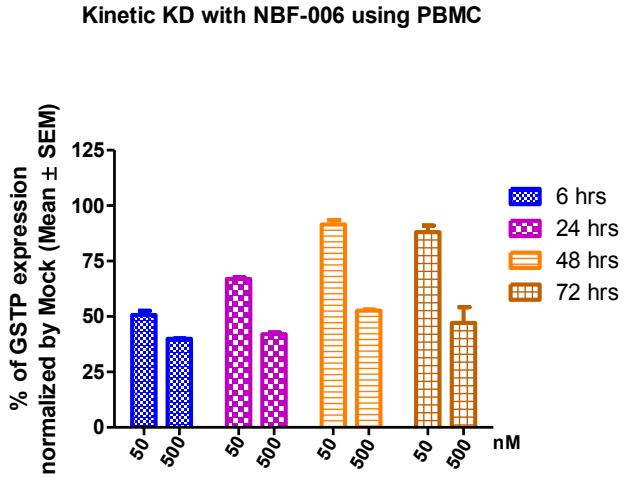


Figure 2: Relative Gene Expression of GSTP in PBMCs by qRT-PCR.

PBMCs were transfected with 50 nM and 500 nM of NBF-006 (pretreated with 5 µg/mL phospholipase A2 for 24 hours which reduces polyethylene glycol from the LNP and allows for in vitro transfection). Following NBF-006 treatment, cells were lysed, total RNA isolated, and GSTP mRNA levels were measured by qRT-PCR. Target gene mRNA level was normalized to RPLPO gene. Values represent mean ± standard error with triplicates.

Based on these results, timepoints for PBMC isolation from whole blood samples have been selected to be studied in this trial. A quantitative analysis of the mRNA GSTP levels with qRT-PCR in the PBMCs will allow for an assessment of target engagement, and therefore a pharmacodynamic correlation, in patients treated with NBF-006 in a surrogate tissue.

2.3.4 Toxicology Evaluation of NBF-005 and NBF-006 LNPs containing NDT-05-1040 siRNA

NBF-005 and NBF-006 triggered minimal or no immune response (7 cytokine panel) in PBMC samples from 4 healthy human donors at concentrations which cover the projected maximum concentration (C_{max}) of the first two dose levels (0.15 and 0.3 mg/kg) proposed in humans. No severe hemolytic activity was observed at doses up to 10 µM for either NBF-005 or NBF-006, a dose that is 6-fold greater than the projected clinical C_{max} at the highest planned dose of 1.2 mg/kg. No toll-like receptor response was stimulated at NBF-006 doses ranging from 0.0156 µM to 1 µM, which covers the projected C_{max} of the first three dose levels (0.15, 0.3, and 0.6 mg/kg) proposed in humans.

In dose range finding and Good Laboratory Practice (GLP) toxicology studies in monkeys, a mild and transient degree of activation of the classical and alternative complement pathways was evident from the small increases in Bb and C4a; however there was no increase in C5a. C5a is produced when activation of the classical or alternative pathways cascades into activation of the terminal pathway, leading to cleavage of C5 to C5a. C5a is a marker of terminal pathway activation and is the most powerful anaphylatoxin produced during complement activation. C5a has its own pro-inflammatory properties, and its accumulation

is generally associated with adverse effects in monkeys. Conversely, the absence of C5a accumulation may be considered an indication that increases in other split products may not have deleterious consequences. These results indicate that the generally small increases in Bb or C4a were not toxicologically significant.

Minimal changes in hematologic and clinical chemistries were observed in mice and monkeys in repeat-dose GLP toxicology studies. A common microscopic finding was the presence of vacuolation of the tubular epithelial cells or transitional epithelium, and aggregation of vacuolated phagocytic cells, in several organs (kidney, lung, urinary bladder, spleen and lymph nodes). Vacuolation was dose-dependent and showed signs of reversibility following the recovery period. Since the vacuolated phagocytic cells were observed in both NBF-005 and NBF-005 Empty (LNP only) treated animals, vacuolation was considered related to uptake and clearance of the LNP component. One of the NBF-006 LNP components is poly(ethylene glycol)–distearoylphosphatidylethanolamine (PEG-DSPE). Polyethylene glycol (PEG)-containing vacuoles in cells have been observed with several licensed PEGylated drugs with no associated pathological changes or human toxicity. There is evidence PEG vesicles can resolve with time.9 A review published in 2015 showed that PEG-related histologic changes, characterized as cellular vacuolation in certain tissues and cell types, is a common finding in nonclinical toxicology studies of PEGylated drugs. These changes were not associated with pathologic effects such as tissue degeneration, necrosis, and cellular distortion or changes in study endpoints including hematology, clinical chemistry, urinalysis, or organ weight.[10] The body of evidence available for approved PEGylated biopharmaceuticals has not identified any clinically reported functional consequences for compounds where vacuolation was observed in toxicology studies.[10]

Mice were the most sensitive species. Deaths were observed at the 40 mg/kg/week in both the GLP-repeat dose toxicology study and the non-GLP study at this dose. In the GLP-repeat dose toxicology study, 11 out of 126 mice treated with 40 mg/kg/week of NBF-005 and 2 out of 30 animals treated with 40 mg/kg/week of the reference item (empty liposomes) were found dead or euthanized. In the non-GLP study, only one animal died and this was considered an incidental event due to the lack of pathologic findings. The dose of 20 mg/kg/week in mice was a non-toxic dose at which there were no deaths and no overt adverse findings.

2.4 Previous Clinical Studies

There were no previous clinical studies with NBF-006. Dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg) of Part A were evaluated for the first time in 14 patients with advanced NSCLC (n=4), colorectal cancer (n=5), or pancreatic cancer (n=5) in Part A of this study from March 2019. No treatment-related serious adverse events (SAEs), treatment-related grade 3-4 adverse events (AEs), or dose-limiting toxicities (DLTs) have been observed in any patient treated at dose levels 1-4 in Part A of the study. One patient (dose level 2, 0.3 mg/kg) experienced a mild infusion related reaction (grade 2) that was managed with

standard therapy, and the patient could continue treatment in the study. Other reported, possibly related, grade 2 events included diarrhea (1 patient, dose level 1, 0.15 mg/kg), and fatigue and vomiting (1 patient each, dose level 4, 1.2 mg/kg). No clinically meaningful immune activation (complement and cytokines) was observed at dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg).

2.5 Rationale for Starting Dose, Dose Range, and Dosing Schedule

While ribonucleic acid (RNA) therapeutics are not biologics, the starting dose in humans takes into account industry guidance and best practices that advise using the highest non-severely toxic dose (HNSTD) in the most sensitive species studied in the preclinical toxicology studies. The highest non-toxic dose was 20 mg/kg/week in the most sensitive species, mice. The human equivalent dose (HED) is a weekly dose of 1.6 mg/kg. Per the guidance, 1/6th the HNSTD11, which would be a weekly dose of 0.3 mg/kg, is an appropriate starting dose. We have taken additional safety precautions by lowering the starting dose further to 0.15 mg/kg (1/12th the HNSTD). Preclinical efficacy was observed in the dose range of 2-4 mg/kg with maximal efficacy demonstrated at 4 mg/kg in mice (0.3 mg/kg HED).

Based on the toxicology data in the most sensitive species, mice, NBF-006 doses of 5 to 20 mg/kg caused non-severely toxic effects; the HED of this range is 0.41 to 1.63 mg/kg, which overlaps with the range of human doses to be used in this trial. The highest dose, 1.6 mg/kg, in this trial does not exceed the HNSTD equivalent in mice. Based on the well-tolerated doses in Part A up to 1.2 mg/kg, Part A will be further escalated to the top of the projected non-severely toxic dose range (1.6 mg/kg).

Based on the observation of vacuolation in the repeat-dose GLP toxicology studies, a rest period of 2 weeks has been implemented for the initial patient trial to allow for clearance of the LNPs. Vacuolation was dose-dependent and showed signs of reversibility following the 2-week recovery period. The rest period also reduces the burden on the patients. The dosing schedule (4 weekly doses + 2-week rest period) is well supported by the nonclinical xenograft and repeat-dose toxicology studies.

2.6 Potential Risks and Benefits

As this is the first-in-man study of NBF-006, no human data regarding the safety or potential benefit of NBF-006 was available before the study started. Since the clinical study began, 14 patients (IB v 4.0, 26MAR2021) have been treated at dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg) without any signs of overt toxicity. No clinically meaningful immune activation (complement and cytokines) was observed at dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg).

Nucleic acids like the siRNA are rapidly degraded by nucleases when not protected by LNPs. Much of the potential toxicity of NBF-006 would result from the LNP components

themselves. Many clinical studies of LNP-formulated siRNAs have observed dose-dependent inflammatory cytokine elevations.12 Although many early phase trials of similar LNP-formulated siRNAs demonstrated a tolerable safety profile, immunogenicity (e.g., immune responses) could be a potential toxicity of this study treatment, especially at high doses or with frequent dosing of NBF-006.13

Based on other clinical trials with LNP-encapsulated siRNAs, the following are possible risks of NBF-006:

- Elevated cytokine levels or complement activation which could lead to inflammation. The symptoms would be flu-like symptoms, such as back pain, fever, nausea, headache, rash, rapid heartbeat, low blood pressure, temporary tightness in the chest, and trouble breathing. In severe cases, cytokine release syndrome could potentially develop.
- Allergic reaction (rash, wheezing, shortness of breath, heart palpitations, swelling of the face, and lowered blood pressure) to the drug or one of the drug or LNP components.
- In animals, NBF-006 administration led to increased vacuolation in tissues and cells. The appearance of vacuoles was not associated with any changes in organ function and went away over time.

Please see the current IB for further details about the potential risks and benefits associated with this study.

2.7 Characteristics of a Well-Conducted Trial

The following characteristics of an adequate and well-conducted trial will be implemented:

1. The Investigators will be well qualified by scientific training and experience.

2. Detailed electronic Case Report Forms (eCRFs) will be completed for every patient.

3. Requirements for institutional ethics review as set forth by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC), Title 21 Code of Federal Regulations (CFR) Part 56, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union Good Clinical Practice (GCP) Directive 2005/28/EC, the International Council for Harmonization (ICH) Guideline for GCP, Sections 3 and 4, and the terms of the Declaration of Helsinki (2013), will be followed.

4. Requirements for informed consent in accordance with institutional guidelines, Food and Drug Administration (FDA) requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances,

European Union GCP Directive 2005/28/EC, the ICH Guideline for GCP, Section 4.8, and the terms of the Declaration of Helsinki (2013), will be followed.

5. Safety data will be recorded and evaluated.

6. Routine monitoring visits will be conducted by the Sponsor's representative (Theradex Oncology) to ensure data accuracy, if allowed per local regulations. If on-site monitoring visits are not possible due to local regulations, restrictions, and/or guidance, monitoring visits to ensure data accuracy will be conducted remotely.

7. Drug accountability will be strictly maintained.

8. This trial will be conducted according to GCP, the protocol and applicable regulatory requirements. The Safety Review Committee (consisting of Investigators, Theradex Oncology Medical Monitor, and Sponsor) will also review safety data periodically and make recommendations accordingly.

2.8 Patient Population

This study will initially enroll adult male and female patients with progressive or metastatic NSCLC, pancreatic, or colorectal cancer that has failed standard treatment for which no other effective treatment is available or appropriate for the patient.

For dose level 5 (1.6 mg/kg) in Part A and all patients in Part B (dose expansion), the patients must have KRAS-mutant NSCLC.

3.0 TRIAL OBJECTIVES AND PURPOSE

Part A (Dose escalation)

Primary:
- To determine the safety profile, maximum tolerated dose (MTD), and recommended dose of NBF-006 for Part B in patients with advanced NSCLC, pancreatic, or colorectal cancer for dose levels 1-4 (0.15, 0.3, 0.6, and 1.2 mg/kg) and in patients with KRAS-mutated NSCLC for dose level 5 (1.6 mg/kg).

Secondary:
- To evaluate preliminary efficacy of NBF-006 in patients with advanced NSCLC, pancreatic, or colorectal cancer for dose levels 1-4 (0.15, 0.3, 0.6, and 1.2 mg/kg) and in patients with KRAS-mutated NSCLC for dose level 5 (1.6 mg/kg).
- To investigate the PK of NBF-006.

Exploratory:
- To evaluate correlation between biomarkers and clinical outcome.

- To evaluate correlation between KRAS-mutations and clinical outcome.

Part B (Dose expansion)

Primary:
- To evaluate preliminary efficacy and safety profile of NBF-006 in patients with KRAS-mutated NSCLC.

Secondary:
- To investigate the PK of NBF-006.

Exploratory:
- To evaluate GSTP mRNA KD in surrogate tissue (PBMCs) and correlation between biomarkers and clinical outcome.

4.0 TRIAL DESIGN

4.1 Overview of Trial Design

This is an open-label, non-controlled study conducted in two parts –– Part A (dose escalation) followed by Part B (dose expansion) (study schematic in Figure 3).

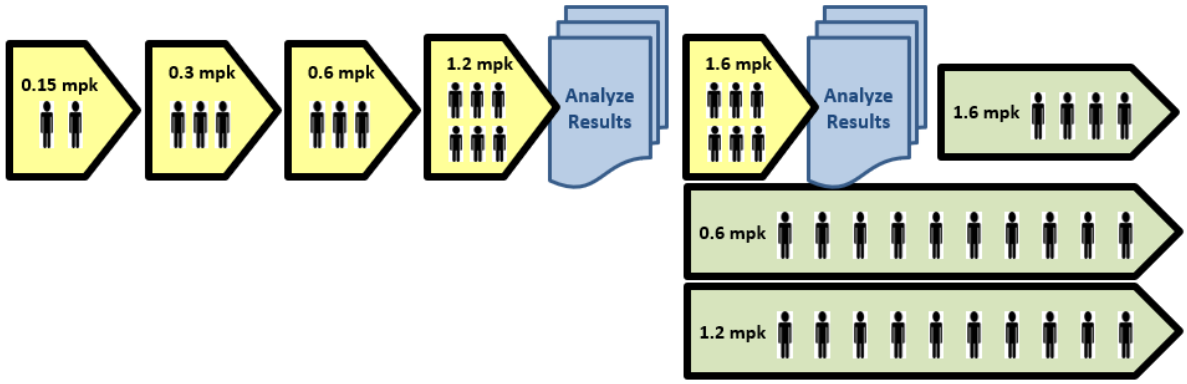


Figure 3: Schematic Overview of the Trial

4.2 End of Study

The end of the study is defined as the date of the last visit of the last patient undergoing the trial.

4.3 Minimizing Bias

This is an open-label, non-placebo-controlled study. Randomization will not be used. Patients enrolled in Part B will be stratified for GSTT1-null genotype to ensure equal allocation to the

cohorts with different doses. Patients treated at the highest dose level in Part B will be balanced for GSTT1-null genotype to match the distribution of patients at the other (stratified) dose levels as much as possible. This will be determined based on the first 6 patients treated at this dose in Part A (not stratified).

4.4 Drug Product

NBF-006 is a sterile, injectable, parenteral product containing 10 mg of the active ingredient per vial. The vial is stored frozen at -20 °C ± 5 °C until use.

NBF-006 is an LNP formulation that incorporates five (5) key lipid components (i.e., Lp-081, cholesterol, dioleoyl phosphatidylethanolamine, dioleoyl phosphatidylcholine, and PEG-DSPE) to encapsulate siRNA API (NDT-05-1040), forming the siRNA LNP complex for drug delivery. The API, NDT-05-1040 siRNA, is a synthetic, double-stranded RNA. NBF-006 is reconstituted for use with 60 mM Acetate Diluent. The Acetate Diluent is provided with the drug product.

4.5 Duration of Therapy

Upon completion of Cycle 1, in the absence of disease progression or unacceptable toxicity, patients may continue to be treated with NBF-006 at the same dose and schedule until disease progression, death, withdrawal of consent, Investigator decision to remove patient, or intolerable toxicity, whichever occurs first. A patient may continue on study (even if one or more criterion meets Disease Progression per Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) at the Investigator's discretion if deemed that the drug is well-tolerated and that the patient may continue to receive benefit from continuing treatment.

4.6 Trial Discontinuation

For reasonable cause, either the Investigator or the Sponsor may terminate this study prematurely. Written notification of the termination is required. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements (non-compliance).
- Lack of evaluable and/or complete data.
- Decision to modify the developmental plan of the drug.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

4.7 Drug Accountability/Disposition of Clinical Trial Supplies

Drug accountability records will be maintained for all clinical trial supplies.

All unused clinical trial supplies will be destroyed per the institution's standard operating procedure. Destruction of drug and trial supplies must be documented, and the documentation will be reviewed by/sent to the Sponsor or their Designee.

4.8 Registration

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-study evaluations (see Section 0). Patients must meet all of the eligibility requirements listed in Section 5.0. Patients will be registered on the study by using the Theradex Oncology Interactive Web Response System automated patient registration system (see the Study Operations Manual for specific instructions).

5.0 SELECTION AND WITHDRAWAL OF SUBJECTS

5.1 Inclusion Criteria

1. Part A: Patients with histologically or cytologically confirmed progressive or metastatic NSCLC, pancreatic, or colorectal cancer that have failed standard treatment and for which no other effective treatment is available for that patient up to dose level 4. In dose level 5 (1.6 mg/kg), patients with histologically or cytologically confirmed progressive or metastatic NSCLC with documented KRAS-mutant genotype, who have failed standard treatment and have no other effective treatment available or appropriate for the patient.
   Part B: Patients with histologically or cytologically confirmed progressive or metastatic NSCLC with documented KRAS-mutant genotype, who have failed standard treatment and have no other effective treatment available or appropriate for the patient.
2. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (APPENDIX I).
3. Men and women ≥ 18 years of age.
4. Patients must have recovered from all acute adverse effects (excluding alopecia) of prior therapies to baseline or ≤ Grade 1 prior to study entry.
5. Adequate bone marrow function, defined as an absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L and a platelet count ≥ 100 x 10^9/L.
6. Adequate renal function, defined as serum creatinine ≤ 1.5 x upper limit of normal (ULN) for the institution or calculated creatinine clearance [Cockcroft-Gault method] must be ≥ 60 mL/min/1.73 m^2. If serum creatinine is >1.5 x ULN, then creatinine clearance can be calculated from a 24-hour urine collection.
7. Adequate hepatic function, defined as total bilirubin ≤ 1.5 mg/dL and alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5 x ULN, or ≤ 5 x ULN if known liver metastases.

8. Female patients of childbearing potential must have a negative serum or urine pregnancy test result at time of pre-treatment screening.
9. Patients with reproductive potential must agree to use at least one form of highly effective contraception (APPENDIX III) prior to study entry and for up to 30 days beyond the last administration of study drug.
10. Patients must be capable of providing informed consent and must be willing to provide written informed consent prior to the start of any study-specific procedures.
11. All patients must have measurable tumor per RECIST 1.1.
12. Agree to adhere to all study protocol requirements.

5.2 Exclusion Criteria

1. Prior radiation therapy within 2 weeks; or chemotherapy or non-cytotoxic therapy within 4 weeks or 5 drug half-lives, whichever is shorter (exception: 6 weeks for nitrosoureas or mitomycin C); or monoclonal antibodies within 4 weeks prior to the first dose of study treatment.
2. Concurrent use of any other investigational agent.
3. Known or clinically suspected central nervous system (CNS) or leptomeningeal metastases, unless irradiated or treated a minimum of 4 weeks prior to first study treatment and stable without requirement of corticosteroids for > 1 week.
4. Pregnant or breast feeding. A negative pregnancy test must be documented at baseline for women of childbearing potential. Patients may not breast-feed infants while on this study.
5. Significant cardiovascular disease or condition, including:
   a. Congestive heart failure currently requiring therapy
   b. Need for antiarrhythmic medical therapy for ventricular arrhythmia
   c. Severe conduction disturbance
   d. Angina pectoris requiring therapy
   e. QTc interval > 450 msec (males) or > 470 msec (females) Fridericia's correction
      Note: QTc values up to 500 ms will be acceptable where patient's medical history e.g., bundle branch block, is known to cause mild QTc prolongation and the condition is well controlled.
   f. History of congenital long QT syndrome or congenital short QT syndrome
   g. Uncontrolled hypertension (per the Investigator's discretion)
   h. Class III or IV cardiovascular disease according to the New York Heart Association's Functional Criteria
   i. Myocardial infarction within 6 months prior to first study drug administration
6. Known history of human immunodeficiency virus or active infection with hepatitis B virus or hepatitis C virus.
7. Known uncontrolled intercurrent illnesses, including uncontrolled viral influenza and COVID-19, systemic bacterial infections, and fungal infections.
8. Psychiatric disorder or altered mental status that would preclude understanding of the informed consent process and/or completion of the necessary studies.
9. Known allergic reactions to H1/H2 antagonists.

5.3 Inclusion of Women, Minorities and Children

Both men and women and members of all races and ethnic groups are eligible for this study. Children are not eligible for this study because the safety and tolerability of the proposed dosing schedule has not been determined in adults.

5.4 Withdrawal Criteria

Protocol therapy will be discontinued at any time if any of the following situations occur:

1. Progressive disease (PD).
2. The development of toxicity which, in the Investigator's judgment, precludes further therapy.
3. Patient refusal.
4. Unacceptable AE(s).
5. Lost to follow-up/noncompliance.
6. Intercurrent illness that prevents further administration of treatment.
7. At the discretion of the Investigator.
8. Pregnancy.
9. Study termination.

Additionally, refer to the safety-related stopping rules in Section 8.1.2.11.

5.4.1 Withdrawn Subjects

When a patient is removed from the study, the Investigator will clearly document the reason in the medical record and complete the appropriate eCRF page describing the reason for discontinuation. In addition, every effort should be made to complete the appropriate assessments listed in Section 7.4.

5.4.2 Replacement of Subjects

Patients who discontinue due to toxicity (related to study drug) during Cycle 1, or who do not receive all doses due to toxicity in Cycle 1, will not be replaced. Patients who discontinue or who do not receive all doses for any reason other than toxicity will be replaced. Note, that all patients who enrolled in the study, regardless of their replacement, will be included in assessment of DLT per Section 6.1.3.

5.5 Noncompliance

All instances of protocol deviations will be entered into Monitor Express and will be reviewed and signed off by the Investigator and Theradex Oncology.

6.0 TREATMENT OF SUBJECTS

6.1 Drug Preparation and Administration

NBF-006 is intended for intravenous (IV) infusion use and exposure to direct sunlight should be avoided. Before use, the drug product vial is reconstituted with 5.6 mL of Acetate Diluent to bring the total constituted volume to approximately 6.7 mL, yielding a drug concentration of approximately 1.5 mg/mL. The constituted suspension is diluted into sterile saline diluent to a total volume of 300 mL (or to a total volume of 320 mL for the 1.6 mg/kg dose level) in the clinic for IV infusion to patients. The admixture solution will achieve a final desired drug concentration within acceptable physiological pH and tonicity for IV administration to patients.

NBF-006 infusion will be implemented as a stepwise infusion:

(1) 0.5 mL/min for 10 minutes,
(2) then 1.5 mL/min for 10 minutes, and
(3) finally 6 mL/min for the remaining volume

Total infusion duration of approximately 70 minutes (± 20 minutes).

Doses ranging from 0.15 to 1.6 mg/kg will be evaluated. The drug is administered weekly for 4 weeks followed by a 2-week rest period. The length of each cycle is 6 weeks.

For detailed instructions on vial concentration, preparation, and dispensing, please refer to the Pharmacy Manual.

The target infusion time is 70 minutes, but infusion rate will be adjusted as needed (e.g., due to infusion reaction). Premedication with H1/H2 antagonists should be considered if infusion reactions occur; refer to the management of infusion-related reactions (IRRs) outlined in Section 8.1.2.8.

The reconstituted drug (NBF-006 in Acetate Diluent) is stable in the glass vial for 2 hours at ambient conditions. The reconstituted drug solution is further diluted to the appropriate dose concentration with saline into a DEHP-free IV bag; this IV infusion solution is stable for 4 hours at ambient conditions. The drug product (lyophilized form, reconstituted solution, and IV infusion solution) should be kept out of direct sunlight.

Both NBF-006 and the Acetate Diluent will be provided by the Sponsor. Ordering instructions will be provided.

6.1.1 Dose Escalation Scheme

Part A (Dose escalation; Table 1):
NBF-006 (300 mL, or 320 mL for the 1.6 mg/kg dose level) will be administered via IV infusion over 70 minutes, QW for 4 weeks followed by a 2-week rest period. The length of each cycle is 6 weeks. Patients in dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg) of Part A, will have previously treated progressive or metastatic NSCLC, pancreatic, or colorectal cancer, regardless of KRAS mutation status. Patients in dose level 5 (1.6 mg/kg) of Part A must have previously treated progressive or metastatic NSCLC with confirmed KRAS mutation.

The first dose level (0.15 mg/kg) will be a single patient cohort. If any Grade 2 or greater drug-related event occurs during the first cycle of treatment, the cohort will be expanded up to 3 patients. If a DLT occurs during the first cycle, the cohort will be expanded up to 6 patients before proceeding with dose escalation.

Subsequent cohorts in the dose escalation phase will enroll patients following the standard 3+3 design. If 1 out of 3 patients experience a DLT during the first cycle of treatment, the dose cohort will be expanded up to 6 patients. If no DLT is observed in the first 3 patients enrolled at the highest dose, this cohort will be expanded to 6 patients. If 2 or more out of 6 patients experience DLTs, the MTD has been exceeded, and dose escalation will cease. Up to 3 additional patients will be enrolled at a lower dose if only 3 patients were treated at that dose level, to confirm safety of that dose. MTD will be defined as a dose where 0 or 1 out of 6 patients have DLTs. To collect clinically important information in the target population, and prepare for Part B, the 6-patient cohort(s) must each include at least 3 patients with histologically or cytologically confirmed progressive or metastatic NSCLC, up to dose level 4 (1.2 mg/kg). In dose level 5 (1.6 mg/kg), only patients with previously-treated NSCLC with KRAS mutation will be included. Once safety has been confirmed in Part A at 1.6 mg/kg (i.e. 0-1 DLT in 6 patients), an additional 4 patients with KRAS-mutated NSCLC will be enrolled in Part B of the study at this dose level. Stratification for GSTT1-null genotype patients will not occur in Part A, but whole blood samples will still be collected during the screening visit for Part A dose level 5 (1.6 mg/kg) and batch analyzed at a central lab.

One dose de-escalation is permitted.

Table 1: Part A NBF-006 Dose Levels

Dose level	NBF-006 dose	Number of patients
1	0.15 mg/kg	1-6
2	0.3 mg/kg	3-6
3	0.6 mg/kg	3-6
4	1.2 mg/kg	3-6
5	1.6 mg/kg	3-6

6.1.2 Part B (Dose Expansion)

After MTD is confirmed in Part A for up to dose level 4 (1.2 mg/kg), enrollment in Part B may commence. Part B will enroll patients with previously treated progressive or metastatic NSCLC with confirmed KRAS mutation.

The two dose levels that will be explored further in Part B are 0.6 mg/kg and 1.2 mg/kg. Twenty patients will be enrolled in Part B, with 10 patients enrolled in each of the two cohorts. Both cohorts will be stratified for GSTT1-null genotype patients to ensure equal allocation to the cohorts with different doses. Once dose level 5 (1.6 mg/kg) has been confirmed to be safe in Part A, an additional 4 patients will be enrolled at dose level 1.6 mg/kg, for a planned total of 24 patients in Part B. This last dose level in Part B at 1.6 mg/kg will also be stratified for GSTT1-null genotype patients to be balanced with the previous two expansion cohorts as much as possible. The final proportion of GSTT1-null patients treated at the highest dose level may depend on the first 6 patients treated in Part A (not stratified).

Table 2: Part B NBF-006 Dose Levels

Dose level	NBF-006 dose	Number of patients
3	0.6 mg/kg	10
4	1.2 mg/kg	10
5	1.6 mg/kg	4*

*Dose level 5 pending confirmation of safety in Part A

NBF-006 will be administered by weekly infusion for 4 consecutive weeks of a 6-week cycle.

6.1.3 Dose-Limiting Toxicity (Part A)

AEs will be assessed per National Cancer Institute (NCI) Common Terminology Criteria (CTCAE) version 5.0. DLT is defined as any treatment related toxicity (i.e., not attributable to the underlying active disease, or intercurrent illness) during the first 42 days (Cycle 1) of study treatment meeting any of the criteria described below. Ongoing safety events beyond

Cycle 1 will be reviewed across all cohorts during the study to help inform dose escalation decisions. Note, that all patients who enrolled in the study, regardless of their replacement as per Section 5.4.2, will be included in assessment of DLT.

DLT includes:

1. Treatment-related hematological toxicities as follows:
- Grade 4 neutropenia.
- Any grade neutropenic fever.
- ≥ Grade 3 thrombocytopenia lasting longer than 3 consecutive days.
- ≥ Grade 3 thrombocytopenia with bleeding.
- Any other confirmed hematological toxicity ≥ Grade 4 (a repeat test may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value).

2. Treatment-related non-hematological toxicity ≥ Grade 3 including:
- Electrolyte abnormalities that do not resolve within 48 hours of intervention (a repeat test may be required for confirmation of an isolated abnormality in the absence of clinical signs, symptoms or other abnormal investigations, i.e., a suspected spurious value).
- ≥ Grade 3 IRRs.
- ≥ Grade 3 cytokine release syndrome.
- Any hepatic toxicity meeting Hy's Law criteria.
- Grade 3 nausea/vomiting or diarrhea or other self-limited or medically controllable toxicities that last > 72 hours regardless of medical intervention.

3. Any other treatment-related toxicity, i.e., greater than at baseline, which is clinically significant and/or unacceptable, does not respond to supportive care and results in a disruption of the dosing schedule of more than 14 days.

4. Any death not clearly due to the underlying disease or extraneous causes.

DLT excludes:
- Alopecia of any grade.

6.1.4 Maximum Tolerated Dose (Part A)

The definition of MTD will be based upon review of safety data and DLTs corresponding to the first cycle of therapy in at least 6 evaluable patients. MTD will be defined as a dose where 0 or 1 out of 6 patients have DLTs.

6.2 Dose Interruptions/Withholding for Infusion Reactions or Other Reasons

Guidelines for management of IRRs, including circumstances for interrupting or

discontinuing dosing, are in Section 8.1.2.8.

Study drug may be withheld from a patient based on the Investigator's decision in the event of intercurrent illness, AEs, administrative reasons, or other reasons. If the patient's condition subsequently improves, or the situation that resulted in withholding study drug rectifies itself, the Investigator may resume dosing on the next practical dosing day.

Do not "make up" for missed or skipped doses i.e. if Week 3 dose is missed, do not administer a dose during the rest period (Week 5 or 6). Patients who miss a dose during Cycle 1 may be replaced per Section 5.4.2. The interruption and/or missed dose(s) should be recorded.

6.3 Concomitant Treatment

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents (with exception of the Acetate Diluent), chemotherapy, immunotherapy, hormonal, or biologic therapies while on study treatment. Palliative radiotherapy is allowed as medically indicated after completion of the first treatment cycle, and after discussion with medical monitor.

Supportive treatment may include anti-emetic, anti-diarrheal, anti-pyretic, anti-histamines, analgesics, antibiotics, and blood products. Treatment with denosumab or bisphosphonates, to prevent skeletal-related events in patients with bone metastases, is allowed throughout the trial.

At the discretion of the treating physician, patients may receive anti-histamine prophylaxis according to the standard of care (SOC) in clinical practice.

In case of IRRs, patients may be pretreated as needed with an H1 antagonist (e.g., diphenhydramine, hydroxyzine, or chlorpheniramine) and an H2 antagonist (e.g., famotidine) dosed in accordance with approved labelling or SOC. If premedication is administered parenterally, it should be given within 30 minutes of the start of infusion (SOI); if premedication is given orally, it should be given 60-90 minutes prior to SOI.

6.4 Monitoring Subject Compliance

This study will be monitored by Nitto BioPharma, Inc. or its Contract Research Organization (Theradex Oncology) according to ICH E6 guidelines of GCP. The study site monitor will regularly visit the study sites to ensure that the study is conducted according to the protocol and GCP principles.

7.0 STUDY EVALUATIONS

7.1 Schedule of Study Evaluations

Study evaluations for Part A and Part B are summarized in Table 3 and Table 4, respectively, and described in Sections 0 through 7.5.

Table 3: Study Calendar (Part A)

Part A Evaluations	Pre-treat-ment[a]	Cycle 1						Cycle 2						Cycle 3 & beyond				EOT	30-day safety FU visit (±3)
		Wk 1 D1	Wk 2 D8 ±3	Wk 3 D15 ±3	Wk 4 D22 ±3	Wk 5 D29-35	Wk 6 D36-42	Wk 1 D1	Wk 2 D8 ±3	Wk 3 D15 ±3	Wk 4 D22 ±3	Wk 5 D29-35	Wk 6 D36-42	Wk 1 D1	Wk 2 Wk 3 Wk 4	Wk 5	Wk 6		
Informed consent (incl. optional biopsy consent)	X																		
Medical history	X																		
Physical exam	X	X[b]						X						X				X	X
Weight	X	X[b]						X						X				X	X
Vital signs[e]	X	X[b]	X	X	X			X	X	X	X			X				X	
ECG[f]	X	X[b]			X													X	
ECOG performance status	X	X[b]						X						X				X	X
Tumor measurement[g] (tumor markers, if applicable)	X						X						X				X	X	
Hematology[h]	X	X[b]	X	X	X			X	X	X	X			X				X	X
Blood chemistry[i]	X	X[b]	X	X	X			X	X	X	X			X				X	X
Urinalysis	X	X[b]						X						X				X	X
Blood sample for immune activation biomarkers[j]		X																	
Pregnancy test	X[k]							X						X				X	
Blood sample for ADA assay[c]		X		X				X						X				X	X
PK blood sampling[d]		X	X		X			X											
Blood sample for exploratory biomarkers	X																		
Blood sample for GSTP KD[n]		X	X																
Confirmation of KRAS mutation[l] (dose levels 1-4 optional; dose level 5 mandatory)	X																		
GSTT1 genotyping[p]	X																		
Optional biopsy[o]	X				X														
NBF-006 administration[m]		X	X	X	X			X	X	X	X			X	X				
Concomitant medications	X	<---------- throughout study ---------->																X	

Adverse events		<---------- throughout study ---------->	X	X

a: Screening assessments may be performed within 28 days of study to treatment initiation, unless specified.

b: For Cycle 1 Day 1, these tests may be performed within 3 days prior to Cycle 1 Day 1. Physical exam and pre-treatment tests done within 3 days of Cycle 1 Day 1 do not need to be repeated for Wk1D1 unless clinically indicated.

c: ADA assay timepoints:

- Cycle 1, Day 1: pre-dose
- Cycle 1, Day 15: pre-dose
- Cycle 2, Cycle 4, Cycle 6, Cycle 8, etc. (i.e., every even numbered cycle), up to one year: Day 1 pre-dose
- Year 2 and beyond: every 6 months
- EOT
- 30-day safety follow up visit

d: PK timepoints:

- Cycle 1, Day 1:
  - Before start of infusion (SOI),
  - During the infusion: 20 m (±5min) after the start of the last infusion step implemented at 6 mL/min rate
  - End of Infusion (EOI); after EOI: 0.5 hr (±5min), 2 hr (±10min), 6 hr (±15min), 24 hr (±1hr), 48 hr (±2hr), 72 hr (±3hr)
- Cycle 1, Day 8: pre-dose
- Cycle 1, Day 22:
  - Before SOI
  - During the infusion: 20 min (±5min) after the start of the last infusion step implemented at 6 mL/min rate
  - End of Infusion (EOI); after EOI: 0.5 hr (±5min), 2 hr (±10min), 6 hr (±15min), 24 hr (±1hr), 48 hr (±2hr), 72 hr (±3hr)
- Cycle 2, Day 1: pre-dose

e: Vital signs, including blood pressure, heart rate, respiration rate, and temperature. During Cycle 1: Before SOI, EOI; after EOI: 1hr (±5min), 2hr (±10min). Other days: only before SOI and EOI.

f: Standard 12-lead ECG (in triplicate) while patient is in semi-recumbent position. Perform at screening, Cycle 1 First and fourth doses: within 15 minutes prior to SOI, then 15 min (±5min), 30 min (±10min), 1 hr (±10min) (at EOI)

g: Tumor measurement by RECIST version 1.1 and tumor markers will be collected at baseline and at the end of every even numbered cycle in Part A, dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg) and at the end of every cycle for dose level 5 (1.6 mg/kg), if applicable; the same method used at baseline for a patient should be used consistently for all evaluations throughout the study. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at 4 weeks but no later than 5 weeks for patients in dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg) in Part A after the criteria for response are first met. Response will be confirmed at 4 weeks or at the next scheduled scan (at Week 6 of the following cycle) for patients in dose level 5 (1.6 mg/kg) in Part A. If a confirmative scan is done after 4 weeks, the next scheduled scan at Week 6 of the following cycle may be omitted. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 5 weeks.

h: Hematology, including hemoglobin, white blood cell with differential, and platelet count.

i: Blood chemistry, including sodium, potassium, blood urea nitrogen, glucose, SGOT/SGPT (ALT/AST), alkaline phosphatase, total protein, total bilirubin, albumin, creatinine, and calcium.

j: Blood samples collected during Cycle 1 (Week 1) for all patients treated in Part A of the study for determination of complement (CH50, Bb, C3a, C5a) and cytokines (IFN-γ, IL-1β, IL-6, TNF-α):

- Pre-dose
- 10 ± 3 minutes after SOI
- 60 ± 10 minutes after EOI

- 6 hr ± 15 minutes after EOI
- 24 hr ± 1 hr after EOI

k: Pregnancy test; for women of childbearing potential, a negative pregnancy test (urine or serum) must be done within 7 days prior to study treatment initiation and documented.

l: Confirmation of KRAS mutation: optional for Part A dose levels 1-4 and mandatory for Part A dose level 5 (1.6 mg/kg). Obtain archive sample if available; otherwise, a fresh biopsy (low or minimal risk only) is required. If such type of biopsy is needed but cannot feasibly be collected, the Sponsor and Medical Monitor should be consulted. Genomic tumor profile report is acceptable in lieu of a biopsy. **Note:** if at any time during the trial a biopsy is performed as part of routine medical care, we may request a sample.

m: NBF-006 is administered IV QC (minimum 4 days apart) preferably on a Monday or Tuesday (to accommodate the PK schedule) during Cycle 1.

n: GSTP KD time points collected in the 6 patients from Part A at dose level 5 (1.6 mg/kg):

- Cycle 1, Day 1:
  - Before SOI
  - After EOI: 6 hr (±15min), 24 hr (±1hr)
- Cycle 1, Day 8: before SOI

o: Optional biopsy collected during screening and 24 (±3) hours after the 4th dose in cycle 1. Only for patients signing the optional biopsy consent, and when the biopsy can be safely obtained.

p: In Part A of the study, patients will not be stratified for the GSTT1- null genotype, but whole blood samples will still be collected during the screening visit and batch-analyzed at a central laboratory.

Note: Each patient must remain in clinic for a 6-hour safety observation period after each NBF-006 infusion, until the safety review committee has reviewed a 3-patient cohort and recommended a reduced observation time at that dose level. Please see Section 8.1.2.8 for details.

Table 4: Study Calendar (Part B)

Part B Evaluations	Pre-treat-ment[a]	Cycle 1						Cycle 2						Cycle 3 & beyond				EOT	30-day safety FU visit (±3)
		Wk 1 D1	Wk 2 D8 ±3	Wk 3 D15 ±3	Wk 4 D22 ±3	Wk 5 D29-35	Wk 6 D36-42	Wk 1 D1	Wk 2 D8 ±3	Wk 3 D15 ±3	Wk 4 D22 ±3	Wk 5 D29-35	Wk 6 D36-42	Wk 1 D1	Wk 2 Wk 3 Wk 4	Wk 5	Wk 6		
Informed consent (incl. optional biopsy consent)	X																		
Medical history	X																		
Physical exam	X	X[b]						X						X				X	X
Weight	X	X[b]						X						X				X	X
Vital signs[e]	X	X[b]	X	X	X			X	X	X	X			X				X	
ECG[f]	X	X[b]			X													X	
ECOG performance status	X	X[b]						X						X				X	X
Tumor measurement[g] (tumor markers, if applicable)	X						X						X				X	X	
Hematology[h]	X	X[b]	X	X	X			X	X	X	X			X				X	X
Blood chemistry[i]	X	X[b]	X	X	X			X	X	X	X			X				X	X
Urinalysis	X	X[b]						X						X				X	X
Blood sample for immune activation biomarkers [j]		X																	
Pregnancy test	X[k]							X						X				X	
Blood sample for ADA assay [c]		X		X				X						X				X	X
PK blood sampling [d]		X	X		X			X											
Blood sample for exploratory biomarkers	X																		
Blood sample for GSTP KD[n]		X	X																
Confirmation of KRAS mutation [l] (Part B mandatory)	X																		
GSTT1 genotyping[p]	X																		
Optional biopsy[o]	X				X														
NBF-006 administration [m]		X	X	X	X			X	X	X	X			X	X				
Concomitant medications	X	<---------- throughout study ---------->																X	
Adverse events		<---------- throughout study ---------->																X	X

a: Screening assessments may be performed within 28 days of study to treatment initiation, unless specified.

b: For Cycle 1 Day 1, these tests may be performed within 3 days prior to Cycle 1 Day 1. Physical exam and pre-treatment tests done within 3 days of Cycle 1 Day 1 do not need to be repeated for Wk1D1 unless clinically indicated.

c: ADA assay timepoints:

- Cycle 1, Day 1: pre-dose
- Cycle 1, Day 15: pre-dose
- Cycle 2, Cycle 4, Cycle 6, Cycle 8, etc. (i.e., every even numbered cycle), up to one year: Day 1 pre-dose
- Year 2 and beyond: every 6 months
- EOTs
- 30-day safety follow up visit

d: PK timepoints:

- Cycle 1, Day 1:
  - Before start of infusion (SOI),
  - During the infusion: 20 m (±5min) after the start of the last infusion step implemented at 6 mL/min rate
  - End of Infusion (EOI); after EOI: 0.5 hr (±5min), 2 hr (±10min), 6 hr (±15min), 24 hr (±1hr)
- Cycle 1, Day 8: pre-dose
- Cycle 1, Day 22:
  - Before SOI
  - During the infusion: 20 m (±5min) after the start of the last infusion step implemented at 6 mL/min rate
  - End of Infusion (EOI); after EOI: 0.5 hr (±5min), 2 hr (±10min), 6 hr (±15min), 24 hr (±1hr)
- Cycle 2, Day 1: pre-dose

e: Vital signs, including blood pressure, heart rate, respiration rate, and temperature. During Cycle 1: Before SOI, EOI; after EOI: 1hr (±5min), 2hr (±10min). Other days: only before SOI and EOI.

f: Standard 12-lead ECG (in triplicate) while patient is in semi-recumbent position. Perform at screening, Cycle 1 First and fourth doses: within 15 minutes prior to SOI, then 15 min (±5min), 30 min (±10min), 1 hr (±10min) (at EOI)

g: Tumor measurement by RECIST version 1.1 and tumor markers will be measured at baseline and at the end every cycle, if applicable; the same method used at baseline for a patient should be used consistently for all evaluations throughout the study. To be assigned a status of PR or CR, changes in tumor measurements must be confirmed at 4 weeks or at the next scheduled scan (at Week 6 of the following cycle). If a confirmative scan is done after 4 weeks, the next scheduled scan at Week 6 of the following cycle may be omitted. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 5 weeks.

h: Hematology, including hemoglobin, white blood cell with differential, and platelet count.

i: Blood chemistry, including sodium, potassium, blood urea nitrogen, glucose, SGOT/SGPT (ALT/AST), alkaline phosphatase, total protein, total bilirubin, albumin, creatinine, and calcium.

j: Blood samples collected during Cycle 1 (Week 1) for all patients treated in Part B of the study for determination of complement (CH50, Bb, C3a, C5a):

- Pre-dose
- 10 ± 3 minutes after SOI
- 60 ± 10 minutes after EOI
- 6 hr ± 15 minutes after EOI
- 24 hr ± 1 hr after EOI

Dose levels 3 (0.6 mg/kg) and 4 (1.2 mg/kg) did not result in immune activation in Part A and therefore, cytokine activity will not be monitored at those two dose levels in Part B. However if a patient, during or after any infusion of NBF-006, develops IRR symptoms (e.g. backache, fever, nausea, headache, rash, rapid heartbeat, low blood pressure, or trouble breathing), best attempts should be made to collect cytokines as described for Part A with the exception of 10 ± 3 minutes after SOI, which should be collected as close as feasible

to the IRR. If there is no meaningful cytokine induction in the 6-patient dose level 5 (1.6 mg/kg) during Part A, then cytokine testing will also not be needed in the remaining 4 patients at that same dose level (1.6 mg/kg), unless there are symptoms of IRR. **However, complement samples will continue to be collected for all patients.**

k: Pregnancy test; for women of childbearing potential, a negative pregnancy test (urine or serum) must be done within 7 days prior to study treatment initiation and documented.

l: Confirmation of KRAS mutation required for Part B. Obtain archive sample if available; otherwise, a fresh biopsy (low or minimal risk only) is required. If such type of biopsy is needed but cannot feasibly be collected, the sponsor and Medical Monitor should be consulted. Genomic tumor profile report is acceptable in lieu of a biopsy. **Note:** if at any time during the trial a biopsy is performed as part of routine medical care, we may request a sample.

m: NBF-006 is administered IV QC (minimum 4 days apart) preferably on a Monday or Tuesday (to accommodate the PK schedule) during Cycle 1.

n: GSTP mRNA KD time points:

- Cycle 1, Day 1:
  - Before SOI
  - After EOI: 6 hr (±15min), 24 hr (±1hr)
- Cycle 1, Day 8: before SOI

o: Optional biopsy collected during screening and 24 (±3) hours after the 4th dose in cycle 1. Only for patients signing the optional biopsy consent, and when the biopsy can be safely obtained.

p: In Part B of the study, patients will be stratified for the GSTT1- null genotype. Analysis will be done at a central lab from blood samples collected during the screening visit. Initial patients may be enrolled before the GSTT1 status is known.

Note: Each patient must remain in clinic for a 6-hour safety observation period after the first dose, 2 hours after EOI for remaining doses in Cycle 1. The observation period may be further reduced to 30 minutes starting Cycle 2, after Medical Monitor and Investigator safety review. Please see Section 8.1.2.8 for details.

7.2 Pre-treatment

Within 28 days of study treatment initiation (Cycle 1 Day 1):

- Sign informed consent including optional biopsy consent.
- Medical history
- Physical exam
- Weight
- Vital signs
- ECOG performance status (APPENDIX I)
- Hematology
- Blood chemistry
- Urinalysis
- Electrocardiogram (ECG) (for this and all other timepoints, a standard 12-lead ECG is taken while patient is in a semi-recumbent position)
- Confirmation of KRAS mutation:
    - Optional for Part A dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, and 1.2 mg/kg). Depending upon availability and patient consent, we may request archival tumor sample and/or results of genomic tumor profile, but these are not required to confirm patient eligibility for Part A.
    - Requirement for Part A dose level 5 (1.6 mg/kg) and all patients in Part B. Genomic tumor profile results can be used. Otherwise, a tumor tissue sample (archival or fresh) can be tested locally for eligibility. Fresh biopsy (if needed) may be obtained only if it has minimal risk of complications for the patient. If such type of biopsy is needed but cannot feasibly be collected, the Sponsor and Medical Monitor should be consulted.
    - Liquid biopsy may also be used to confirm KRAS status. In the case that both a liquid and tumor biopsy is available, the following criteria will be used to evaluate eligibility:

		Tumor	
		Wildtype	**Mutant**
Liquid	**Wildtype**	Fails Inclusion # 1	Meets Inclusion # 1
	Mutant	Meets Inclusion # 1	Meets Inclusion # 1

- Collect samples to be used for exploratory biomarkers to measure GST family members including GSTP.
- GSTT1 samples will also be collected for both Parts A and B, but GSTT1 genotype will only be used for stratification in Part B.
- Optional tumor biopsy.
- Concomitant medications

Within 14 days of study treatment initiation (Cycle 1 Day 1):

- Imaging for tumor measurements

Within 7 days of study treatment initiation (Cycle 1 Day 1):

- Pregnancy test

7.3 During Treatment

Each patient must remain in clinic to be monitored for infusion related reactions after receiving a dose of NBF-006. A 6-hour safety observation period is required after completion of the first dose in both Part A and Part B. The observation period after subsequent doses may be reduced, as detailed in Section 8.1.2.8.

After completion of at least 3 cycles of study treatment (i.e., after receiving ≥12 doses of NBF -006 over the course of 18 weeks), no more than one dose of NBF-006 may be omitted during a cycle for convenience reasons (to improve patient's quality of life), at the investigator's discretion after discussion with medical monitor.

7.3.1 Cycle 1

7.3.1.1 Week 1 (Day 1, first dose)

- Physical Exam (may be done within 3 days prior)
- Weight (may be done within 3 days prior)
- Vital signs
- ECG
- ECOG (may be done within 3 days prior)
- Hematology (may be done within 3 days prior)
- Blood chemistry (may be done within 3 days prior)
- Urinalysis (may be done within 3 days prior)
- Immune activation biomarkers (pre- and post-dose; see Section 8.6)
- Anti-drug antibody (ADA) assay sampling (pre-dose)
- PK blood sampling (pre- and post-dose; see Section 8.3)
- Blood sample for GSTP KD (pre- and post-dose, see Section 8.8)
- NBF-006 administration
- Concomitant medications
- AEs

7.3.1.2 Week 2 (Day 8 ± 3)

- Vital signs
- Hematology
- Blood chemistry

- PK blood sampling (pre-dose)
- Blood sample for GSTP KD (pre-dose)
- NBF-006 administration
- Concomitant medications
- AEs

7.3.1.3 Week 3 (Day 15 ± 3)

- Vital signs
- Hematology
- Blood chemistry
- ADA assay sampling (pre-dose)
- NBF-006 administration
- Concomitant medications
- AEs

7.3.1.4 Week 4 (Day 22 ± 3)

- Vital signs
- ECG
- Hematology
- Blood chemistry
- PK blood sampling (pre- and post-dose)
- NBF-006 administration
- Concomitant medications
- AEs
- Optional biopsy 24 (±3) hours after completion of the 4th dose in cycle 1.

7.3.1.5 Weeks 5 (Day 29-35)

Rest

7.3.1.6 Week 6 (Day 36-42)

- Tumor measurement (use same method as baseline) performed at the end of every even cycle for Part A dose levels 1-4 and performed at the end of every cycle for Part A dose level 5 and all patients in Part B.

7.3.2 Cycle 2

7.3.2.1 Week 1 (Day 1 should occur within 3 days of Day 42 of previous cycle)

- Physical Exam
- Weight

- Vital signs
- ECOG
- Hematology
- Blood chemistry
- Urinalysis
- Pregnancy test
- ADA assay sampling (pre-dose)
- PK blood sampling (pre-dose)
- NBF-006 administration
- Concomitant medications
- AEs

7.3.2.2 Week 2 (Day 8 ± 3)

- Vital signs
- Hematology
- Blood chemistry
- NBF-006 administration
- Concomitant medications
- AEs

7.3.2.3 Week 3 (Day 15 ± 3)

- Vital signs
- Hematology
- Blood chemistry
- NBF-006 administration
- Concomitant medications
- AEs

7.3.2.4 Week 4 (Day 22 ± 3)

- Vital signs
- Hematology
- Blood chemistry
- NBF-006 administration
- Concomitant medications
- AEs

7.3.2.5 Week 5 (Day 29-35)

Rest

7.3.2.6 Week 6 (Day 36-42)

- Tumor measurement (use same method as baseline) performed at the end of every even cycle for Part A dose levels 1-4 and performed at the end of every cycle for Part A dose level 5 and all patients in Part B.

7.3.3 Cycle 3 and Beyond

7.3.3.1 Week 1 (Day 1 should occur within 3 days of Day 42 of previous cycle)

- Physical Exam
- Weight
- Vital signs
- ECOG
- Hematology
- Blood chemistry
- Urinalysis
- Pregnancy test
- ADA assay sampling pre-dose every even numbered cycle, e.g., Cycle 4, Cycle 6, Cycle 8, etc.) up to 1 year. Year 2 collection occurs every 6 months.
- NBF-006 administration
- Concomitant medications
- AEs

7.3.3.2 Week 2 (Day 8 ± 3)

- NBF-006 administration
- Concomitant medications
- AEs
- Perform safety exams (e.g., vital signs, hematology, blood chemistries) as clinically indicated

7.3.3.3 Week 3 (Day 15 ± 3)

- NBF-006 administration
- Concomitant medications
- AEs
- Perform safety exams (e.g., vital signs, hematology, blood chemistries) as clinically indicated

7.3.3.4 Week 4 (Day 22 ± 3)

- NBF-006 administration
- Concomitant medications

- AEs
- Perform safety exams (e.g., vital signs, hematology, blood chemistries) as clinically indicated

7.3.3.5 Week 5 (Day 29-35)

Rest

7.3.3.6 Week 6 (Day 36-42)

- Tumor measurement (use same method as baseline) performed at the end of every even cycle for Part A dose levels 1-4 and performed at the end of every cycle for Part A dose level 5 and all patients in Part B.

7.4 End of Treatment (to be performed within 30 ± 3 days after last treatment)

The following assessments will be performed for all patients who are terminating treatment due to any reason. The End of Treatment (EOT) visit should be performed immediately after the patient discontinues treatment and should be no later than 30 ± 3 days after the last dose.

- Physical Exam
- Weight
- Vital signs
- ECG
- ECOG
- Tumor measurement (use same method as baseline)
- Hematology
- Blood chemistry
- Urinalysis
- Pregnancy test
- ADA assay sampling
- Concomitant medications
- AEs

7.5 30 Day Safety Follow up Visit (±3)

- Physical Exam
- Weight
- ECOG
- Hematology
- Blood chemistry
- Urinalysis

- ADA assay sampling
- AEs

If the EOT visit is performed 30 ± 3 days after the last dosing, the safety follow-up visit can be omitted.

8.0 STUDY ASSESSMENTS

8.1 Safety Assessments

8.1.1 Safety Analysis

Safety data will be tabulated for all patients and include vital signs, laboratory parameters, and AEs.

8.1.2 Reporting of Adverse Events

8.1.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The AE reporting period starts on Cycle 1 Day 1; if an AE occurs before the first dose of study drug it will be considered a non-treatment emergent AE. At each evaluation, patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an AE will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms.

All AEs (except Grade 1 and 2 laboratory abnormalities that do not require an intervention), regardless of causal relationship, are to be recorded in the eCRF and source documentation. The Investigator must determine the intensity of any AEs according to the NCI CTCAE Version 5.0 (APPENDIX II) and their causal relationship. Those AEs not covered by these criteria will be graded as follows:

1. Mild: Discomfort noticed, but no disruption of normal daily activity. Prescription drug not ordinarily needed for relief of symptom but may be given because of personality of patient.

2. Moderate: Discomfort sufficient to reduce or affect normal daily activity. Patient is able to continue in study; treatment for symptom may be needed.

3. Severe: Incapacitating, severe discomfort with inability to work or to perform normal daily activity. Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or patient hospitalized.

4. Life-Threatening: Symptom(s) place the patient at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more serious from, might have caused death.

5. Fatal: Event caused the death of the patient.

AEs will be followed until resolution or stabilization while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization, unless, in the Investigator's opinion the event is unlikely to resolve due to the patient's underlying disease, or until the patient starts a new treatment regimen or the patient is lost to follow-up.

8.1.2.2 Attribution Definitions

An AE is considered to be associated with the use of the Investigational Product if the attribution is determined as possible, probable or definite. Attribution of AEs will be recorded in the eCRF as:

- Unrelated: The AE is clearly NOT related to the study treatment.
- Unlikely: The AE is doubtfully related to the study treatment.
- Possible: The AE may be related to the study treatment.
- Probable: The AE is likely related to the study treatment.
- Definite: The AE is clearly related to the study treatment.

8.1.2.3 Definition of an Unexpected Adverse Event

An unexpected AE is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current IB; or, if an IB is not required or available, the specificity or severity of which is not consistent with the risk information described in this protocol or in the regulatory agency study authorization application.

Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the IB) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

8.1.2.4 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in death,
2. Is life-threatening (i.e., the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe),
3. Requires in-patient hospitalization or prolongation of existing hospitalization excluding that for pain management, disease staging/re-staging procedures, or catheter placement unless associated with other serious events,
4. Results in persistent or significant disability/incapacity, or
5. Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

8.1.2.5 Reference Safety Information

The Reference Safety Information (RSI), in the current, approved IB, is a list of expected Serious Adverse Reactions which are classified using Preferred Terms according to the Medical Dictionary for Regulatory Activities (MedDRA). The RSI section will be used for assessing the expectedness of the study medication.

8.1.2.6 Pregnancy

Any pregnancy detected during the study, or that occurs within 30 days after stopping study medication, must be reported immediately to the Investigator. Pregnancy, in and of itself, is not regarded as an AE, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication. If the patient becomes pregnant while on-study, the study drug should be immediately discontinued. Pregnancy information about a female patient or a female partner of a male patient should be reported immediately from the time the Investigator first becomes aware of a pregnancy or its outcome. This will be performed by the Investigator completing a Pregnancy Form and emailing it or faxing it to the Theradex Oncology Safety Desk (see Section 8.1.2.7); contact the Theradex Oncology Safety Desk for the Pregnancy Form.

Any pregnancy complication, spontaneous abortion, elective termination of a pregnancy for medical reasons, outcome of stillbirth, congenital anomaly/birth defect, or SAE in the mother will be recorded as an SAE and will be reported as described in Section 8.1.2.7.

8.1.2.7 Reporting of Serious Adverse Events

AEs classified as serious require expeditious handling and reporting to Theradex Oncology to comply with regulatory requirements.

For any SAE that occurs while a patient is on-study; within 30 days of the last study drug administration, regardless of any opinion as to the relationship of the SAE to the study drug; or if any SAE that the Investigator feels is related to the study drug occurs later than 30 days after the last study drug administration, the Theradex Oncology Safety Desk must be notified immediately (within 24 hours of becoming aware of the event) by email, fax or telephone. Notification by email is preferred. The email address, fax and telephone numbers listed below may be used during both business and non-business hours. During non-business hours a recorded message will provide the telephone caller with the contact information for the on-call monitor.

All SAEs require that a Serious Adverse Event Report Form be completed and forwarded either via facsimile or as a PDF via email to Theradex Oncology at the fax number or email listed below within 24 hours of becoming aware of the event.

SAEs will be reported to: Theradex Oncology Safety Desk
Telephone: (609) 799-7580
Fax: (609) 799-1567
Email: SafetyDeskUS@Theradex.com

8.1.2.8 Post-Infusion Observation Period

Observe/monitor for any signs and symptoms of IRRs, such as back pain, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes, or anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.).

During Part A of the study, each patient must remain in clinic for a minimum 6-hour safety observation period after each NBF-006 infusion until at least three patients at a specific dose level have been reviewed by the Safety Review Committee.

Reductions in the observation period at a given dose level may be recommended by the Safety Review Committee (consisting of Investigators, Theradex Oncology Medical Monitor, and Sponsor) after at least three patients have received a full cycle of treatment (defined as at least four doses and 2-week drug holiday) at that dose level.

Recommendations by the Safety Review Committee for a reduced observation period will be contingent upon:

- Absence of any significant safety concerns following a complete review of all clinical and laboratory data for all treated subjects at the given dose level and the preceding dose levels,
- Absence of any late-onset (>2 hours post-dose) IRRs or IRR symptoms that continue beyond 2 hours post-dose, and lack of any severe or serious IRRs,
- Review and consideration of cytokine and complement activation data at the given dose prior to making a recommendation to shorten the observation period.

If the Safety Review Committee recommends a reduced observation period, the minimum observation period allowed will be 2 hours following EOI from Cycle 2 onward during Part A of the study. Further reductions in the observation period may be suggested by the safety review committee as additional data has accumulated.

For Part B of the study, each patient must remain in clinic for a 6-hour safety observation period after the first dose, 2 hours after EOI for remaining doses in Cycle 1. The observation period may be further reduced to 30 minutes starting Cycle 2, after Medical Monitor and Investigator safety review. The observation period may be lengthened, if clinically indicated.

8.1.2.9 Management of Infusion-Related Reactions

The guidelines on dose modification and toxicity management for IRRs are outlined in Table 5. All toxicities are graded according to NCI CTCAE Version 5.0.

Table 5: Dosing Modification and Toxicity Management Guidelines for Infusion-Related Reactions

Severity Grade	Dose Interruption or Modification	Toxicity Management
Grade 1	The infusion should be temporarily interrupted and then resumed when symptoms are resolved.	If symptoms have not resolved in 15 minutes: – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator – Consider premedication prior to subsequent doses. – H1 antagonist (e.g., diphenhydramine, hydroxyzine, or chlorpheniramine) and an H2 antagonist (e.g., famotidine) dosed in accordance with approved labelling or the SOC before the start of investigational treatment administration (if premedication is administered parenterally, it should be given within 30 minutes of SOI; if premedication is given orally, it should be given 60-90 minutes prior to SOI). If the infusion reaction does not resolve within one hour after administration of acetaminophen and/or antihistamines the dosing should not be resumed the same day. Rechallenge should be discussed with the Medical Monitor, and premedication must be given if the patient receives any further doses.
Grade 2	The infusion should be temporarily interrupted and then resumed when symptoms are resolved.	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe IRRs per institutional standards (e.g., IM epinephrine, followed by IV antihistamines, and IV glucocorticoid)

8.1.2.10 Safety Data Review

The Medical Monitor will be responsible for ongoing safety data for the study. This will include a review of all AEs (serious and non-serious AEs) as they are reported by the study site.

Safety data will be reviewed periodically by a Safety Review Committee consisting of Theradex Oncology Medical Monitor, Sponsor, and Investigator. Details are provided in the Safety Plan. They will make decisions on dose modifications, cohort dose escalation,

transition to dose expansion phase (Part B), and may recommend changes to the post-infusion observation period.

8.1.2.11 Safety-Related Stopping Rules

If there is Grade 5 toxicity definitely, probably or possibly attributed to NBF-006 within 30 days of the last NBF-006 dose, the study may be temporarily or permanently stopped, pending a review by the Sponsor, Medical Monitor, and Investigators. During that time, no drug can be administered to any patient, until a decision is made.

8.2 Efficacy Assessments

Patients with measurable disease will be assessed at baseline and during the study by standard criteria. For the purpose of this study, patients should be reevaluated at the end of every even numbered cycle in Part A, dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg), and at the end of every cycle for dose level 5 (1.6 mg/kg) in Part A and for all dose levels tested in Part B patients. In the event objective response (partial response [PR] or complete response [CR]) is noted, changes in tumor measurements must be confirmed by repeat assessments that should be performed at 4 weeks but no later than 5 weeks for patients in dose levels 1-4 in Part A after the criteria for response are first met. Response will be confirmed at 4 weeks or at the next scheduled scan (at Week 6 of the following cycle) for patients in dose level 5 in Part A and all patients in Part B. If a confirmative scan is done after 4 weeks, the next scheduled scan (at Week 6 of the following cycle) may be omitted. For stable disease (SD), follow-up measurements must meet the SD criteria at least 5 weeks after study entry.

8.2.1 Definitions

Response and progression will be evaluated in this study using the international criteria (version 1.1) proposed by the RECIST Committee.14 Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST 1.1 criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

8.2.1.1 Measurable Disease

Measurable disease is defined by the presence of at least one measurable lesion. Measurable lesions are defined as those that can be accurately measured in at least one dimension [longest diameter (LD) in the plane of measurement to be recorded] with a minimum size of:

- 10 mm by computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm)

- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest x-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm).

8.2.1.2 Non-measurable Disease

All other lesions (or sites of disease), including small lesions (LD < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) are considered non-measurable disease. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses/abdominal organomegaly identified by physical exam and not followed by CT or magnetic resonance imaging (MRI).

Bone lesions, cystic lesions and lesions previously treated with local therapy must be considered as follows:

Bone lesions:
- Bone scan, positron emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques (i.e., CT or MRI) can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:
- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable or non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

8.2.1.3 Target Lesions

All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the LD) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize the objective tumor response.

8.2.1.4 Lymph Node Assessment

For lymph nodes, measurements should be made of the short axis, which is defined as perpendicular to the LD of node assessed in the plane of measurement:

- Target lesion if short axis ≥ 15 mm
- Non-target lesion if short axis is ≥ 10 but < 15 mm
- Normal if short axis < 10 mm

For baseline, add the actual short axis measurement to the sum of LD of non-nodal lesions.

8.2.1.5 Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression”. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the eCRF (e.g., ‘multiple enlarged pelvic lymph nodes’ or ‘multiple liver metastases’).

8.2.1.6 Response Assessments After Palliative Radiotherapy

Palliative radiotherapy is allowed as medically indicated after completion of the first treatment cycle, and after discussion with medical monitor. Lesions assigned as targets at baseline should preferably not be included in the radiotherapy field, as it would preclude further response assessment per RECIST. Following palliative radiotherapy of RECIST target lesions, the irradiated lesion(s) and overall response assessment should be NA/Not evaluated, but remaining target and non-target lesions should continue to be monitored (an individualized schedule for radiology assessment is acceptable).

8.2.2 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. When lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may be reviewed at the end of the study.

Chest x-ray. Chest CT is preferred over chest x-ray, particularly when progression is an important endpoint. Lesions on chest x-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. Contrast enhancement should normally be used, unless the patient is allergic. MRI is acceptable in certain situations (e.g., at the Investigator's discretion for CNS metastases, or in cases with iodine contrast allergy).

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound (US). US should not be used to measure tumor lesions. US examinations cannot be reproduced in their entirety for independent review at a later date because they are

operator dependent. If new lesions are identified by US, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Cytology, Histology. These techniques can be used to differentiate between PR and CR in rare cases (e.g., residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain).

8.2.3 Response Criteria

8.2.3.1 Evaluation of Target Lesions

Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR):	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions is also considered progression.
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

8.2.3.1.1 Assessment of Target Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline exam), even if the nodes regress to below 10 mm on study. In order to qualify for CR, each node

must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

8.2.3.1.2 Target Lesions that Become "too small to measure"

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned.

8.2.3.1.3 Lesions that Split or Coalesce on Treatment

When non-nodal lesions fragment, the LD of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the LD should be the maximal LD for the 'coalesced lesion'.

8.2.3.2 Evaluation of Non-target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).
Non-CR/Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
Progressive Disease (PD):	Unequivocal progression of existing non-target lesions. (The appearance of one or more new lesions is also considered progression.) To achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation.

8.2.3.3 New Lesions

The finding of a new lesion should be unequivocal (i.e., not attributed to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor, such as a 'new' healing bone lesion). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. If a new lesion is equivocal, continued therapy and

follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm this is definitely a new lesion, then progression should be declared using the date of the initial scan.

8.2.3.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The patient's best overall response assignment will depend on findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

It is assumed that at each protocol-specified time point, a response assessment occurs. Table 6 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline. When patients have non-measurable disease, Table 7 should be used.

Table 6: Time point response: Patients with target (+/- non-target) disease

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR / non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR=complete response, PR=partial response, SD=stable disease PD=progressive disease, NE=not evaluable			

Table 7: Time point response: Patients with non-target disease only

Non-target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR / non-PD	No	Non-CR / non-PD*
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR=complete response; PD=progressive disease; NE=not evaluable * Non-CR/non-PD is preferred over SD for non-target disease		

Best response determination for studies where confirmation of CR or PR is required: CR or PR may be claimed only if the criteria for each are confirmed by a repeat assessment at 4 weeks but no more than 5 weeks later for patients in dose levels 1-4 in Part A (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg), after the criteria for response are first met. Response will be confirmed after 4 weeks or at the next scheduled scan (at Week 6 of the following cycle) for patients in dose level 5 (1.6 mg/kg) in Part A and all patients in Part B. If a confirmative scan is done after 4 weeks, the next scheduled scan (at Week 6 of the following cycle) may be omitted. In this circumstance, the best overall response can be interpreted as in Table 8.

Table 8: Best overall response when confirmation of CR and PR required

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR=complete response; PR=partial response; SD=stable disease; PD=progressive disease; NE=nonevaluable

* If CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

8.2.4 Confirmatory Measurement/Duration of Response

8.2.4.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at 4 weeks but no later than 5 weeks for patients in dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg) in Part A after the criteria for response are first met. Response will be confirmed after 4 weeks or at the next scheduled scan (at Week 6 of the following cycle) for patients in dose level 5 (1.6 mg/kg) in Part A and all patients in Part B. If a confirmative scan is done after 4 weeks, the next scheduled scan (at Week 6 of the following cycle) may be omitted. In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 5 weeks.

8.2.4.2 Duration of Overall Response

The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

8.2.4.3 Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

8.3 Pharmacokinetics

Plasma concentrations of NDT-05-1040 will be measured from blood samples collected at the following timepoints for Part A:

- Cycle 1, Day 1:
  - Before SOI,
  - During the infusion: 20 m ± 5 m after the start of the last infusion step implemented at 6 mL/min rate
  - EOI; after EOI: 0.5 hr (±5m), 2 hr (±10m), 6 hr (±15m), 24 hr (±1hr), 48 hr (±2hr), 72 hr (±3hr)
- Cycle 1, Day 8: pre-dose
- Cycle 1, Day 22:
  - Before SOI
  - During the infusion: 20 m ± 5 m after the start of the last infusion step implemented at 6 mL/min rate
  - EOI; after EOI: 0.5 hr (±5m), 2 hr (±10m), 6 hr (±15m), 24 hr (±1hr), 48 hr (±2hr), 72 hr (±3hr)
- Cycle 2, Day 1: pre-dose

Plasma concentrations of NDT-05-1040 will be measured from blood samples collected at the following timepoints for Part B. (Note: timepoints are the same as the Part A PK sample collection with the exception of the 48 and 72 hr timepoint collections, which will not be measured in Part B):

- Cycle 1, Day 1:
  - Before SOI,
  - During the infusion: 20 m ± 5 m after the start of the last infusion step implemented at 6 mL/min rate
  - EOI; after EOI: 0.5 hr (±5m), 2 hr (±10m), 6 hr (±15m), 24 hr (±1hr)

- Cycle 1, Day 8: pre-dose
- Cycle 1, Day 22:
  - Before SOI
  - During the infusion: 20 m ± 5 m after the start of the last infusion step implemented at 6 mL/min rate
  - EOI; after EOI: 0.5 hr (±5m), 2 hr (±10m), 6 hr (±15m), 24 hr (±1hr)
- Cycle 2, Day 1: pre-dose

8.4 Anti-Drug Antibodies (ADAs)

Blood samples will be collected at the following timepoints for possible evaluation for ADAs:

- Cycle 1, Day 1: pre-dose
- Cycle 1, Day 15: pre-dose
- Cycle 2, Cycle 4, Cycle 6, Cycle 8, etc. (i.e., every even numbered cycle), up to one year: Day 1 pre-dose
- Year 2 and beyond: every 6 months
- EOT
- 30-Day Follow-up Visit after Last Dose

8.5 KRAS Genotyping

Depending upon availability and patient consent, we may request archival tumor sample and/or results of genomic tumor profile, but these are not required to confirm patient eligibility for dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg) in Part A.

Confirmation of KRAS mutation is a requirement for dose level 5 (1.6 mg/kg) in Part A and for all patients in Part B. Genomic tumor profile results can be used. Otherwise, a tumor tissue sample (archival or fresh) can be tested locally for eligibility. Fresh biopsy (if needed) may be obtained only if it has minimal risk of complications for the patient. If such type of biopsy is needed but cannot feasibly be collected, the sponsor and Medical Monitor should be consulted.

Liquid biopsy may also be used to confirm KRAS status. In the case that both a liquid and tumor biopsy is available, the following criteria will be used to evaluate eligibility:

		Tumor	
		Wildtype	**Mutant**
Liquid	**Wildtype**	Fails Inclusion # 1	Meets Inclusion # 1
	Mutant	Meets Inclusion # 1	Meets Inclusion # 1

8.6 Immune Activation Biomarkers

Cytokines:
Blood samples will be collected during Cycle 1 (Week 1) for all patients in Part A of the study for determination of cytokines (IFN-γ, IL-1β, IL-6, TNF-α):

- Pre-dose
- 10 ± 3 minutes after SOI
- 60 ± 10 minutes after EOI
- 6 hr ± 15 minutes after EOI
- 24 hr ± 1 hr after EOI

Dose levels 3 (0.6 mg/kg) and 4 (1.2 mg/kg) did not result in immune activation in Part A and therefore, cytokine activity will not be monitored at those two dose levels in Part B. However, if a patient, during or after any infusion of NBF-006, develops IRR symptoms (e.g., backache, fever, nausea, headache, rash, rapid heartbeat, low blood pressure, or trouble breathing), best attempts should be made to collect cytokines as described for Part A with the exception of 10 ± 3 minutes after SOI, which should be collected as close as feasible to the IRR.

If there is no meaningful cytokine induction in the 6-patient dose level 5 (1.6 mg/kg) during Part A, then cytokine testing will also not be needed in the remaining 4 patients in Part B at that same dose level (1.6 mg/kg), unless there are symptoms of IRR.

Complement:
Blood samples will be collected during Cycle 1 (Week 1) for all patients in Part A and Part B of the study for determination of complement (CH50, Bb, C3a, C5a):

- Pre-dose
- 10 ± 3 minutes after SOI
- 60 ± 10 minutes after EOI
- 6 hr ± 15 minutes after EOI
- 24 hr ± 1 hour after EOI

8.7 Exploratory Biomarkers

Blood sample will be collected at baseline. PBMCs will be isolated from patient blood samples for exploratory studies. Tumor tissue (archival samples or those procured for routine medical care during the course of the study) may be retained from all patients in Parts A and B, for biomarker testing. Biomarkers may include (but are not limited to) GSTP or related proteins of the GST family.

8.8 GSTP Knockdown

Blood samples will be collected at the following timepoints for evaluation of GSTP KD in the 6 patients from Part A at 1.6 mg/kg dose level and from all patients in Part B of the study:

- Cycle 1, Day 1:
  - Before SOI
  - After EOI: 6 hr (±15m), 24 hr (±1hr)
- Cycle 1, Day 8: before SOI

Patients who are willing to provide exploratory pre- and on-study biopsies will be sampled prior to the first dose and 24 hours after the 4th dose in cycle 1, if clinically feasible. If possible, lesions selected as RECIST target lesions should not be biopsied.

8.9 GSTT1 Genotyping

In Part A dose level 5 (1.6 mg/kg) of the study, patients will not be stratified for the GSTT1-null genotype, but whole blood samples will still be collected during the screening visit and batch analyzed at a central lab.

Patients in Part B of the study will be stratified across all cohorts for the GSTT1-null genotype to ensure that all dose levels receive even distribution of GSTT1-null patients. Analysis will be done at a central lab from blood samples collected during the screening visit.

9.0 STATISTICS

Demographic data and disease-related characteristics will be summarized using descriptive statistics (count and percent, mean, median, standard deviation, minimum, maximum). All patient data, efficacy and safety data will be summarized. Results from Part A and Part B will be presented separately.

9.1 Analysis Populations

The Intent-to-Treat population will include all participants who were enrolled (signed consent) into the study, irrespective of whether study medication was administered or not.

Safety Evaluable Population: All patients who received any component of study treatment.

Efficacy Evaluable Population: Patients with measurable disease by RECIST 1.1 who had a baseline assessment and at least one post-baseline assessment. Responses must be confirmed at a second imaging evaluation that should be performed at 4 weeks but no later than 5 weeks for patients in dose levels 1-4 (0.15 mg/kg, 0.3 mg/kg, 0.6 mg/kg, 1.2 mg/kg) in Part A after response criteria are met. Response will be confirmed after 4 weeks or at the next scheduled scan (at Week 6 of the following cycle) for patients in dose level 5 (1.6 mg/kg) in Part A and all patients in Part B. If a confirmative scan is done after 4 weeks, the next scheduled scan (at Week 6 of the following cycle) may be omitted. Responders (PR and CR) with confirmatory imaging will be denoted as PR and CR. Those with only one evaluation documenting PR or CR will be denoted as partial response-unconfirmed (PR-UC) and complete response (CR-UC). The primary evaluation of efficacy will focus on PR and CR but analyses incorporating PR-UC and CR-UC will also be performed.

9.2 Endpoints

9.2.1 Primary

Part A: number of patients with DLTs and AEs.

Part B: best overall response (CR, PR, SD) per RECIST 1.1 and safety (DLT, AEs), duration of overall response, duration of stable disease.

9.2.2 Secondary

Part A: best overall response (CR, PR, SD) per RECIST 1.1 and PK parameters (C_{max}, clearance [CL], volume of distribution [V_{ss}], terminal elimination half-life [$T_{1/2}$], area under the curve $[AUC]_{0-t}$) of siRNA, duration of overall response, duration of stable disease.

Part B: PK parameters (C_{max}, CL, V_{ss}, $T_{1/2}$, AUC_{0-t}, $AUC_{0-\infty}$) of siRNA.

9.3 Safety

Safety will be assessed by means of physical examination, weight, vital signs, performance status, laboratory evaluations (hematology, biochemistry), ECG, pain assessment and recording of concurrent illness/therapy and AEs. NCI CTCAE version 5.0 will be used to grade all toxicities. All related AEs will be monitored until resolution. Patients will be monitored for safety and concomitant medications throughout the study.

Safety data will be summarized for the safety evaluable population. These data will include AEs and laboratory parameters. AE terms will be coded using the most current version of MedDRA®.

9.4 Efficacy

Response to treatment will be assessed according to RECIST 1.1. The objective evaluation will be performed at baseline and at the end of even numbered cycles for dose levels 1-4 in Part A and at baseline and at the end of every cycle for dose level 5 in Part A and all patients in Part B of the study.

The efficacy endpoints include best overall response (BOR), disease control rate (DCR= rate of SD+PR+CR), duration of response (DOR), duration of CR, and duration of stable disease (SD).

9.4.1 Duration of Overall Response

DOR is measured from the time of CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented. Only patients with a confirmed CR or PR are included in the analysis. For a patient without evidence of PD, DOR will be censored.

9.4.2 Duration of Stable Disease

Stable Disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started. Duration of stable disease will be analyzed in a similar method as DOR.

9.5 Exploratory/Other Studies

Separate reports will be generated for the analysis of ADAs, immune activation biomarkers, GSTP KD, and other biomarker activity.

9.6 Sample Size

This is an exploratory trial and therefore no sample size calculations have been performed. The number of patients in Part A (up to 20) is based on the planned number of dose escalation cohorts required to identify the MTD. The planned number of patients in Part B is approximately 20-24.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

10.1 Monitoring of the Study and Regulatory Compliance

The project manager, or designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the initiation site visit the eCRFs will be

reviewed. Other pertinent study materials will also be reviewed with the Investigator's research staff. During the course of the study, the monitor will make regular site visits in order to review protocol compliance, examine eCRFs and individual subject's medical records and assure that the study is being conducted according to pertinent regulatory requirements. All eCRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient confidentiality is maintained.

10.2 Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current (within 2 years) signed and dated curriculum vitae, a completed FDA Form 1572 and a financial disclosure statement to Theradex Oncology. All Sub-Investigators will be required to provide a current curriculum vitae and a financial disclosure statement to Theradex Oncology.

10.3 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative (Theradex Oncology). Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial subjects, or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/IEC by the Principal Investigator.

10.4 Publication Policy

The publication of the results of the study will be subject to the terms and conditions of the clinical trial agreement between the Sponsor and Investigators. Sponsor approval is required for publication of any data from this trial.

11.0 ETHICAL CONSIDERATIONS

11.1 Informed Consent

The Investigator will obtain written informed consent from each patient, or their authorized representative, participating in the study. The form must be signed, witnessed and dated before any screening assessments are performed. The informed consent form will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for GCP, Section 4.8, and the terms of the Declaration of Helsinki (2013). Copies of the signed document should be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

11.2 Institutional Review Board/Independent Ethics Committee

The study will not be initiated without approval of the appropriate IRB/IEC and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be approved by the IRB/IEC in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH/GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/IEC will be kept informed by the Investigator, Theradex Oncology or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected AEs.

11.3 Patient Privacy

In order to maintain patient confidentiality, all eCRFs, study reports, and communications relating to the study will identify patients by initials and assigned patient numbers; patients should not be identified by name. In accordance with local, national or federal regulations, the Investigator will allow the Sponsor or designee personnel access to all pertinent medical records in order to verify the data gathered on the eCRFs and to audit the data collection process. Regulatory agencies such as the U.S. FDA may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the patient as outlined in the patient consent form.

12.0 DATA HANDLING AND RECORD KEEPING

12.1 Data to be Entered Directly in the Electronic Case Report Form

The eCRF will be the source record.

12.2 Recording of Data

Data collected during the study will be entered in the patient's eCRF by the investigational site staff. The staff will keep records of the patient's visit in the files considered as source documents for the site, e.g., hospital chart, research chart. The Investigator will be responsible for the recording of all data on the eCRF and for submitting the data to the Sponsor or their designee in a timely manner. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the eCRF. The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data.

12.3 Study Records

U.S. Federal laws require that an Investigator maintain all study records for the indication under investigation for two years following the date a Product Licensing Application is approved or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

13.0 REFERENCES

1 Cox AD, Fesik SW, Kimmelman AC, Luo J, Der CJ. Drugging the undruggable Ras: mission possible? Nature reviews Drug discovery. 2014;13(11):828-851.

2 Castellano E, Downward J. RAS Interaction with PI3K: More Than Just Another Effector Pathway. Genes Cancer. 2011 Mar,2(3):261-274.

3 Mills SZ, Ikeda S, Reddy S, Gatalica Z, Kurzrock R. Landscape of Phosphatidylinositol-3-Kinase Pathway Alterations Across 19 784 Diverse Solid Tumors. JAMA Oncol. 2016;2(12):1565-1573.

4 Sunaga N, Shames DS, Girard L, et al. Knockdown of Oncogenic KRAS in Non-Small Cell Lung Cancers Suppresses Tumor Growth and Sensitizes Tumor Cells to Targeted Therapy. Mol Cancer Ther. 2011 Feb;10(2): 336–346.

5 E Laborde, Glutathione transferases as mediators of signaling pathways involved in cell proliferation and cell death, Cell Death and Differentiation. 2010 Sep;17(9),1373–1380.

6 Tew KD, Manevish Y, Grek C, Xiong Y, Uys J, Townsend DM. The Role of Glutathione S-transferase P in signaling pathways and S-glutathionylation in Cancer, Free Radic Biol Med. 2011 Jul 15; 51(2): 299–313.

7 Thorn CF, Ji Y, Weinshilboum RM, Altman RB, Klein TE. PharmGKB summary: very important pharmacogene information for GSTT1. Pharmacogenet Genomics. 2012 Aug;22(8):646-51. doi: 10.1097/FPC.0b013e3283527c02. PMID: 22643671; PMCID: PMC3395771.

8 Wang T, Arifoglu P, Ronai Z, Tew KD, Glutathione S-transferase P1–1 (GSTP1–1) Inhibits c-Jun N-terminal Kinase (JNK1) Signaling through Interaction with the C Terminus. J Biol Chem. 2001 Jun 15;276(24):20999-1003.

9 Webster R., Elliott V., Park B.K., Walker D., Hankin M., Taupin P. PEG and PEG conjugates toxicity: towards an understanding of the toxicity of PEG and its relevance to PEGylated biologicals. In: Veronese F.M. (eds) PEGylated Protein Drugs: Basic Science and Clinical Applications. Milestones in Drug Therapy. Birkhäuser Basel. 2009.

10 Ivens IA, Achanzar W, Baumann A, Brandu-Baiocco A, Cavagnaro J, Dempster M et al. PEGylated Biopharmaceuticals: Current Experience and Considerations for Nonclinical Development. Toxicologic Pathology, 43: 959-983, 2015.

11 Hansen AR, Cook N, Ricci MS, Razak A, Le Tourneau C, McKeever K et al. Choice of Starting Dose for Biopharmaceuticals in First-in-Human Phase I Cancer Clinical Trials. Oncologist. 2015 Jun;20(6):653-659.

12 Kumar V et al. Shielding of Lipid Nanoparticles for siRNA Delivery: Impact on Physicochemical Properties, Cytokine Induction, and Efficacy. Molecular Therapy - Nucleic Acids. 2014;3, e210.

13 Zatsepin, Timofei S, Yuri V Kotelevtsev, and Victor Koteliansky. “Lipid Nanoparticles for Targeted siRNA Delivery – Going from Bench to Bedside.” International Journal of Nanomedicine 11 (2016): 3077–3086. PMC. Web. 21 July 2018.

14 Eisenhauer EA, Therasse P, Bogaerts J et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45:228-247.

APPENDIX I – ECOG Performance Status

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX II – Common Terminology Criteria for Adverse Events (CTCAE) v5.0

Available from the Cancer Therapy Evaluation Program website:
https: //ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

APPENDIX III – Acceptable Contraceptive Methods

● Male or female condom with or without spermicide ● Cervical cap, diaphragm, or sponge with spermicide
Highly Effective Contraceptive Methods That Are User Dependent [a] *Failure rate of <1% per year when used consistently and correctly.*
● Combined (estrogen- and progesterone-containing) hormonal contraception [b] ○ Oral ○ Intravaginal ○ Transdermal ○ Injectable
● Progestogen-only hormonal contraception [b] ○ Oral ○ Injectable
Highly Effective Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
● Progesterone-only contraceptive implant [b, c] ● Intrauterine hormone-releasing system (IUS) [b] ● Intrauterine device (IUD) ● Bilateral tubal occlusion
● **Vasectomy** Vasectomy is a highly effective contraception method provided that the partner is the sole male sexual partner of the female of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.
● **Sexual abstinence** Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)
Notes: Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. a) Typical use failure rates are lower than perfect-use failure rates (i.e., when used consistently and correctly). b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days, (corresponding to time needed to

eliminate study treatment plus 30 days for study treatments with genotoxic potential) after the last dose of the study treatment.
c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.