*Affix Patient Label Here*

**Masonic Cancer Center, University of Minnesota**

## CONSENT TO PARTICIPATE IN RESEARCH
# Phase II Trial of Exemestane in Previously Treated Post-Menopausal Women with Advanced Non-Small Cell Lung Cancer

**Principal Investigator: Manish R Patel, DO**
Department of Medicine, Division of Hematology, Oncology and Transplantation

For questions about research appointments, the research study, research results, or other concerns, you may contact Dr. Patel either by phone at 612-273-3000 or by email (patel069@umn.edu).

**Supported By:** Pfizer, the maker of exemestane, is supplying the drug free of cost for the purpose of this study.

**What is research:**
Doctors and investigators are committed to your care and safety. There are important differences between research and treatment plans:

- The goal of research is to answer one or more questions about a new treatment approach to learn if it is safe and effective. Researchers learn things by following the same plan with a number of participants. You, as an individual, may or may not be helped by volunteering for a research study; however, your participation helps answer the research question(s). Often one or more of the drugs offered on a research study are only available on a research study.
- The goal of routine (standard) treatment is to help you get better or to improve your quality of life using drugs and other methods that have been proven (often through previous research studies). Standard treatments are available from any cancer doctor.

Research and clinical care are often combined. One purpose of this consent document is to provide you clear information about the specific research activities of this study.

If your doctor is also responsible for this research study, you have the right to discuss this study with another person who is not part of the research team before deciding whether to participate in the research.

## *Key Information About This Research Study*

The following is a short summary to help you decide whether or not to be a part of this research study. More detailed information is listed later on in this form.

**Why are you being asked to take part in this research study:**
You are invited to take part in this research study because you have non-small cell lung cancer. Currently you are receiving immune checkpoint blockade (ICB) therapy (pembrolizumab, atezolizumab, or nivolumab) but your disease is worsening. This study "adds" a once a day oral drug, exemestane, to your current ICB therapy to see if the combination slows or stops the disease progression.

**What you should know about a research study:**

- The research study will be explained to you.
- You will receive a copy of this consent form to review.
- You can ask all the questions you want before you decide
- It is up to you whether or not you take part in this study.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.

**Why is this research being done:**
Exemestane is an oral (taken by mouth) drug approved by the United States Food and Drug Administration (FDA), for the treatment of breast cancer in post-menopausal women. This study open only to post-menopausal women and will be used to treat non-small cell lung cancer (NSCLC), instead of breast cancer.

Tumor growth in some types of a cancer is fueled by the naturally occurring female hormone estrogen. The cancer grows in the presence of estrogen and stops or slows if the estrogen supply is cut-off. Breast cancer is the most recognized tumor fueled by estrogen and at diagnosis, it has been the standard for decades to determine if the tumor is estrogen-receptor positive (ER+) or estrogen-receptor negative (ER-). Women with ER+ tumors receive estrogen blocking drugs as part of their long-term treatment.

More recently in laboratory studies, it has been recognized that the enzyme aromatase is present in more than three-fourths of non-small cell lung cancer and its presence is associated with a poor outcome in post-menopausal women. This suggests that the estrogen made by aromatase within the lung tumor is fueling tumor growth, and a drug like exemestane could block this growth. This study is based on laboratory (pre-clinical) work conducted by Jill M Siegfried, PhD of the Department of Pharmacology at the University of Minnesota.

This study is investigating if the addition of exemestane to ongoing therapy with pembrolizumab, atezolizumab, or nivolumab slows or stops the cancer growth.

**Duration of study treatment:**
Exemestane, once a day by mouth, will be added to your current anti-cancer therapy and may continue as long as you do not have additional worsening of your disease as checked by imaging studies every 6 weeks.

**What you need to do to participate:**
If you are interested in taking part in this study, routine tests and evaluations are done to determine if you qualify for the study. This is called a screening period.

If you are eligible and agree to take part in this study, you will take exemestane once a day by mouth every day while continuing on your current therapy. For this study, you will need to come to clinic once every 3 weeks. If you are receiving pembrolizumab or atezolizumab, this study's schedule can be synced with your infusion every 3 weeks. Nivolumab is given every 2 or 4 weeks, so the visits for this study will not always match with your infusion days.

More detailed information about the study procedures can be found under **"What is involved in this study?"**

**Is there any way that being in this study could be bad for you:**
Adding exemestane to your current therapy may result in different or more severe side effects, but this is not expected. By agreeing to this study, you may be continued on your current therapy longer than usual to see if adding the exemestane is of benefit.

Repeat imaging studies will be done approximately 6 weeks after your start exemestane; however, if there were evidence of rapidly worsening disease, treatment would be stopped earlier.

More detailed information about the risks of this study can be found under ***"*Risks of being in this study*".***

**Will being in this study help you:**

It is not known if adding exemestane to your current treatment will slow the tumor progression. That is why this study is being done. More detailed information about the benefits of this study can be found under **"Benefits of taking part in this research"**

**Alternative to being in this research:**

You do not have to be in this study. The study doctor will talk to you about other things you can do for your lung cancer, including the important risks and benefits.

Your regular medical care at this study center will not change if you decide not to be in the study. Some other things you may be able to do include:

- standard chemotherapy
- other investigational treatments at this institution or at other research centers
- no treatment at this time with comfort care for your symptoms

Your doctor can provide you with additional information regarding your options.

## *Detailed Information About This Research Study*

The following is more detailed information about this study in addition to the information listed above.

**How many people will be enrolled in this study:**

Up to 29 women with NSCLC will be treated in this study at the University of Minnesota.

**What is involved in this study:**

The first step is to determine if you qualify (are eligible) for this study and if you are healthy enough to undergo the planned treatment. If after learning about the study and reading this consent form, you are interested in the study, you will be asked to sign this form. By signing this form, you are giving permission to undergo routine tests and procedures to see if you qualify for the study treatment. This is known as study screening.

The following routine tests or procedures will be done during the screening period. These tests and procedures are part of your regular cancer care and may be done even if you do not join the study. If you have had some of these tests or procedures recently, they may not have to be repeated. This will be up to your study doctor:

- Medical history including review of menopausal status
- Review of current medications
- A physical examination and review of any symptoms related to your cancer and/or previous treatments
- Routine blood tests (requiring 4 – 5 tablespoons of blood) to evaluate bone marrow, kidney, and liver function, as well as general health status
- If you are younger than 55 years of age or are older, but have had a period in the previous year additional blood may be collected to check your estrogen level to confirm menopause
- CT scan of chest, abdomen and pelvis
- MRI or CT scan of your head if have symptoms that could be associated with tumor spread to the brain
- A bone density test (DEXA scan) if you have not had one in the previous 12 months

- Any additional tests or evaluations, felt necessary by the medical staff, to evaluate your current health

In addition, the following will be done for research related testing:

- Collection of approximately 5 tablespoons (70 - 80 mL) of additional blood for research related testing at the time you are having blood collected for your medical care

**What will happen during this study:**

If you are eligible and agree to participate in this study the following will occur:

Once a Day:

You will be instructed to take one exemestane tablet by mouth following a meal once a day at approximately the same time each day. You are asked to record your dose and any side effects that you experience on the provided drug log. If you forget a dose, but remember within 8 hours of the scheduled time, take it (with food). If you miss a dose by more than 8 hours, do not take that day's dose and record 0 on the provided drug log. Regardless, return to your normal dosing schedule the next day.

Even though you take exemestane every day, each 3 week period is considered 1 treatment cycle.

**Note:** Use of estrogens (i.e. hormone replacement therapy) and phytoestrogen supplements (i.e. black cohosh) are prohibited during exemestane treatment.

**Every 3 Weeks:**

You will return to clinic every 3 weeks for a brief physical exam and routine blood work requiring about 1 tablespoon. Bring your completed drug log and all study medication bottles (including empties). You will receive a new supply of exemestane and a new drug log. In addition you will be asked to complete a questionnaire regarding how you have felt during the previous 7 days and what impact the cancer and its treatment has had on your daily activities. Completing the questionnaire, which is the same each time, will take 10 to 15 minutes.

**Every 6 Weeks:**

A reassessment of your disease is done by repeating the CT scan of the chest, abdomen and pelvis.

**Every 12 Months:**

The bone density test will be repeated as taking exemestane (or any AI) lowers the level of estrogen in the body which may lead to reduction in bone mineral density (BMD) over time. The lower a BMD, the greater the risk of osteoporosis and fracture.

**End of Treatment Visit (Approximately 4 weeks after your last exemestane dose):**

- Review of symptoms, side-effects and any changes in any medications you are taking
- Blood tests (about 1 tablespoon of blood) to evaluate bone marrow, kidney, and liver function, as well as adrenal function tests
- A repeat CT of your chest, abdomen and pelvis if not done in the previous 6 weeks

**Follow-Up Through 1 Year from the 1st Dose of Exemestane**

Direct study participation ends with the final treatment visit, however your medical record may be reviewed or your referring doctor contact for up to 1 year from the first dose of exemestane.

**Research Related Sample Collection:**

In addition to the usual tests and procedures, an additional blood sample (70 - 80 mL or approximately 5 tablespoons) will be collected for research purposes before you begin treatment; before Cycles 2, 3, 5, and at the End of Treatment visit. Whenever possible the blood will be collected at the same time you are having blood drawn for your medical care. The blood will be tested in Dr. Siegfried's laboratory at the University of Minnesota. She is looking for changes in the blood with treatment that may be a "marker" or early indicator of disease response and genetic mutations (changes) that may prevent exemestane from working.

Dr. Siegfried also will examine previously collected tumor samples for hormone-related proteins. If during the study you have a biopsy as part of your medical care, a small sample will be sent to Dr. Siegfried's lab where it will be examined for changes as compared the earlier biopsy tissue required at study enrollment.

The samples will be labeled with an indirect identifier (a unique code assigned to you at study enrollment) so that anyone looking at the sample will not know it belongs to you. A link between the code and your name and other identifying information will be kept in a secure database maintained by the University Of Minnesota.

Neither you nor your health insurance will be charged for the tests done for research purposes. The results will not be placed in your medical record nor will they influence your treatment.

**Leaving this research study:**
You can leave the research study at any time if you change your mind about taking part in the study. Leaving will not be held against you.

If you decide to leave the research study, please contact the investigator or the study staff at the contact information on the 1st page of this document.

A member of the study team may ask you some questions about being in the study. If you decide to leave the study let your study doctor know so you can receive the proper supportive care.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. This means that your choice not to be in this study will not negatively affect your right to any present or future medical care.

If you stop being in the research, already collected information about you may not be removed from the study database. You will be asked whether the investigator can collect information from your routine medical care, such as your medical records. If you agree, this information will be handled the same as the information obtained for the research study.

**Risks of being in this study:**
Your cancer may continue to grow or spread even though you are taking exemestane.

While receiving exemestane in combination with your current immune checkpoint blockade (ICB) therapy (pembrolizumab, atezolizumab, or nivolumab), you may experience side effects. You may experience all, some, or none of these side effects and the side effects may vary in severity. The severity may be mild, moderate or severe, up to and including death. Also, there is always the risk of a rare or previously unknown side effect occurring.

Other drugs will be given to make side effects less serious and uncomfortable or your doctor may decrease or withhold the dose of one or both drugs. Many side effects go away shortly after the study drugs are stopped, but in some cases side effects can be serious, long-lasting or permanent, even fatal.

**Risks of Exemestane**
In general, exemestane is well tolerated at this dose when given long term to post-menopausal women with breast cancer. It is thought that adding exemestane to ongoing immune checkpoint blockade the risks profile for neither drug will be different.

**Rare, but potentially serious side effects:**
Bone loss: Exemestane lowers the level of estrogen in the body and may reduce bone mineral density (BMD) over time, possibly increasing the risk of bone fracture. A DEXA scan will be done at baseline if you have not had one done in the previous 12 months and every 12 months while receiving exemestane. The results of each DEXA scan will be reviewed with you and if a decrease in BMD occurs, what your options are.

Chest pain, heart failure, or stroke: A small number of women had chest pain, heart failure, or a stroke while taking exemestane.

**Occurring in less than 1 out of 100 women**
Gastric (stomach) ulcer: Signs of a gastric ulcer may include abdominal pain, blood in your stool, or low blood counts (hemoglobin)

Cholestatic hepatitis: This is condition where the flow of bile is reduced or stopped. Signs may include whites of the eyes or skin appear yellowish (jaundice), swelling of the belly

and/or feet and legs, itch skin, or dark colored urine. Cholestasis usually corrects itself once the underlying cause (medication, gall stones, tumor) is removed.

**The most common exemestane side effects** (more than 10 out of 100 women experience):

- hot flashes
- fatigue
- joint pain
- headache
- difficulty sleeping (insomnia)
- increased sweating
- depression
- feeling anxious
- upset stomach
- difficulty breathing
- hair loss or thinning
- an increase by a blood test of a liver enzyme (alkaline phosphatase) that may indicate a bone disorder or liver disease

Use of estrogens (such as hormone replacement therapy or HRT) and phytoestrogen supplements (such as black cohosh) to relieve the menopausal like side effects are prohibited during exemestane treatment.

Only post-menopausal women are enrolled in this study as taking exemestane during pregnancy is known to cause birth defects and/or miscarriages.

Risks of Blood Collection

Risks of having blood drawn for routine blood tests and research purposes include:

- pain at the site of the needle stick
- tenderness and/or bruising at the site of blood collection
- dizziness or light-headedness
- very rarely, infection at the site of the needle stick

Risks of Completing the Quality of Life (QOL) Questionnaire: Completing the questionnaire may remind you of the impact cancer and treatment has had on your everyday life. You may refuse to answer any questions that make you feel uncomfortable.

Risks of a chest, abdomen, pelvis CT scan:
You'll be exposed to ionizing radiation during the scanning to evaluate your disease status. The scientific unit of measurement for radiation dose is the millisievert (mSv). The average amount of radiation received from natural sources of radiation by a Minnesota resident in one year (3 mSv). Each CT scan of the chest, abdomen and pelvis would expose you to 17 mSv radiation. This is equal to approximately 6 years of background radiation. Exposure to radiation may increase your risk of developing a 2nd cancer.

Your disease re-assessment study may be done with contrast (a chemical substance to allow a better view of what is being scanned). You may develop a skin rash or itchiness if you're allergic to the contrast. A life-threatening allergic reaction can also happen, but this is rare. Tell your doctor about any sensitivities to medications, or any kidney problems you have. IV contrast can increase the risk of kidney failure if you're dehydrated or have a pre-existing kidney problem.

**Risks of genetic research:**
The risks to you and your family from genetic research are very low. Your samples will be identified only with your study code number.

The analysis of genetic data will be focused on the gene expression in the tumor. Only genetic results regarding this target condition will be reported. No other results that are related to other diseases or conditions will be reported, even if that genetic variant can be associated with cancer, neurological disease or another condition.

A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law generally will protect you in the following ways:

- Health insurance companies and group health plans may not request your genetic information that we get from this research.
- Health insurance companies and group health plans may not use your genetic

information when making decisions regarding your eligibility or premiums.
- Employers with 15 or more employees may not use your genetic information that we get from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment.

Be aware that this federal law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance.

**Costs of Taking Part in the Research Study:**
Exemestane will be provided free of cost by its manufacturer Pfizer. Research related testing on blood and tumor samples will be paid for by research funds.

You and/or your insurance company will be responsible for the remaining costs related to this treatment including but not limited to, all costs associated with continuing with the immune checkpoint blockade (ICB) therapy (pembrolizumab, atezolizumab, or nivolumab), clinic visits, routine lab work, scans or imaging for disease assessment, and any medications given to prevent or treat side effects. You will be responsible for any costs your insurance does not cover, such as deductibles and co-payments. In some cases, insurance will not pay for services ordinarily covered because these services were performed in a research study. You should check with your insurance to see what services will be covered by your insurance and what you will be responsible to pay.

**Research Related Injury:**
In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner to you or your insurance company. If you think that you have suffered a research related injury, let the study physicians know right away.

**Benefits of Taking Part in This Research:**
There may be no benefits to you from your taking part in this research. The goal of adding exemestane to immune checkpoint blockade (ICB) therapy (pembrolizumab, atezolizumab, or nivolumab) is to see if it can slow disease progression. That is why this study is being done. Things learned from this study may benefit others in the future with lung cancer.

**Duration of Study Participation:**
You will receive a minimum of 6 weeks of exemestane and may continue it as long as your cancer does not continue to progress (grow worse) unless one or more of the following occurs:

- you experience unacceptable side effects
- you decide you do not want to continue with the treatment
- you are unable to comply with the study requirements
- your study doctor believes, for any reason, continuing on treatment is not in your best interest
- if the study is stopped early

If you need to stop the immune checkpoint blockade (ICB) therapy (pembrolizumab, atezolizumab, or nivolumab) because of side effects, you may be permitted to continue exemestane alone on the same schedule as long as you meet the above requirements.

Disease and survival status obtained from your medical record or other sources will be collected for up to 1 year from the study enrollment in any patient receiving at least one dose of drug.

You will be told about any new information that may affect your health, welfare, or choice to stay in the research.

**Confidentiality and Privacy:**
Efforts will be made to limit the use and disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information including those that have responsibilities for monitoring or ensuring compliance include:

- Research personnel from the Masonic Cancer Center at the University of Minnesota and/or their designee,
- The Institutional Review Board (IRB), the committee that provides ethical and regulatory oversight of research, and other representatives of this institution,
- Any federal, state, or local governmental agency that regulates the study (such as the U.S. Food and Drug Administration (FDA), the U.S. Department of Health & Human Services (DHHS), and the Office for Human Research Protections (OHRP))

Pfizer may receive reports of serious adverse events with indirect identifiers (using the code assigned to you at study enrollment).

To this extent, confidentiality is not absolute.

If you decide to participate in this study, some private health information about you will be stored in a computer database at the Masonic Cancer Center at the University of Minnesota information will include your name and medical record number, date of birth, diagnosis, race/ethnicity, and information about your participation in this study. The purpose of storing this information is to assist the Cancer Center in creating reports about research and in making sure that research studies are being done correctly. Your information will not be used for any other purpose. There are no plans to erase information from the database. It will be stored indefinitely at the Masonic Cancer Center.

The sponsor/investigator, monitors, auditors, the IRB, the University of Minnesota Research Compliance Office and other University compliance units, the US Office of Research Integrity (ORI), the US Office for the Protection of Human Research Protections (OHRP), the US Food and Drug Administration (FDA) may be granted direct access to your medical records to conduct and oversee the research. By signing this document you are authorizing this access.

The results of this study will be used for teaching, publications, or for presentation at scientific meetings. The results also may be summarized in the background section of future research studies and publications. Results will never include information to allow an individual patient to be identified.

A description of this clinical trial will be available at http://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 after the study is completed. You may search this web site at any time.

**Use of Identifiable Health Information**

Your personal health information (PHI) created or received for the purposes of this study is protected under the federal regulation known as HIPAA. Refer to the attached HIPAA authorization for details concerning the use of this information.

**Contacts and Questions**

The physicians involved in your care are available to answer questions you may have concerning this study at any time. The study's principal investigator, Dr. Manish Patel, may be reached at (612) 273-3000.

This research has been reviewed and approved by an IRB within the Human Research Protections Program (HRPP). To share feedback privately with the HRPP about your research experience, call the Research Participants' Advocate Line at 612-625-1650 (Toll Free: 1-888-224-8636) or go to https://research.umn.edu/units/hrpp/research-participants/questions-concerns. You are encouraged to contact the HRPP if:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research participant.
- You want to get information or provide input about this research.

**Feedback:**
After the study, you may be asked to complete a survey that asks about your experience as a research participant. You do not have to complete the survey if you do not want to. If you do choose to complete the survey, your responses will be anonymous.

If you are not asked to complete a survey, but you would like to share feedback, please contact the study team or the HRPP. See the "Contacts and Questions" of this form for the lead physician's and HRPP contact information.

## Optional Storing Of Leftover Research Samples

If any samples (blood and/or tumor) remain after the studies directly related to this study are completed, they will be stored for up to 15 years for future analysis as new tests associated with this research becomes available. These samples will be the property of and under the control of Dr. Jill Siegfried at the University of Minnesota and they will not be used for studies other than ones to learn about lung cancer and/or the role of hormone receptors.

There will be no cost to you for storing and future testing of the leftover samples. You will not be paid for allowing your samples to be used for future research. Because it is not known how soon these samples will be used, you will not be given the results of the tests.

Fifteen years after the end of the study any remaining samples will be destroyed. However, if you agree to storage now and later change your mind, you may request to have any remaining identifiable samples destroyed by contacting the study doctor or another member of the study staff (contact information on page 1 of this form).

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**Consent for Storage of Leftover Research Samples:**

☐ YES, I consent (agree) to the storing of any leftover samples for future research

☐ NO, I do not consent (do not agree) and want any leftover samples destroyed once research directly related to this study is completed.

**STATEMENT OF CONSENT:**

Your signature documents your permission to take part in this research. You will be provided a copy of this signed document.

_____ _____

Signature of Participant Date

_____

Printed Name of Participant

_____ _____

Signature of Person Obtaining Consent Date

_____

Printed Name of Person Obtaining Consent

*Use the witness signature block on the next page only if a witness to the consent process is required*

☐ ***CHECK IF NOT APPLICABLE (WITNESS IS NOT REQUIRED)***

*Use the legally authorized representative (LAR) signature block on the page after next only if the subject is unable to consent to research for herself:*

☐ ***CHECK IF NOT APPLICABLE (LAR IS NOT REQUIRED)***

*Affix Patient Label Here*

**WITNESS STATEMENT:**
The participant was unable to read or sign this consent form because of the following reason:

☐ The participant is unable to read the information

☐ The participant is visually impaired

☐ The participant is non-English speaking

☐ The participant is physically unable to sign the consent form. Please describe:

_____

☐ Other *(please specify)*:

_____

**For the Consent of Non-English Speaking Participants when an Interpreter is Used:**
As someone who understands both English and the language spoken by the participant, I represent that the English version of the consent form was presented orally to the participant in the participant's own language, and that the participant was given the opportunity to ask questions.

_____ _____
Signature of Interpreter Date

_____
Printed Name of Interpreter

**OR:**

**For the Consent of a Participant when a Non-Interpreter (General Witness) is Used:**
As someone who understands both English and the language spoken by the participant, I represent that the English version of the consent form was presented orally to the participant in the participant's own language, and that the participant was given the opportunity to ask questions.

_____ _____
Signature of Witness Date

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## LEGALLY AUTHORIZED REPRESENTATIVE STATEMENT:

Your signature documents your permission for the named subject to take part in this research.

Printed Name of Subject

Signature of Legally Authorized Representative — Date

Printed Name of Legally Authorized Representative — Date

Signature of Person Obtaining Consent — Date

Printed Name of Person Obtaining Consent — Date