INFORMED CONSENT DOCUMENT

Project Title: **Phase II Study of Abraxane with Gemcitabine for Relapsed Small Cell Cancer or Those with Progression on First Line Therapy**

Principal Investigator: **Muhammad Furqan, MD**

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This consent form describes the research study to help you decide if you want to participate. This form provides important information about what you will be asked to do during the study, about the risks and benefits of the study, and about your rights as a research subject.

- If you have any questions about or do not understand something in this form, you should ask the research team for more information.
- You should discuss your participation with anyone you choose such as family or friends.
- Do not agree to participate in this study unless the research team has answered your questions and you decide that you want to be part of this study.

WHAT IS THE PURPOSE OF THIS STUDY?

This is a research study. We are inviting you to participate in this research study because you have small cell lung cancer and have had progressive disease after one line of treatment for your cancer.

The purpose of this research study is to see if Abraxane and Gemcitabine given together will be effective in treating your lung cancer. This combination of chemotherapy drugs has been studied in patients with pancreatic cancer and has shown increased survival in that group.

Abraxane is considered investigational, which means that it has not been approved by the U.S. Food and Drug Administration for the treatment of relapsed small cell lung cancer. Gemcitabine is also considered investigational, as it has not been approved by the U.S. Food and Drug Administration for the treatment of relapsed small cell lung cancer. However, Abraxane is approved for the treatment of squamous cell cancer of the lung and for pancreatic cancer in combination with gemcitabine.

HOW MANY PEOPLE WILL PARTICIPATE?

Approximately 57 people will take part in this study conducted by investigators at the University of

Iowa.

HOW LONG WILL I BE IN THIS STUDY?

If you agree to take part in this study, your involvement could last up to five years. This study consists of treatment "cycles" and each cycle is 21 days long. You will return to the hospital for treatment on Days 1 and 8 of each cycle and continue this until you experience disease progression, or unacceptable side-effects. Once you complete all cycles of the study, you will have an End of Treatment visit approximately 28 days after your last dose of study drug. Visits will range from 1 to 4 hours in length.

Visits will then be scheduled every 2 months (+/- 3 weeks) until your disease progresses. If you have disease progression or start a new anti-cancer therapy, you will then be contacted by telephone every 12 weeks (+/- 4 weeks) to see how you are doing. These phone calls will continue for 3 years from your screening date or until the end of the study, whichever occurs first.

WHAT WILL HAPPEN DURING THIS STUDY?

Before you begin the study:
You will need to have the following procedures to find out if you can be in the study. Many of these procedures are part of your regular cancer care and would be done even if you do not join the study.

- Medical history (including history of previous and current conditions and treatments)
- Physical examination (complete physical examination including height and weight)
- Pregnancy test (this test is mandatory in women of child-bearing potential). Results of the pregnancy test must be negative for you to participate in this study.
- Approximately 3-4 teaspoons of blood will be drawn for standard lab tests
- CT scan, chest x-ray or MRI scan will be done within 30 days prior to registration

Within 3 days before each treatment:

- Physical examination (physical examination including weight)
- Approximately 3-4 teaspoons of blood will be drawn for standard lab tests

During each cycle of treatment (1 cycle = 21 days):

- Abraxane will be given intravenously over 30 minutes on Days 1 and 8.
- Gemcitabine will be given intravenously over 30 minutes on Days 1 and 8, following the Abraxane.
- During Cycles 1 and 2 only, approximately 3-4 teaspoons of blood will be drawn each week for standard lab tests

Every 2 cycles (approximately every 6 weeks):

- CT scan, chest x-ray or MRI scan done

End of Treatment (approximately 28 days after your last dose):

- Physical examination (physical examination including height and weight)
- Approximately 3-4 teaspoons of blood will be drawn for standard lab tests

Long-term follow-up after end of treatment:
We would like to follow you even after you're done receiving treatment. You'll have visits scheduled every 2 months until your disease progresses. After disease progression, we will check your medical chart, or contact you by telephone every 12 weeks (+/- 4 weeks) to see how you are doing. This will continue for 3 years from your screening date or until the end of the study, whichever occurs first.

Below is a table that shows the tests and procedures for this study:

Test and Procedures	**Within 30 days prior to therapy**	**Within 15 days prior to therapy (screening visit)**	**Within 3 days prior to or day of each treatment**	**Active monitoring Phase**			**Followup after treatment[3]**
				Weekly for first two cycles	**Every two cycles**	**End of treatment**	
History and physical examination		X	X			X	X
Height and weight[2]	X		X			X	
Pregnancy test		X[1]					
Blood draw for standard laboratory tests		X	X	X		X	X
Adverse Event Assessment		X	X			X	
Tumor measurement by CT, MRI or X-ray	X				X		X

1. For women of childbearing age only. Must be done within 7 days prior to registration.
2. Height only needs to be collected at baseline.
3. Visits scheduled every 2 months (+/- 3 weeks) until disease progression. Once there is disease progression or a new anti-cancer therapy has been started, you will be contacted by telephone every 12 weeks (+/- 4 weeks) for 3 years from your screening date or until the end of the study, whichever occurs first.

Blood draw used in testing may be drawn at a local lab rather than by the research team at UIHC.

WHAT ARE THE RISKS OF THIS STUDY?

You may experience one or more of the risks indicated below from being in this study. In addition to these, there may be other unknown risks, or risks that we did not anticipate, associated with being in this study.

The following is a list of the most medically significant or most common side effects reported in completed studies considered to be related to Abraxane. In some cases, side effects can be serious, long-lasting, or can cause death. Some side effects go away soon after you stop the study drug/therapy and some may never go away. The study doctor may change the dose of Abraxane or give you medicines to

help lessen the side effects. This is not a complete list of all side effects that may occur. For more information about risks and side effects, please ask the study doctor.

Very common (a 10% or more chance that this will happen):

• anemia (a decrease in the number of red blood cells (which may make you feel weak or tired))
• low number of white blood cells with or without fever (that may make it easier get infections)
• a decrease in the number platelets, the cells that help your blood to clot (which may lead to unusual bleeding or bruising under the skin)
• constipation
• diarrhea
• nausea
• vomiting
• stomach pain
• pain, swelling or sores on the inside of the mouth
• neuropathy, a disorder of the nerves which can cause tingling or numbness, with weakness, or decreased sensation or movement
• dizziness
• headache
• feeling tired or weak
• pain (including muscle, joints, bone, and chest pain)
• swelling caused by fluid held in the tissues, especially of the ankles, feet or fingers
• fever
• chills
• decreased appetite
• change in taste
• weight loss
• difficulty sleeping
• depression
• cough
• shortness of breath
• hair loss
• rash, possibly red, bumpy or generalized
• itchiness
• changes in nails, including discoloration or separation from nailbed
• abnormal liver function test results
• dehydration (loss of water and minerals in the body)
• nose bleed
• decreased potassium levels in the blood

Common (between a 1% to less than 10% chance that this will happen):
• bone marrow depression which is a severe reduction of red or white blood cells and platelets (at nearly the same time) which can cause weakness, bruising, or make infections more likely
• infections, including pneumonia or of the lung, mouth, gallbladder, urinary tract, nail, or hair follicle, (which may be bacterial, fungal or viral)
• a very severe infection of the blood which may include a decrease in blood pressure

• inflammation of the lung passages
• thickening, inflammation or scarring in the lungs which may cause breathlessness, cough
• inflammation of the bowel causing abdominal pain or diarrhea
• blockage of the intestine
• trouble swallowing
• indigestion or upset stomach
• abnormal chemistry or electrolyte blood test results
• abnormal kidney function test results
• acute kidney failure
• blood in the urine
• lack of muscle coordination
• muscle weakness
• anxiety
• nasal congestion
• mouth or throat pain
• dry mouth, nose, and throat
• coughing up blood or bloody sputum
• blood clot in the lungs or in deep vein
• fluid in the chest cavity
• red or flushed skin
• dry skin
• hand-foot syndrome, involving reddening, swelling, numbness and peeling of palms and soles of feet
• high blood pressure
• low blood pressure
• a decrease in the heart's ability to pump blood to all parts of the body and possibly heart failure
• faster heart beat
• watery eyes
• changes in vision or blurry vision
• infusion site reactions (described as discomfort, bleeding or bruising/swelling at the needle site, and in some instances infection or leaking of IV fluid outside of blood vessel into the surrounding tissue)
• localized swelling due to buildup of lymph fluid

Uncommon (between a 0.1% to less than 1.0% chance that this will happen):
• a decrease in the left side of the heart's ability to pump blood to all parts of the body
• irregular or slow heart beat
• stopping of the heart
• allergic reaction (may include skin inflammation, rash, trouble breathing, trouble speaking, fever), sometimes fatal
• syndrome involving abnormal blood clotting, with decreased platelets, bruising (including tiny red or purple spots under the skin) and possibly leading to blood clots
• edema/swelling and cyst formation of the macular area of the retina
• irritation and redness of the thin membrane covering the eye
• inflammation of the cornea
• too much fluid in the body
• feeling unwell
• sleepiness

• scaly or peeling skin
• potentially life threatening allergic reaction of the skin and oral mucous membranes (may include lesions in the mouth, itching and blistering skin)
• hives
• a loss of nerve function in the muscles of the face

Additional side effects observed during post-marketing surveillance of Abraxame, not otherwise noted above include:
• a loss of nerve function in the muscles of the face or the eyes
• lack of movement in the vocal cords with possible voice changes
• skin sensitivity to sunlight
• potentially life threatening allergic reaction [may include skin rash with skin blistering]
• skin or tissue damage from prior radiation therapy can become damaged again, when a person receives chemotherapy after having had radiation therapy. This is referred to as radiation recall and may involve redness, peeling, pain, and swelling. Skin changes have been noted to range from mild redness to tissue death. Radiation recall may also occur in the lungs and other internal organs.

Elderly
In subjects 65 years old and older with metastatic breast cancer who received Abraxane alone, a higher incidence of nose bleed, diarrhea, dehydration (loss of water and minerals in the body), feeling tired or weak and swelling caused by fluid held in the tissues, especially of the ankles, feet or fingers has been reported.

Abraxane in combination with gemcitabine

• In subjects with metastatic pancreatic cancer, who received the combination of Abraxane and gemcitabine, there may be an increase of blood infections. Contact your study doctor immediately if you develop a fever. Your study doctor will evaluate if your fever is an early sign of a serious infection, which may require treatment.

• A particular lung illness, known as pneumonitis (thickening, inflammation or scarring in the lungs with breathlessness, or cough), appears to occur more often (4%) when the two drugs are given together. This lung illness requires early detection and treatment as it may be life- threatening or even fatal. Therefore, it is important that you promptly tell your study doctor if you have worsening shortness of breath, difficulty breathing, fever, or a dry cough (not productive), for further evaluation and possible treatment.

• Acute renal or kidney failure and hemolytic uremic syndrome (a syndrome involving abnormal blood clotting, with decreased platelets, bruising including tiny red or purple spots under the skin, and possibly leading to blood clots) have been reported commonly and uncommonly, respectively, in combination of Abraxane with gemcitabine.

• A very rare condition known as Posterior Reversible Encephalopathy Syndrome that causes problems with the nervous system due to leaking of fluid outside of blood vessels has occurred when gemcitabine is given alone or in combination with other chemotherapy medications. Therefore, you should tell your doctor if you have one or more of the following symptoms; headache, abnormal shaking of the body,

sleepiness, increased blood pressure, feeling confused, abnormal vision including loss of vision, loss of muscle control or muscle weakness, numbness or tingling in extremities

• A very rare condition known as Capillary Leak Syndrome that causes leaking of fluid outside of blood vessels has occurred when gemcitabine is given alone or in combination with other chemotherapy medications. Therefore, you should tell your study doctor if you have one or more of the following symptoms: fatigue; lightheadedness or fainting; pain in arms, legs, or stomach or all over body; swelling in face or body; difficulty breathing; low blood pressure.

Additional side effects observed during post-marketing surveillance of gemcitabine, not otherwise noted above include:
• an inflammation of the small blood vessels described as pain, heat, and redness to the affected part of the body.
• dying tissue due to lack of blood supply described as skin discoloration, severe pain, foul smelling leakage from a sore, and may include swelling, and increased temperature to the affected region of the body.

Elderly
In subjects 65 years old and older who received Abraxane and gemcitabine, a higher incidence of diarrhea, decreased appetite, dehydration (loss of water and minerals in the body) and of nose bleed has been reported compared to subjects less than 65 years old. In subjects 75 years old and older, a higher incidence of serious adverse reactions and adverse reactions leading to treatment discontinuation has been reported.

Pregnancy Risk

Females: Abraxane can cause harm to an unborn child if given to a pregnant woman. You cannot take part in this study if you are pregnant or breast-feeding. Because of the possible risks to an unborn child, if you are a female who can become pregnant, you will be asked to take a pregnancy test prior to starting study drug treatment and throughout your study participation.

If you decide to take part in this study, you should avoid becoming pregnant while receiving study medication. You must commit to abstinence from heterosexual contact, or agree to use medical doctor-approved contraception throughout the study without interruption, while receiving study medication or for a longer period if required by local regulations. If you become pregnant while receiving study medication or within 28 days after taking your last dose of study medication, you must tell the study right away. If this happens, study medication will be discontinued. The study doctor will follow you and your pregnancy to completion.

Males: If you have a partner of childbearing potential, you should avoid fathering a child while receiving study medication and for 6 months after your last dose of study medication. You must agree to complete abstinence from heterosexual contact or use a condom during sexual contact with a female of child bearing potential while receiving study medication and within 6 months after your last dose of study medication. If your partner becomes pregnant while you are receiving study medication or within 6 months after you took your last dose of study medication, you must tell the study doctor right away.

WHAT ARE THE BENEFITS OF THIS STUDY?

We don't know if you will benefit from being in this study.

However, we hope that, in the future, other people might benefit from this study because the knowledge gained might help to develop better treatments for small cell lung cancer.

WHAT OTHER TREATMENT OPTIONS ARE THERE?

Before you decide whether or not to be in this study, your doctor will discuss the other options that are available to you. Instead of being in this study, you could have the option of other chemotherapy treatment or other investigational research studies. You also have the option of receiving no treatment for your cancer. Please talk to your doctor about these options.

WILL IT COST ME ANYTHING TO BE IN THIS STUDY?

You may have costs for being in this research study. The study drug, Abraxane, will be provided to you free-of-charge by Celgene Corporation. The cost of gemcitabine will be the responsibility of you or your insurance carrier. All of the tests and procedures done as standard of care for your disease will be the responsibility of you or your insurance carrier.

We encourage you to determine your health insurer's policy about paying for treatment in a research study.

You and/or your medical/hospital insurance carrier will remain responsible for your regular medical care expenses.

WILL I BE PAID FOR PARTICIPATING?

You will not be paid for being in this research study.

WHO IS FUNDING THIS STUDY?

Celgene Corporation is providing some grant funding for this research study. This means that the University of Iowa is receiving a grant from Celgene Corporation to help support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from Celgene Corporation for conducting this study.

WHAT IF I AM INJURED AS A RESULT OF THIS STUDY?

- If you are injured or become ill from taking part in this study, medical treatment is available at the University of Iowa Hospitals and Clinics.

- The University of Iowa does not plan to provide free medical care or payment for treatment of any illness or injury resulting from this study unless it is the direct result of proven negligence by a University employee.
- If you experience a research-related illness or injury, you and/or your medical or hospital insurance carrier will be responsible for the cost of treatment.

WHAT ABOUT CONFIDENTIALITY?

We will keep your participation in this research study confidential to the extent permitted by law. However, it is possible that other people such as those indicated below may become aware of your participation in this study and may inspect and copy records pertaining to this research. Some of these records could contain information that personally identifies you.

- federal government regulatory agencies,
- the U.S. Food and Drug Administration
- Celgene Corporation may also inspect any part of your medical record for the purposes of auditing the conduct of the study.
- auditing departments of the University of Iowa, and
- the University of Iowa Institutional Review Board (a committee that reviews and approves research studies)

In the future, Celgene Corporation may continue to use your health information that is collected as part of this study. For example, Celgene Corporation may combine information from this study with the results of other studies to re-analyze the safety and effectiveness of the study medication, to evaluate other products or therapies, to develop a better understanding of a disease, or to improve the design of future research studies. Celgene Corporation may also share information from the study with regulatory agencies in foreign countries.

To help protect your confidentiality, we will use unique identification code numbers only on data forms, have locked storage areas, and use password-protected computer files. If we write a report or article about this study or share the study data set with others, we will do so in such a way that you cannot be directly identified.

The University of Iowa Hospitals and Clinics generally requires that we document in your medical record chart that you are participating in this study. The information included in the chart will provide contact information for the research team as well as information about the risks associated with this study. We will keep this Informed Consent Document in our research files; it will not be placed in your medical record chart.

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.

WILL MY HEALTH INFORMATION BE USED DURING THIS STUDY?

The Federal Health Insurance Portability and Accountability Act (HIPAA) requires University of Iowa Health Care or UI Health Care Cancer Services – Quad Cities to obtain your permission for the research team to access or create "protected health information" about you for purposes of this research study. Protected health information is information that personally identifies you and relates to your past, present, or future physical or mental health condition or care. We will access or create health information about you, as described in this document, for purposes of this research study and for your treatment. Once University of Iowa Health Care or UI Health Care Cancer Services – Quad Cities has disclosed your protected health information to us, it may no longer be protected by the Federal HIPAA privacy regulations, but we will continue to protect your confidentiality as described under "Confidentiality."

We may share your health information related to this study with other parties including federal government regulatory agencies, the University of Iowa Institutional Review Boards and support staff, and Celgene Corporation. Celgene may also inspect any part of your medical record for the purposes of auditing the conduct of the study.

You cannot participate in this study unless you permit us to use your protected health information. If you choose *not* to allow us to use your protected health information, we will discuss any non-research alternatives available to you. Your decision will not affect your right to medical care that is not research-related. Your signature on this Consent Document authorizes University of Iowa Health Care or UI Health Care Cancer Services – Quad Cities to give us permission to use or create health information about you.

Although you may not be allowed to see study information until after this study is over, you may be given access to your health care records by contacting your health care provider. Your permission for us to access or create protected health information about you for purposes of this study has no expiration date. You may withdraw your permission for us to use your health information for this research study by sending a written notice to:

Muhammad Furqan, MD
University of Iowa Hospitals and Clinics
200 Hawkins Drive, C-21 GH
Iowa City, IA 52242
Phone: 319-356-1527

However, we may still use your health information that was collected before withdrawing your permission. Also, if we have sent your health information to a third party, such as the study sponsor, or we have removed your identifying information, it may not be possible to prevent its future use. You will receive a copy of this signed document.

IS BEING IN THIS STUDY VOLUNTARY?

Taking part in this research study is completely voluntary. You may choose not to take part at all. If you decide to be in this study, you may stop participating at any time. If you decide not to be in this

study, or if you stop participating at any time, you won't be penalized or lose any benefits for which you otherwise qualify.

What if I Decide to Drop Out of the Study?

You are free to stop participating in this study at any time. If you stop, you will not lose any medical benefits except for any benefits that you might have been receiving in connection with this study. All information collected from you before you stop the study may still be used by the study doctor or Sponsor.

If you want to stop participating in the study, please tell the study doctor. He can tell you about stopping all or part of the study activities and what other care is available for you.

Will I Receive New Information About the Study while Participating?

If we obtain any new information during this study that might affect your willingness to continue participating in the study, we'll promptly provide you with that information.

Can Someone Else End my Participation in this Study?

Under certain circumstances, the researchers or the study sponsor might decide to end your participation in this research study earlier than planned. This might happen because in our judgment, it would not be safe for you to continue because your condition has become worse, you need treatment not allowed by the study, we have decided to stop the research, you were non-compliant with the study therapy regimen or because you may benefit from a new therapy.

WHAT IF I HAVE QUESTIONS?

We encourage you to ask questions. If you have any questions about the research study itself, please contact: Dr. Muhammad Furqan at 319-356-1527 or Katy D'Aprile, RN in the Quad Cities at 563-355-7733. If you experience a research-related injury, please contact: Dr. Muhammad Furqan at 319-356-1527 or Katy D'Aprile, RN in the Quad Cities at 563-355-7733. If it is after 5 PM or on a weekend, call 319-356-1616 and ask for the Hematology/Oncology Fellow on call. If you are a subject in the Quad Cities, please 563-355-7733 after hours.

If you have questions, concerns, or complaints about your rights as a research subject or about research related injury, please contact the Human Subjects Office, 105 Hardin Library for the Health Sciences, 600 Newton Rd, The University of Iowa, Iowa City, IA 52242-1098, (319) 335-6564, or e-mail irb@uiowa.edu. General information about being a research subject can be found by clicking "Info for Public" on the Human Subjects Office web site, http://hso.research.uiowa.edu/. To offer input about your experiences as a research subject or to speak to someone other than the research staff, call the Human Subjects Office at the number above.

This Informed Consent Document is not a contract. It is a written explanation of what will happen during the study if you decide to participate. You are not waiving any legal rights by signing this Informed Consent Document. Your signature indicates that this research study has been explained to you, that your questions have been answered, and that you agree to take part in this study. You will receive a copy of this form.

Subject's Name (printed): _____

Do not sign this form if today's date is on or after EXPIRATION DATE: 12/10/21.

_____ _____

(Signature of Subject) (Date)

Statement of Person Who Obtained Consent

I have discussed the above points with the subject or, where appropriate, with the subject's legally authorized representative. It is my opinion that the subject understands the risks, benefits, and procedures involved with participation in this research study.

_____ _____

(Signature of Person who Obtained Consent) (Date)