Nitto BioPharma Inc.

Informed Consent Form

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

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Sample Informed Consent Form (ICF)

Study title: **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**

Key Information

This Study is for Research Purposes, Participation is Voluntary
You are being asked to take part in a research study sponsored by Nitto BioPharma, Inc. Research studies include only people who choose to take part. The study staff members will explain the study to you and will answer any questions you might have. You should take your time to make your decision.

Purpose, Duration, Overview of Study
The main purposes of this study are to evaluate if an experimental drug called NBF-006 might have an effect on your cancer, and to confirm it can be safely administered to humans. NBF-006 is an investigational product, which means it is a drug that has not yet been approved by the Food and Drug Administration (FDA) but is authorized by the FDA to be tested on patients. The active part of the drug may cause cells in your tumor and other parts of the body to make less of a “detoxifying” molecule that could help tumors to grow, but it is not yet known if this study drug will actually shrink tumors in humans. This study will test different dose levels of NBF-006 to determine any side effects the study drug may have and the optimal dose level that is safe in humans. We will also investigate what effects, if any, the drug may have on your tumor by measuring the size of your tumor and monitoring you to see if the tumor does or does not spread.

This study will consist of two parts: an escalation phase (Part A) and an expansion phase (Part B). Part A of the study will be a dose finding study where each cohort (patient group) receives a higher dose level than the previous cohort. Dose levels will increase until there are unacceptable side effects, or when the study reaches the highest planned dose level. Part B of the study plans to use dose levels that are established as safe in Part A of the study. The highest dose level in Part A and all dose levels in Part B will test whether patients who have advanced non-small cell lung cancer (NSCLC) with a confirmed mutation in a gene called “KRAS”, that have failed other treatment options or did not have an effective therapy option, will respond to treatment.

If you agree to join the study and are determined to be eligible, you will receive NBF-006, and be asked to complete a group of tests. Most of the procedures are ordinarily part of routine cancer care, and the KRAS confirmation can often be done (or is already done) with tissue collected previously. Some tests and procedures will be needed more often than normal because you are in a clinical trial. For patients in the highest dose of Part A and for all patients in Part B of the study, genetic testing will be performed, which includes your genetic setup for a detoxifying enzyme called GSTT1. Some people lack functional copies of the gene (normal variant), which may have an impact on the effectiveness of the drug.

The dose level of NBF-006 that you receive will depend on when you enter the study. For the dose escalation part of the study (Part A), doses will be increased in cohorts of three patients. Once a safe dose has been confirmed in Part A, additional patients will be enrolled in the dose expansion part of the study (Part B) at the dose levels that were determined to be safe in Part A. You will receive a dose of NBF-006 administered via intravenous infusion (IV) once per week for 4 consecutive weeks. After the completion of the fourth dose, you have a 2-week rest period before you start the next cycle of treatment (1 cycle = 6 weeks).

You may participate in the study for as many cycles as you wish, as long as you are not experiencing any side effects associated with the study drug that your study doctor feels are not acceptable. Your study doctor may stop you from taking part in this study at any time if he or she believes it is in your best interest, or if you do not follow the study rules, or if the study is stopped.

Foreseeable Risks, Discomforts

The safety profile of NBF-006 in humans is not completely understood since this is the first study in which the drug is being given to humans. Fourteen patients were treated in the first phase of the study, among these, no serious nor severe side effects considered related to NBF-006 were observed. Since May 2021, more than 20 additional patients have been treated with NBF-006, one event of increased pleural fluid has been reported as possibly related to study treatment, but no other serious nor severe treatment-related reactions were reported. Mild side effects thought to be at least possibly related to NBF-006 were observed in more than one patient (out of >35 treated) have included diarrhea (2 patients), nausea (3 patients), vomiting (3 patients), tiredness (4 patients), joint aches (2 patients), and “infusion related reactions” (4 patients). The infusion related reactions have presented with various symptoms (e.g., high blood pressure, rapid heartbeat, chest tightness, flushing), that resolved with allergy medication and pausing the infusion. So far, none of these symptoms caused patients to discontinue the study.

A rare but serious side effect which may occur is an allergic reaction to the study drug or one of the ingredients in the study drug. An allergic reaction may include:

- rash
- wheezing
- shortness of breath
- heart palpitations
- swelling of the face
- lowered blood pressure

Although rare, allergic reactions can be life-threatening or fatal. If you do have an allergic reaction, you will receive immediate treatment.

In studies performed in animals, one common observation under the microscope with NBF-006 was “vacuolation” (lipid- or fat-filled tiny sacs or droplets) in tissues and cells. Vacuolation is related to the dose of NBF-006 and goes away over time in animals. There is no direct correlation between vacuolation and any changes in organ function.

There may be other risks associated with needle sticks, tumor biopsy, reproductive risks (effects that NBF-006 may have on an unborn baby are not known), or risks associated with the CT scan, ECG, or

MRI. For example, CT scans involve exposure to some degree of radiation. You should talk to your study doctor about any side effects that you have while taking part in the study.

Expected Benefits

Taking part in this study may or may not make your health better. While study doctors hope the study drug, NBF-006, will be useful against your cancer, there is no proof of this yet. We do know that the information from this study will help doctors learn more about NBF-006 as a treatment for your type of cancer. This information could help other people with cancer in the future.

Alternatives to this Research Study

If you decide not to participate in this study, your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment/getting palliative care

You should discuss your choices with your study doctor. Your decision to enroll in this study is strictly voluntary, and, if you do enroll, you can end your participation at any time for any reason without forfeiting the standard clinical care that is provided to you.

Patient Information Sheet

You are being invited to take part in a clinical trial, a type of research study. You are being asked to take part in this study because you have cancer that has not responded to, or has failed standard treatment or other experimental therapies. Your study doctor will explain the clinical study to you. Clinical studies include only people who choose to take part. In order to decide whether or not you want to take part in this clinical study, you should understand enough about its risks and benefits to make an informed judgment. This process is known as informed consent. Please read the following information carefully, and discuss it with friends, family and your doctor if you wish. Take time to decide whether or not you wish to take part. If you have any questions, you can ask your study doctor for more explanation.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

1. Why is this study being done?

The main purpose of this study is to test the safety of an experimental drug called NBF-006. NBF-006 is an investigational product, which means it is a drug that has not yet been approved by the Food and Drug Administration (FDA), but is authorized by the FDA to be tested on patients. This drug has been tested in animals and this is the first study in which it is being tested in people. This study will test different dose levels of NBF-006 to determine any side effects the drug may have and the optimal dose level that is safe in humans. We will also investigate what effects, if any, the drug may have on your tumor.

2. How many people will take part?

The study will be conducted at multiple sites. Approximately 44 patients will take part in the study which will be conducted in 2 parts, Part A and Part B:

- Part A (Dose escalation): Will include approximately 20 patients who have advanced non-small cell lung cancer (NSCLC), pancreatic, or colorectal cancer that has not responded to, or failed, one or more prior therapies, including treatment with the highest dose level of drug for patients who have NSCLC with a confirmed “KRAS” gene mutation. Part A is a dose escalation or dose finding study where each cohort (patient group) receives a higher dose level than the previous cohort. Dose levels will increase until there are unacceptable side effects, or when the study reaches the highest planned dose level. Patients at the highest dose level in Part A will be evaluated for the GSTT1-null genotype, during the screening visit. This is a normal variant, the frequency of which varies in different populations. You will not be excluded from the study based on the result of the GSTT1-null genotype.

- Part B (Dose expansion): This part will open in parallel with the highest and last dose level in Part A. Part B plans to include approximately 24 patients (treated at different dose levels that were determined to be safe during Part A). The study will include patients who have advanced NSCLC that has not responded to, or failed, one or more prior therapies. Patients must have tumors with

confirmed KRAS mutation as determined by a genetic test performed in a laboratory, which is an analysis that is already done for most patients with lung cancer. Patients in this portion of the study will be evaluated for the GSTT1-null genotype, during the screening visit. This is a normal variant, the frequency of which varies in different populations. The result of the test may determine which group you are allocated to (i.e., which dose level), but you will not be excluded from the study based on the result of the GSTT1-null genotype.

3. Do I have to take part?

You are free to decide whether or not to take part in this study. If you decide to participate, you will be asked to sign and date this consent form and be given a copy of it to keep. If you decide to participate, you will be free to leave the study at any time. You do not have to give a reason, and it will not affect the standard of care you receive. If you decide not to take part, or you decide to leave the study, your doctor will discuss appropriate alternatives with you.

4. What will happen to me if I decide to take part?

Before you begin the study:
You will need to have the following examinations, tests, or procedures to find out if you can be in the study. Some of these examinations, tests, or procedures are part of regular care for patients with cancer and may be done even if you do not decide to participate in this study. If you have had some of these procedures within 28 days, they may not need to be repeated. This will be decided by your study doctor.

- Sign and date this informed consent form.
- Medical History: We will ask basic questions (age, gender, race) and about your prior surgeries, prior and ongoing medical illnesses, and prior treatments for your disease.
- Physical Exam: a full exam, including height and weight.
- Vital Signs: Temperature, blood pressure, pulse, and respiratory rate will be measured.
- Concomitant medications: We will ask you to list your current medications.
- ECG: ECGs measure the electrical activity of the heart. This is an indication of the overall health of your heart.
- ECOG Performance Score: This is a standard way of measuring, on a scale of 0 to 4, how well you feel performing normal everyday activities.
- Routine blood hematology and blood chemistry tests.
- Urinalysis.
- KRAS mutation confirmation:
    - This is a requirement for patients in the highest dose level in Part A and all patients in Part B and will affect your ability to participate in this study. Confirmation of KRAS mutation can be done with existing results of your genomic tumor profile, if available, or by testing an archival tumor tissue sample. If neither is available, a fresh biopsy is needed. We will only take a biopsy if it has low risk of complications.
- Blood sample for exploratory biomarkers to better understand who may respond to NBF-006 treatment. In Part B of the study, one genetic biomarker, GSTT1, will be used to arrange patients across dose groups so that there are an even number of patients lacking the GSTT1 biomarker in each group (lacking GSTT1 is a normal variant seen in a proportion of the population).

- Optional biopsy: Patients with metastases that are suitable for a biopsy will be asked if they are willing to have a biopsy done before the study and about 24 hours after the 4th treatment in Cycle 1 of the study, if clinically reasonable. These samples will be analyzed to see if the study drug has the desired effect on the target protein in the tumor cells.
- Concomitant medications

Within 14 days of study treatment:
- Tumor measurement by CT scan (x-rays) or other method to take images of your tumor.

Within 7 days of study treatment:
- Pregnancy test: for women of child-bearing potential only.

During the study:
You will have the following tests and procedures. Most of the procedures are part of regular cancer care. Some tests and procedures will be needed more often than normal because you are in a clinical trial.

The dose level of NBF-006 that you receive will depend on when you enter the study. For the dose escalation part of the study (Part A), increasing doses will be evaluated; dose levels will increase until there are unacceptable effects, or when the study reaches the highest planned dose level. Three of the dose levels that were confirmed safe in Part A will be explored further in the expansion part of the study (Part B). You will receive a dose of NBF-006 administered via IV infusion (approximately 70 minutes) once per week, for 4 consecutive weeks. After each infusion in Part A, you will stay in the clinic for up to 6 hours for safety observation and other procedures explained in the next pages. After the completion of the fourth dose, you have a 2-week rest period before you start the next cycle of treatment (1 cycle = 6 weeks). In Part A, after the "safety review committee" (which consists of representatives of the sponsor, the Medical Monitor, the research organization helping the sponsor, and the investigators), assesses safety at a given dose level, the observation period may be reduced to as few as 2 hours following the end of infusion from Cycle 2 onward. In Part B, the observation period is 6 hours after the first dose but is shortened if you tolerate treatment without any acute reactions.

<u>During Cycle 1</u>:
Week 1
- Dose of NBF-006
- Physical Exam
- Weight
- Vital signs
- ECG
- ECOG
- Routine blood hematology and blood chemistry tests
- Urinalysis
- Test for immune activation biomarkers: We want to make sure the study drug does not activate your body's immune system. We will draw blood samples and measure for proteins that the body produces in excess when the immune system is activated (1 pre- and 4 post-dose blood draws), including one draw which requires you to return the day after your dose of NBF-006), in Part A of the study. If no immune activation is observed in Part A of the study

at the dose level you will be treated at, some of these tests will not be done for Part B of the study.
- Test for anti-drug antibodies (ADA): Similar to the test for immune activation biomarkers, this looks for a specific type of protein (antibody) that might be made by your body to recognize this study drug as part of an immune response (1 pre-dose blood draw).
- Pharmacokinetic (PK) blood samples will be collected to measure the levels of the study drug and how long the study drug lasts in the body In Part A, there are 9 blood draws, which require you to return the second and third day. In Part B there are 7 blood draws, including one draw which requires you to return the day after your dose of NBF-006.
- Blood sample to evaluate GSTP decrease: GSTP is a protein that is present in many types of cancer and may help cancer cells grow. NBF-006 is meant to reduce the levels of GSTP protein in your tumor. Blood samples will be collected in order to determine if GSTP expression (by analysis of mRNA) is reduced in your body (1 pre-dose and 2 post-dose blood draws), including one draw which requires you to return the day after your dose of NBF-006).
- Concomitant medications.
- We will monitor for adverse events and you will be asked to monitor for adverse events outside of the clinic. You will be asked about any side effects you experience.

Week 2
- Dose of NBF-006
- Vital signs
- Routine blood hematology and blood chemistry tests
- PK blood sampling (1 pre-dose blood draw)
- Blood sample to evaluate GSTP decrease (1 pre-dose blood draw)
- Concomitant medications
- Adverse events

Week 3
- Dose of NBF-006
- Vital signs
- Routine blood hematology and blood chemistry tests
- Blood sample for ADA assay (1 pre-dose blood draw)
- Concomitant medications
- Adverse events

Week 4
- Dose of NBF-006
- Vital signs
- ECG
- Routine blood hematology and blood chemistry tests
- PK blood sampling - In Part A there are 9 blood draws, which require you to return the second and third day. In Part B there are 7 blood draws, including one draw which requires you to return the day after your dose of NBF-006.
- Concomitant medications
- Adverse events
- Optional biopsy: If you agreed to do optional biopsies in the study, the second biopsy will be collected approximately 24 hours after the 4th dose in Cycle 1.

Week 5
Rest

Week 6

- Tumor measurement by the same method (for example CT scan) used at the beginning of the study. If the tumor measurement shows that you may have responded to study treatment, you will be asked to come for another measurement 4-5 weeks later to confirm the results If a measurement is done at 4-5 weeks, then the Week 6 measurement may be skipped.

<u>During Cycle 2</u>:
Week 1

- Dose of NBF-006
- Physical Exam
- Weight
- Vital signs
- ECOG
- Routine blood hematology and blood chemistry tests
- Urinalysis
- Pregnancy test for women of child-bearing potential
- Blood sample for ADA assay (1 pre-dose blood draw)
- PK blood sampling (1 pre-dose blood draw)
- Concomitant medications
- Adverse events

Week 2

- Dose of NBF-006
- Vital signs
- Routine blood hematology and blood chemistry tests
- Concomitant medications
- Adverse events

Week 3

- Dose of NBF-006
- Vital signs
- Routine blood hematology and blood chemistry tests
- Concomitant medications
- Adverse events

Week 4

- Dose of NBF-006
- Vital signs
- Routine blood hematology and blood chemistry tests
- Concomitant medications
- Adverse events

Week 5

Rest

Week 6

- Tumor measurement by the same method used at the beginning of the study. If the tumor measurement shows that you may have responded to study treatment, you will be asked to come for another measurement 4-5 weeks later to confirm the results. If a measurement is done at 4-5 weeks, then the Week 6 measurement may be skipped.

<u>During Cycle 3 and Beyond</u>:

Week 1

- Dose of NBF-006
- Physical Exam
- Weight
- Vital signs
- ECOG
- Routine blood hematology and blood chemistry tests
- Urinalysis
- Pregnancy test for women of child-bearing potential
- Blood sample for ADA assay (1 pre-dose blood draw before your first dose of Cycle 4, Cycle 6, Cycle 8 etc. [every even numbered cycle]). After 1 year, the frequency will decrease to once every 6 months.
- Concomitant medications
- Adverse events

Week 2

- Dose of NBF-006
- Concomitant medications
- Adverse events
- Vital signs if needed
- Routine blood hematology and blood chemistry tests if needed

Week 3

- Dose of NBF-006
- Concomitant medications
- Adverse events
- Vital signs if needed
- Routine blood hematology and blood chemistry tests if needed

Week 4

- Dose of NBF-006
- Concomitant medications
- Adverse events
- Vital signs if needed
- Routine blood hematology and blood chemistry tests if needed

Week 5

Rest

Week 6

- Tumor measurement by the same method used at the beginning of the study

When You Finish Taking NBF-006 (to be performed within 30 ± 3 days after your last study treatment):

The following assessments will be performed for all patients who are discontinuing study treatment due to any reason (except a withdrawal of consent to participate that also includes refusal of any follow-up visits). This visit should be performed immediately after you discontinue study treatment and should be no later than 30 days after your last dose.

- Physical Exam
- Weight
- Vital signs
- ECG
- ECOG
- Tumor measurement (use same method as baseline)
- Routine blood hematology and blood chemistry tests
- Urinalysis
- Pregnancy test
- Blood sample for ADA assay
- Concomitant medications
- Adverse events

At Your Follow-Up Visit, About 30 Days After You Finish Taking NBF-006:
This visit does not have to be performed if your end of treatment visit was performed at 30 ± 3 days after last treatment.

- Physical Exam
- Weight
- ECOG
- Routine blood hematology and blood chemistry tests
- Urinalysis
- Blood sample for ADA assay
- Adverse events

5. What do I have to do?

There are no specific restrictions on what you can eat or do but you do need to report for the study visits. You cannot receive other experimental treatments for your tumor while you are on this trial. You should contact the study nurse or study doctor if you develop any side effects or problems of any sort. If, for any reason you are not able to keep your appointment for infusion of study drug or the necessary tests (for example, blood tests, CT scans), then the study treatment may have to be stopped. If this happens you will be instructed on what to do (for example, what alternate day to come to clinic).

6. How long will I be in the study?

You will be asked to continue participating in this study as long as you wish, as long as you are not experiencing any unacceptable side effects associated with the study drug.

7. Can I stop being in the study?

You can decide to stop at any time. It is important to tell your study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely. It may be necessary for you to have certain tests or procedures if you decide to stop, to ensure your safety. Your study doctor will discuss with you what follow-up care and testing could be most helpful to you.

Your study doctor may stop you from taking part in this study at any time if he or she believes it is in your best interest, or if you do not follow the study rules, or if the study is stopped.

8. What side effects or risks can I expect from being in the study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, study doctors do not know all the side effects that may happen. Side effects could be mild or very serious. Your study doctor may give you medicines to help lessen side effects. Side effects may disappear after you stop NBF-006. In clinical trials of a new drug, side effects can be serious, long lasting, or may never go away. There is also a risk of death when taking part in a clinical trial of a new experimental drug. You may also be required to follow procedures specific to the hospital where you are being treated in order to reduce your risk for COVID-19.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Among the first 35 patients treated in the study, there were 388 side effects reported in 29 patients. There were 10 patients experiencing severe side effects, of which only one, collection of fluid surrounding lungs, was reported as possibly related to study treatment. Mild side effects thought to be at least possibly related to NBF-006 observed in more than one patient (out of 35 treated) have included:

- fatigue
- infusion-related reaction
- vomiting
- nausea
- diarrhea
- joint pain

Only one patient had to discontinue study treatment as a result of side effects that occurred during the study. The side effects (collection of fluid around their lungs and inflammation of lung tissue) were suspected as possibly related to study treatment, but continuous growth of the patient's lung cancer, which can lead to similar symptoms, was also documented shortly after.

Infusion-related reactions have been observed in four patients, and required symptomatic treatment (usually with allergy medicines) and/or interrupted infusion. All patients have been able to continue with therapy. Infusion-related reactions have been described in clinical trials with similar drugs and drug formulations, as the active ingredient or one of the drug components may interact with the body's immune system and trigger inflammatory responses throughout the body. This can result in:

- Back pain
- Fever
- Nausea
- Headache
- Rash
- Rapid heartbeat
- Low blood pressure
- Temporary tightness in your chest, and trouble breathing
- Make you feel very ill like you have the flu.

“Cytokine release syndrome” is an extreme case of the body's inflammatory response; it can be life-threatening or fatal but is unlikely to occur with close monitoring. Such “infusion-related reactions” may be handled by interrupting the infusion of the study drug into your vein and then decreasing the rate of infusion. Medicines, such as antihistamines (which may cause drowsiness), can also be used to treat these infusion reactions, or possibly prevent them.

A rare but serious side-effect to a drug which may occur is an allergic reaction to the drug or one of the ingredients in the drug. An allergic reaction may include:

- A rash
- Wheezing
- Shortness of breath
- Heart palpitations
- Swelling of the face
- Lowered blood pressure.

Although rare, allergic reactions can be life-threatening or fatal. If you do have an allergic reaction, you will receive immediate treatment for it. If you have a history of allergic reactions to similar drugs, then being in this study may pose an extra risk for you and you should inform your study doctor of this beforehand.

NBF-006 contains a lipid (fat) component which forms a "container" around the drug. The lipids are called nanoparticles due to their microscopic size (nanometers, or one billionth of a meter in diameter). Other lipid nanoparticles have a history of being safe and tolerable in humans, but this study is the first time that NBF-006 is being given to humans. In toxicology studies performed in animals, one common microscopic observation with NBF-006 was vacuolation (the formation of lipid-filled tiny sacs or droplets) in tissues and cells. Vacuolation is related to the dose of NBF-006 and goes away over time in animals. It is not known what causes vacuolation, though it is thought to be part of the normal process by which cells in the body take up and eventually clear the lipids from the blood. There is no direct correlation between vacuolation and any changes in organ function.

Risks associated with needle sticks:
The study drug is diluted into an IV bag, and then the needle is inserted into your vein to inject the study drug. An injection site reaction may include:

- Redness
- Changes in skin color
- Tenderness
- Swelling.

More severe reactions may include clotting within the vein, marked inflammation of the vein and surrounding tissue or bloodstream infection, but these are very uncommon.

In this study, blood samples are frequently collected for routine and other lab tests. The most common risks associated with taking blood samples from the arm include pain where the needle is introduced, minor bleeding or bruising, light-headedness, and on rare occasions, infections.

Risks associated with tumor biopsy:
During the study, a biopsy to obtain samples from your tumor will be done if you say "Yes" to the optional biopsy at the end of this consent form. This is generally considered a safe procedure that is commonly performed. Although serious complications are not expected to occur, they can be life-threatening in rare cases.

Before the procedure, a numbing medication may be applied to the tumor site. During the procedure you may experience some discomfort when the needle is inserted. After the procedure, you may have minor pain and/or swelling or soreness at the biopsy site that can be relieved by over-the-counter pain medications. Minor bruising and/or bleeding under the skin at the biopsy site may occur.

Reproductive risks:
The effects that NBF-006 may have on an unborn baby are not known. You should not become pregnant or father a baby while taking part in this study. It is important you and your partner understand that you need to use a highly effective method of birth control *during the study treatment period and for 30 days after you finish taking NBF-006.* Check with your study doctor about what kind of birth control methods you and your partner should use and how long to use them for. Some methods might not be approved for use in this study.

If you are pregnant or breast feeding you may not take part in this study. If you are able to have children (for example, not post-menopausal or surgically sterilized), you must have a negative blood or urine pregnancy test before joining the study and confirmed again before each NBF-006 treatment cycle. *If you become pregnant or think you may be pregnant while on the study, you must notify your study doctor immediately.* The study staff will collect information about the pregnancy, its outcome, and the health of the child after birth.

If you decide to take part in the study, you should report any problems you have at your next clinic visit. You will also be given a contact number to telephone if you become concerned in any way at any time or need immediate advice on any symptoms.

Risks from imaging scans:

During your participation in this research study, you will be exposed to radiation from scheduled imaging scans, CT and MRI scans.

CT scans, like other x-ray-imaging exams, expose you briefly to a small, targeted amount of ionizing radiation, which helps create an image of structures inside your body. CT scans provide more-detailed images of more types of tissue than traditional x-rays do, which allow your doctor to detect and locate many medical conditions. Iodine containing contrast material is sometimes used. Patients with a history of allergy to iodine or contrast materials should notify their physician and radiology staff. Intravenous contrast can cause injury to the kidney, but this is rare in people without underlying kidney disease.

MRI scan is a painless radiology technique and there are no known side effects of MRI scan, although high doses of "gadolinium" (which is analogous to the iodine contrast that may be used for CT scans) can cause kidney injury in patients with underlying kidney disease. The benefits of an MRI scan relate to its precise accuracy in detecting abnormalities of the body. Patients who have any metallic materials, surgical clips, or foreign material (artificial joints, metallic bone plates, prosthetic device, etc.) can significantly distort the images obtained by MRI scanner. Patients who have heart pacemakers, metal implants, or metal chips or clips in or around the eyeballs cannot be scanned with an MRI because of the risk that the magnet may move the metal in these areas and cause injury.

The principal investigator for this research study has determined and verified that some of the imaging scans prescribed for this study would typically be performed as part of the standard medical care required to adequately monitor your current illness.

Radiation exposure may be decreased if non-radiation imaging is used, such as MRI. If you are especially concerned with radiation exposure, or you have had a lot of x-rays or imaging scans already, you should discuss this with the principal investigator for this study or your regular doctor.

Other risks:

Electrocardiogram (ECG): The ECG test is a recording of the electrical activity of your heart and is harmless. The sticky pads used may be cold when applied and sometimes cause some discomfort or redness or itching. If the skin under the patches needs to be shaved, irritation from shaving also could occur.

9. Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While study doctors hope the study drug, NBF-006, will be more useful against your cancer than the usual treatment, there is no proof of this yet. We do know that the information from this study will help study doctors learn more about NBF-006 as a treatment for solid tumors. This information could help other people with cancer in the future.

10. What other choices do I have if I do not take part in this study?

Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment or getting palliative care, also called comfort care. Comfort care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel.

Discuss your choices with your study doctor before you decide if you will take part in this study.

11. What if new information becomes available?

Sometimes, during the course of a research project, important new information becomes available on the drug that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to stay on the study. If you decide to stop, you should tell your study doctor. Withdrawal from the study will not affect your ability to receive standard medical care. If you decide to stay on the study, you may be asked to sign and date an updated informed consent form.

On receiving new information, your study doctor might think it is in your best interests to stop your participation in the study. If so, he or she will explain the reasons for his or her decision.

12. Will my medical information be kept confidential?

If you agree, your primary physician will be told that you are taking part in this study.

Federal regulations give you certain rights related to your health information. These include the right to know who will be able to get the information and why they may be able to get it. The study doctor must get your authorization (permission) to use or give out any health information that might identify you.

What information may be used and given to others?

If you choose to be in this study, the study doctor will get personal information about you. This may include information that might identify you. The study doctor may also get information about your health including:

- Medical and research records (which may include dates of birth, admissions, social security number)
- Records about phone calls related to your health
- Records about your study visits
- Records of physical exams
- Laboratory, x-ray, and other test results
- Records about study medications
- Records about any study drug you received

Who may use and give out information about you?
Information about your health may be used and given to others by the study doctor and staff. They might see the research information during and after the study.

Who might get this information?
Your information may be given to the sponsor of this research. "Sponsor" includes any persons or companies that are working for or with the sponsor, or are owned by the sponsor.

For this study, "sponsor" includes:
- Nitto BioPharma, Inc.
- Theradex Oncology, an agent for the sponsor

Information about you and your health which might identify you may be given to:

- Your Insurance Company
- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries
- Governmental agencies to whom certain diseases (reportable diseases) must be reported
- _____
  Name of IRB
- _____
  Name of site

Why will this information be used and/or given to others?
Information about you and your health that might identify you may be given to others to carry out the research study. The sponsor will analyze and evaluate the results of the study. In addition, people from the sponsor and its consultants will be visiting the research site. They will follow how the study is done to make sure, for example, that the protocol is being followed and data are being correctly collected, and they will be reviewing your information for this purpose.

The information may be given to the FDA. It may also be given to governmental agencies in other countries. This is done so the sponsor can receive marketing approval for new products resulting from this research. The information may also be used to meet the reporting requirements of governmental agencies.

The results of this research may be published in scientific journals or presented at medical meetings, but your identity will not be disclosed.

<*Insert IRB name*> may review the information. The Institutional Review Board (IRB) is a group of people who perform independent review of research as required by regulations to ensure that the rights and welfare of human subjects engaged in clinical research are protected.

What if I decide not to give permission to use and give out my health information?
By signing this consent form, you are giving permission to use and give out the health information listed above for the purposes described above. If you refuse to give permission, you will not be able to be in this research.

May I review or copy the information obtained from me or created about me?
You have the right to review and copy your health information. However, if you decide to be in this study and sign this permission form, you will not be allowed to look at or copy your study-collected information until after the research is completed.

May I withdraw or revoke (cancel) my permission?
You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to continue being in this study.

When you withdraw your permission, no new health information about you will be gathered after that date. Information that has already been gathered may still be used and given to others. This would be done if it were necessary for the research to be reliable. You understand that the revocation will not apply to your insurance company when the law provides your insurance company with the right to contest a claim under your policy.

Is my health information protected after it has been given to others?
All health care providers subject to HIPAA (Health Insurance Portability and Accountability Act) are required to protect the privacy of your information. The research staff at <*insert site name*> are required to comply with HIPAA and to ensure the confidentiality of your information. Some of the individuals or agencies who might have access to your information may not be subject to HIPAA and therefore may not be required to provide the same type of confidentiality protection. They could use or disclose your information in ways not mentioned in this form. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

If you give permission to give your identifiable health information to a person or business, the information may no longer be protected. There is a risk that your information will be released to others without your permission. Your personal information may be disclosed if required by law.

Your records for this study may be sent by facsimile transmission (FAX machine) or over the Internet. It is possible that your records could accidentally be sent to the wrong person.

Will my individual results from the research be given to me?
Results of research testing may be given to you or your doctor. This will be done only if the results may be necessary for your care.

<u>Expiration of Authorization</u>
Unless otherwise revoked, this authorization does not expire.

13. What will happen to the results of this study?

When the study is finished and the results have been analyzed, the information gained may be published in a medical/scientific journal, and/or presented at scientific meetings, and used for further research purposes. You <u>will not</u> be identified in any publication.

14. What will happen to the additional biological samples taken?

Any additional biological (blood or tumor tissue) samples will be stored at the clinical trial site or hospital until shipped to the laboratories doing the analyses. The samples will be analyzed and then destroyed. The samples will only be accessible to clinical site or hospital staff and to laboratory staff once sent to the laboratory. The data from the analysis will be accessible to representatives of the laboratory, Nitto BioPharma, Inc. (the Sponsor) and Theradex Oncology (designated CRO), and your study doctor. The results will be reported independently of this study. You will not be named or identified in any way in any report.

15. Will genetic tests be done?

Yes; one genetic test is done for determining eligibility, the other(s) are exploratory in nature and may be performed separately from this study. This study has a separate informed consent form for the genetic tests.

The screening tumor biopsy, or acquisition of your genomic tumor profile, if a report is available, will involve examination of genetic variations of KRAS, a gene that is often mutated in NSCLC, pancreatic, and colorectal cancer.

For the highest dose level in Part A and all dose levels of Part B, we require genetic testing for KRAS mutations associated with your tumor to determine if you are eligible for this study. Therefore, we require a screening tumor biopsy. If an archival sample was taken previously, we can request it from your doctor instead of taking a fresh sample. Or, if you have your genetic tumor profile, we can request a copy of that report instead of taking a tumor biopsy. The result of these genetic tests will determine your eligibility for participation in this portion of the study.

In patients at the highest dose level in Part A and all patients in Part B of the study, a blood test will be collected during screening to study if you are lacking a specific gene for detoxification. This genotype (genetic makeup) called *GSTT1 null*, is a normal variant in the population, and has, in some studies, been associated with an increased risk for development of cancer. Preliminary research indicates that patients with the GSTT1-null genotype may benefit more from treatment with NBF-006.

The exploratory tests will examine a blood sample taken at screening. We are interested in genes that may help predict who may or may not respond to the study drug.

16. Who is organizing and funding this study?

This study is being organized and funded by Nitto BioPharma, Inc., the sponsor. Their company is located in San Diego, California. The doctors conducting the study are not being directly paid by the sponsor, but a payment will be made to their institution to cover the costs of performing the study. Your study doctor will tell you if he or she has any financial or other ties with Nitto BioPharma, Inc.

17. What are the costs of taking part in this study?

You will not be paid for taking part in this study.

The study drug, NBF-006, will be supplied at no charge while you take part in this study. Although not likely to occur, should the study drug stop being available, your study doctor will talk to you about your options.

Your blood and tissue samples may be used to identify patients with cancer who may be more likely to respond favorably to the investigational drug. In this case, the "biomarker" used to identify these patients could be regarded as a "companion biomarker," to help determine those patients suitable for treatment, which is marketed commercially along with the drug. You would not share in any commercial profit from the use of the drug or biomarker.

You and/or your health plan or insurance company may need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at:http://cancer.gov/clinicaltrials/understanding/insurance-coverage.

You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

18. What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, *<insert investigator's name>*, if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him or her on telephone number *<insert telephone number>.*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

19. What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular benefits. Leaving the study will not affect your medical care.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.
In the case of injury resulting from this study, you do not lose any of your legal rights to seek compensation by signing this form.

You can speak with the IRB at <*insert site name*> for questions about your rights in this study.

Contact <*insert IRB contact name*> at <*insert contact's telephone number*> for more information.

20. Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor, <*insert doctor's name*> at <*insert doctor's telephone number*>.

Or you may contact your study nurse <*insert nurse's name*> at <*insert nurse's telephone number*> or study coordinator <*insert study coordinator's name*> at <*insert study coordinator's telephone number*>.

The <*insert IRB's name*> at <*insert site name*> has reviewed and approves this study.

Contact <*insert IRB contact name*> at <*insert contact telephone number*>> for more information.

INFORMED CONSENT FORM FOR CLINICAL RESEARCH

Study title: 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 (NSCLC), Pancreatic, or Colorectal Cancer Followed by a Dose Expansion Study in Patients with KRAS-Mutated Non-Small Cell Lung Cancer

Patient Statement

I, the undersigned, have been told about this research study. I have been informed about the procedures to be followed, the possible risks and the benefits that I may experience as a result of my taking part. I have read the description of this research (or had it translated into a language I understand) and had the opportunity to ask questions. I understand that my participation is voluntary and that I may withdraw from the study at any time without penalty or loss of any benefits I may otherwise be entitled to. I agree to take part in this research study.

I understand that any of my medical records may be inspected by Nitto BioPharma, Inc., the sponsor of this NBF-006 study, and their representatives, or by people from the Institutional Review Board or by regulatory authorities (for example, the FDA) to check that the study is being carried out correctly. I give permission for these parties to have access to my medical records. I give permission for my physician to be notified in writing of my participation in this study.

I may contact Dr. <*insert investigator's name*> at any time with questions about this study.

I have been given a copy of the patient information sheet and consent form.

I will be enrolled to the following study phase (choose one):

☐ Part A Dose Escalation
☐ Part B Dose Expansion

Name of Patient (print)	Date	Signature
Name of Person Conducting Informed Consent Discussion (print)	Date	Signature

INFORMED CONSENT FORM FOR GENETIC TESTING

Study title: **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 (NSCLC), Pancreatic, or Colorectal Cancer Followed by a Dose Expansion Study in Patients with KRAS-Mutated Non-Small Cell Lung Cancer**

Patient Statement

I, the undersigned, have been told about the genetic testing involved with this study.

I agree to provide a screening tumor biopsy to confirm my KRAS status. I understand my decision does affect my eligibility for this study and by choosing "No" I may not be eligible to participate in this study.	Yes ☐	No ☐
I agree to provide two *optional* biopsies for additional testing prior to the first dose and approximately 24 hours after my 4th dose in Cycle 1 of NBF-006. I understand my decision does not affect my eligibility for this study and I can participate in regardless of my decision	Yes ☐	No ☐
I agree to provide a copy of my genomic tumor profile or allow access to the results. I understand my decision does affect my eligibility for this study and by choosing "No" I may not be eligible to participate in this study.	Yes ☐	No ☐
I have read and understood that exploratory genetic tests may be performed on my blood sample.	Yes ☐	No ☐

Name of Patient (print)	Date	Signature
Name of Person Conducting Informed Consent Discussion (print)	Date	Signature