Official Title: LCI-GI-APX-NIN-001: Nintedanib in Metastatic Appendiceal Carcinoma
IRB-Approved Date: 10/20/2017
NCT03287947

CAROLINAS HEALTHCARE SYSTEM
CONSENT TO PARTICIPATE IN A RESEARCH STUDY

Sponsor / Study Title:	**Levine Cancer Institute, Nintedanib In Metastatic Appendiceal Carcinoma**
Protocol Number:	**LCI-GI-APX-NIN-001**
Principal Investigator:	**Jimmy Hwang, MD**
Telephone:	[redacted] **(24 Hours)** [redacted] **(24 Hours)**
Address:	**Levine Cancer Institute** [redacted]

This form is for use in a research study that may involve subjects who may or may not have the capacity to consent to take part in the study. Accordingly, when the subject cannot legally consent to take part, pronouns "you" and "your" should be read as referring to the subject rather than the person (legally authorized representative) who is signing this form for the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. During the course of the study, if the subject regains the capacity to consent, informed consent should be completed and the subject offered the ability to leave the study if desired.

INTRODUCTION

Dr. Hwang and his associates (the investigators) are asking you to participate in a research study at Levine Cancer Institute (LCI) and Carolinas HealthCare System (CHS) of patients with metastatic cancer of the appendix.

You are being asked to take part in this study because you have cancer of the appendix which has spread and your first treatment, with standard chemotherapy, has failed or was not tolerated. The purpose of this study is to see if your cancer can be controlled by treatment with nintedanib.

This is a clinical trial, a type of research study. Your study doctor and the study team will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You have also been told that you have the option not to participate. You may discuss your decision with your friends and family. You can also discuss it with

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your health care team. If you have any questions, you can ask your study doctor for more explanation.
This study is being carried out under the sponsorship of Levine Cancer Institute (LCI). Boehringer Ingelheim Pharmaceuticals is the company that makes nintedanib and will provide the study drug that will be used in this study.

WHY IS THIS STUDY BEING DONE?

Cancer of the appendix is a rare disease, so there is limited data regarding its treatment. The study drug, nintedanib, is approved by the U.S. Food and Drug Administration (FDA) for treating a medical condition called an idiopathic pulmonary fibrosis, a progressive condition which may lead to death.

Nintedanib has shown antitumor activity in clinical trials of lung and ovarian cancer, and has been studied in advanced colorectal cancer; however, nintedanib is not currently FDA approved for the treatment of appendix cancer. Given the similarities between appendiceal and colorectal cancer, and potentially ovarian cancer, and the limited information about the best way of treating metastatic appendiceal carcinomas, further investigation with nintedanib is needed.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

You will be one of approximately 39 subjects participating in this study at Levine Cancer Institute.

HOW THE STUDY WORKS

Before you begin the study (Pre-treatment/Screening/Prior to 1st dose of study drug):

In order to participate in this study, you will need to:

- Review, sign, and date this informed consent document and
- Provide authorization for the release of your medical records for research purposes.

In order to check if you are eligible to participate, the following will be done:

- Information will be collected from your medical record about your demographics (i.e. age, race, etc.), medical history, your current disease, any treatments received before, and any medications you are taking. All of your medical history (oncological and relevant non-oncological) findings that occurred prior to your signing this document will be documented.
- If you are a woman who can have children, a urine or blood pregnancy test will be done. The test results must be negative in order to be in the study. You must also not be breastfeeding to participate in the study.
- Office visit to conduct a physical exam and collect your height, weight, and vital signs (like temperature, pulse rate, respiratory rate, blood pressure).
- Review of medications and supplements that you are currently taking
- Collect about two tablespoons of blood for laboratory tests to check your blood counts and determine how well your kidneys, liver, and other organs function.

- Urinalysis (examination of the urine)
- Scans of your chest, abdomen and pelvis will be done using an x-ray machine that uses a computer to take pictures or computerized tomography (CT) scan.

Specimen Collection for the Purposes of Research:

If you agree to participate in this study, blood and ascites fluid may be collected and stored for future research. Ascites is a kind of fluid that may accumulate in the stomach. If your symptoms indicate a removal of the fluid, a procedure called a paracentesis will take place in order to remove it. A portion of this fluid (at least about 2 teaspoons) will be collected and stored for future analysis. At the same time you have blood drawn for routine labs, we will draw 1 tube of blood (about 2 tablespoons) for future research. If the future analysis is not performed, your blood and/or ascites samples(s) will be destroyed.

If you need to undergo repeated paracentesis, we would collect fluid each time for testing, and a portion of this will be stored.

If you qualify for the study and agree to participate, you will be enrolled and we will make arrangements to supply you with the study drug. The first dose of study drug should be taken on the day of your enrollment visit on Cycle 1 Day 1.

During the study (Intervention):

During the treatment period, each 28 day period of time is considered a "cycle." The cycles are repeated every 28 days and you are expected to complete at least 2 cycles, unless a study treatment delay is needed due to side effects. You will be removed from this study if your disease worsens during or after these 2 months. After this period, you may continue to participate in the study **only** if your disease is stable (about the same) or you are responding to the study treatment.

Study treatment will be given to you to take home. You will take two 100mg nintedanib capsules by mouth in the morning and two 100mg capsules in the evening (approximately every 12 hours) with food and a full glass of water (8 oz.). If side effects or complications from study treatment occur, your study doctor may tell you to temporarily stop taking the study drug or to adjust the dose.

In addition to taking nintedanib twice daily, you must also do the following:

- Swallow the capsule whole. Capsules should not be broken or crushed.
- Keep the capsules in their original bottle.
- If you miss a dose, you should not replace the missed dose but proceed to the next scheduled dose when it is due.
- If vomiting occurs after taking a dose, an extra dose should not be taken.
- Do not take any new prescription or herbal medication without first speaking with your study doctor or the clinical study staff.

You will meet with your study doctor and/or clinical study staff every four weeks on Day 1 of each cycle for as long as you are being treated on the study. During these visits, you will have a physical exam, ECOG performance status (we will ask you how you are doing in terms of your ability to take care of yourself, your daily and physical activities) and we will take some blood (about 2 tablespoons) for research purposes and to check your blood counts, kidney and liver function. We will also check your vital signs and weight and ask about any side effects you may have experienced. We may ask that you have additional office visits and/or laboratory testing if you have symptoms or side effects.

In addition to the visits on Day 1 of each cycle as referenced above, we will ask you to have your blood pressure taken and report to the study team member during a phone call for the first three weeks of Cycles 1 and 2. You may have your blood pressure taken at home if you have a blood pressure machine or you may go to another clinic of your choice (i.e. local pharmacy) for a blood pressure reading.

There are multiple drugs (prescription and over the counter medications and dietary/herbal supplements including what are sometimes called "complementary" or "alternative" medicines) that may interact with nintedanib. Your study doctor or study staff will review all of the medications and supplements you are currently taking before starting you on this investigational drug. You should not take any new medications or dietary supplements without discussing with your study doctor or study staff first.

A CT scan of your chest, abdomen, and pelvis (or acceptable alternative testing) will be planned at the completion of cycle 2 of receiving the study drug. You will continue to receive the study drug until your cancer gets worse, until side effects become unbearable even if they are being medically treated, or until you are too ill to continue. You also have the option to voluntarily discontinue study treatment and withdraw from the study at any time. If neither of the above mentioned scenario happens and you continue to receive the study drug, a CT scan (or acceptable alternative testing) will be necessary at the completion of every 2 cycles (e.g. cycles 4, 6, 8).

In order to document the current status of your disease (which could be a response, stable disease, or progressive disease) we will make all efforts to obtain scans and assess your tumor every 8 weeks (+/- 2 weeks). If you decide to discontinue therapy, every effort will be made to obtain any future scan results unless your disease worsens or you start new treatment.

Your study doctor may also choose to withdraw you from the study for any reason, including if you are unable to adhere to the study schedules and requirements.

After you complete the intervention (End of treatment):

Within 30 days of your last dose of study treatment, you will come in and meet with your study doctor and/or clinical study staff. At this visit, you will have a few procedures done which may

include but not limited to a physical exam, check of the vital signs, check of your current medications and a blood draw.

Following this visit, research staff will contact you every 6 months, until you complete 3 years of follow-up after you stop taking the study drug.

RISKS

You may have side effects while you are on this study. Everyone taking part in the study will be carefully watched for side effects, especially for your liver enzymes. However, doctors don't know all the side effects that may happen. Side effects can be mild or very serious. Your doctor may give you medicines to lessen side effects. In some cases, side effects can be serious in that they can be long lasting, may never go away, may result in hospitalization, or may result in death.

The **very common** (occurring in more than 10% of patients treated with nintedanib) risks in adult patients are:

- diarrhea
- nausea
- vomiting
- increased liver function tests (blood tests that show that show that your liver is not working the way it should)
- tiredness
- decreased appetite
- pain- abdominal pain, muscle cramps, chest pain, back pain, tumor pain
- skin problems such as: itching, rash, hair loss, dry skin, hand foot syndrome, nail disorder
- electrolyte imbalance (electrolytes are minerals in the blood)
- abnormal skin sensations
- bleeding e.g. nose bleeding, coughing up small amounts of blood, rectal bleeding
- mouth ulceration

The **common** (occurring in more than 1% and less than 10% of patients treated with nintedanib) risks in adult patients are:

- taste changes
- constipation
- fever
- high blood pressure
- decrease in weight
- headache
- infections including those in the urine, chest and sinuses
- dry mouth
- flatulence (gas)
- dizziness

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- dehydration
- insomnia
- blood clots in vein (venous thromboembolism) or in arteries (arterial thromboembolism including myocardial infarct)

The **rare** (occurring in less than 1% of patients treated with nintedanib) risks in adult patients are:

- cough
- chills
- vertigo (a feeling that the room is spinning)
- low blood pressure
- eye disorders, such as eye dryness, eye redness, conjunctivitis, vison blurred
- allergic reaction to drug, like itching, rash
- skin swelling
- abnormal heart beats, fast or slow heart beats
- low blood sugar
- changes in kidney function
- perforation (holes in the bowels)
- bleeding into the brain
- low production of the thyroid hormone
- pancreatitis (swelling and inflammation of the pancreas)
- In a few patients, an increase of bilirubin and liver enzymes was observed. This was fully reversible and appeared to be associated with progression of the underlying cancer disease and concomitant development of liver metastases. Enzyme elevations generally returned to normal upon temporarily stopping treatment in the majority of patients, and usually did not happen again after continuation of treatment at a lower dose. Your liver enzyme levels will be monitored closely during the conduct of this study.

  Extra blood samples and ultrasound images may be taken in order to clarify the potential underlying reason for the increased liver enzymes. If the cause of liver function changes cannot be found, further tests may be performed. This may include taking additional blood samples for further analysis of safety parameters, the analysis of the types and amounts of hormones, and the presence of viruses. Please inform your study doctor if you notice yellowing of the skin or of the white part of your eyes, which are signs of an increased bilirubin level in your body.
- Previous animal studies suggest that decreased immune function may also occur when being treated with nintedanib. These animal studies also suggested that nintedanib in combination with natural sunlight or artificial UV radiation may cause effects to the skin or the eye. However, so far, these adverse events have not been reported in clinical trials with humans.

You need to tell your study doctor immediately if you experience any side effects while taking part in the study.

Any medications (including over the counter and herbal supplements) that you are taking while taking nintedanib will be monitored by your study doctor or study staff. Some medications may affect the way nintedanib works. Please notify your study doctor or study staff immediately before you start taking any new medications.

INFORMATION ON BIRTH CONTROL (For Female Trial Participants)

As with any investigational drug, the effect of nintedanib on an unborn child is unknown. If you decide to take part in this trial and you are able to become pregnant, you must be willing to have a pregnancy test done before beginning your participation, and regularly at study visits and at the end of study treatment and beyond for at least 3 months after the last dose of nintedanib. Furthermore, you must avoid becoming pregnant while you take part in this trial. You cannot participate in this trial if you are pregnant, breastfeeding or plan to become pregnant during your trial participation.

You must use a highly effective method of birth control. Some of the acceptable methods of contraception are listed below:

- an oral contraceptive (birth control pills)
- an implantable or injectable contraceptive
- an intrauterine device/system (IUDs / IUSs)
- transdermal patch
- double barrier method (two methods used at the same time)
- bilateral tubal occlusion
- vasectomized sexual partner (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and provided that partner is the sole sexual partner of the participant
- complete sexual abstinence when this is in line with the preferred and usual lifestyle of the study participant. When there is complete sexual abstinence, the patient refrains from any sort of sexual activity that could involve the spill of an ejaculate, even if the spill does not occur

Your doctor will talk to you about the best method of birth control for you.

If you are pregnant or think you could be pregnant, it is important for you to tell your doctor or research staff immediately. If you become pregnant during the trial, you will be removed from the trial and your health and your baby's health will be monitored throughout your pregnancy. Even if you are no longer in the trial, you will be contacted after your baby is born to find out about the baby's health.

For MALE Trial Participants

During study participation and for 3 months after your last study drug dose you should not father a child or donate sperm.

WILL I BENEFIT FROM PARTICIPATING IN THIS STUDY?

The benefits of nintedanib to treat advanced and/or metastatic appendiceal carcinoma are **not** fully known and it might be that you do not gain any benefit by participating in this research. With our current knowledge and understanding, nintedanib **may** have the potential to provide benefits to you or others like you, by slowing down the growth and spread of the tumor.

Information from this study may help you and/or other people with your disease in the future.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT TAKE PART IN THIS STUDY?

You may choose not to participate in this study and receive routine care, or any standard treatment as recommended by your study doctor, such as other chemotherapy, or participation in other clinical trials. Your study doctor can discuss the alternatives and the risks and benefits of these alternatives with you. Please ask any questions you may have and take as much time as you need to make your decision. If you choose not to take part in this study, that will not harm your relationship with your doctor or with CHS.

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

You and/or your health plan/insurance will need to pay for all routine care procedures. You may have to pay for these costs if they are not covered by your insurance company. If you choose to take part in the study, you will receive the study treatment, nintedanib, at no charge to you. Medicines that are not part of the study treatment will not be provided or paid for by LCI.

You will not receive payment for taking part in this study.

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 [redacted] and ask them to send you a free copy.

You may wish to discuss coverage with your insurance company before agreeing to participate in this research study.

WHAT HAPPENS IF I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

If you become ill or are hurt while you are in the study, you will get the medical care that you need right away.

In the event that you are harmed as a result of your participation in this study, inform your doctor immediately so you can access medical treatment. You and/or your health plan will be charged for this treatment in the usual manner. The study will not pay for standard medical treatment. The drug manufacturing company (Boehringer Ingelheim) will not provide any compensation for injury that occurred during the course of this research trial with nintedanib.

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You still have the right to make a claim through the legal system even if you sign this form, accept medical care, or accept payment for medical expenses.

WHAT IF I WANT TO QUIT THE STUDY LATER ON?

Your participation in this study is completely voluntary. You should feel under no pressure to be in the study. If you decide not to be in the study, that will not in any way harm your relations with your doctors or with Carolinas HealthCare System. You are free to stop being in the study if you change your mind after entering it. This would not harm your relations with your doctors or Carolinas HealthCare System. Information contributed to the study will remain in the study even if you choose to withdraw. If you choose to withdraw from the study, please notify the study doctor in writing at the address on page 1 of this consent form.

Your study doctor may choose to involuntarily withdraw you from the study for any reason, including if you are unable to adhere to the study schedule or requirements.

We will tell you about new medical findings that may affect your willingness to continue in the study.

WILL MY MEDICAL INFORMATION BE KEPT PRIVATE?

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Carolinas HealthCare System (CHS)
- Boehringer Ingelheim, the company that manufactures nintedanib
- Government agencies, like the Food and Drug Administration (FDA) that are involved in keeping research safe for people
- Other persons/agencies as required by law or allowed by federal regulations

The records of this study will be kept private. In any sort of report we might publish, we will not include any information that will make it possible to identify a patient. Your record for this study may, however, be reviewed and/or photocopied, by Carolinas HealthCare System, or by representatives of the Food and Drug Administration or other government agencies. To that extent, confidentiality is not absolute.

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

To ensure that your information collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All of your study data will be kept in a secure location.

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AUTHORIZATION

If you wish to take part in this clinical study, you will be asked to sign this consent form. It allows the study sponsor (LCI) and the sponsor-investigator (Dr. Jimmy Hwang) to collect and process any relevant personal health information collected from you during the study. These are activities routinely carried out during all clinical studies.

You have been told that personal information about you (including sensitive personal health information, such as your medical history and your racial/ethnic origin if relevant to the study) will be reviewed, collected on a computer database, stored in electronic or manual files, audited, and/or otherwise processed by:

- the clinical study sponsor-investigator, investigators and research staff
- regulatory or other governmental authorities of the United States and other countries,
- other persons authorized by the study sponsor,
- Carolinas HealthCare System employees,
- other persons or agencies as required by law or allowed by federal regulations.

You have been told that your personal data are being collected and processed to:

- check your suitability to take part in the study,
- monitor activity with the medication (nintedanib) under study.
- compare results with those of other subjects in the study,
- support the development of the other study protocols.

You have been told that your personal information may be processed within the U.S, processing and/or storage by an associated company or a carefully selected third-party organization. By signing this document, you explicitly consent to the transfer of your personal information, including sensitive personal information, collected during this clinical study, for review, processing and/or storage. Your personal health information may be further shared by the groups above. If shared by them, the information will no longer be covered by the Privacy Rule. However, the groups are committed to keeping your personal health confidential.

You may refuse this authorization to transfer your personal information. If you choose not to agree to this authorization, you might be ineligible to participate in the study. If you decide not to sign this authorization, that will not harm your relations with your doctors or with Carolinas HealthCare System.

You have the right to inspect your medical record at any time. Your research record may be unavailable until the conclusion of the study. At that point, it will be available. Please speak with the study doctor if you desire to access your record.

You have been told whenever your personal information is processed, it will be kept confidential and secure, to the best of our ability. It will be used only for the purpose for which it was collected.

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This Authorization does not have an expiration date. You have been told that according to the guidelines for good clinical practice, the study sponsor-investigator will keep your personal information for at least 6 years. If you do not withdraw this Authorization in writing, it will remain until the study is terminated. If you wish to revoke authorization to use your personal information, you will notify the study doctor in writing at the address on page 1 of this consent form.

Some of the data obtained from your record prior to your revocation may still be used if considered necessary for the study.

FINANCIAL DISCLOSURE

None of the doctors asking you to participate in this study has received or will receive money or other benefits for personal use from Boehringer Ingelheim, the company that developed the nintedanib used in this study. However, the funding company will give money or other benefits to a research fund, foundation, educational institution, or other organization with which the doctor or study staff is associated.

GETTING ANSWERS TO YOUR QUESTIONS OR CONCERNS ABOUT THE STUDY

You can ask questions about this consent form or the study (before you decide to start the study, at any time during the study, or after completion of the study). Questions may include:

- Who to contact in the case of a research-related injury or illness;
- Payment or compensation for being in the study, if any;
- Your responsibilities as a study subject;
- Eligibility to participate in the research;
- The study doctor's or study site's decision to exclude you from participation;
- Results of tests and/or procedures;
- Other questions, concerns, or complaints.

Contact the study doctor or study staff at Carolinas Healthcare, listed on the first page of this form, with any questions, concerns or complaints.

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GETTING ANSWERS TO YOUR QUESTIONS ABOUT YOUR RIGHTS AS A RESEARCH SUBJECT

This study has been reviewed by an Institutional Review Board (IRB). This Committee reviewed this study to help ensure that your rights and welfare are protected and that this study is carried out in an ethical manner.

For questions about your rights as a research subject, contact:

- By **mail**:
  Study Subject Adviser
  [redacted]
- or call **toll free**: [redacted]
- or by **email**: [redacted]

Please reference the following number when contacting the Study Subject Adviser: Pro00021617.

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CONSENT AND AUTHROIZATION

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. **I am not giving up any of my legal rights by signing this form**.

_____ ____/____/____ _____
Signature of Research Subject Date Time

_____
Printed Name of Research Subject

_____ ____/____/____ _____
Signature of Legally Authorized Representative (if applicable) Date Time

_____
Printed Name of Legally Authorized Representative (if applicable)

STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject or the subject's legally authorized representative the nature and purpose of the above study. There has been an opportunity for the subject or the subject's legally authorized representative to ask questions about this research study. I have been available to answer any questions that the subject or the subject's legally authorized representative has about this study.

_____ ____/____/____ _____
Signature of Person Explaining Consent Date Time

_____
Printed Name of Person Explaining Consent

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