MC1431 / 15-000340

Randomized Phase II Trial to Evaluate Alisertib Alone or Combined With Fulvestrant for Women With Advanced, Endocrine-Resistant Breast Cancer

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RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: MC1431, A Randomized Phase II Trial to Evaluate Alisertib Alone or Combined with Fulvestrant for Women with Advanced, Endocrine-resistant Breast Cancer

IRB#: 15-000340

Principal Investigator: Dr. Tufia Haddad and Colleagues

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision won't change the access to medical care you get at Mayo Clinic now or in the future if you choose not to participate or discontinue your participation.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you a copy of this form to keep. A copy of this form will be put in your medical record.

CONTACT INFORMATION

You can contact …	At …	If you have questions about …
Principal Investigator: Dr. Tufia Haddad	**Phone:** (507) 284-2511 **Institution Name and Address:** Mayo Clinic 200 1st St. SW Rochester, MN 55905	▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
Mayo Clinic Institutional Review Board (IRB)	**Phone:** (507) 266-4000 **Toll-Free:** (866) 273-4681	▪ Rights of a research participant
Research Subject Advocate **(The RSA is independent of the Study Team)**	**Phone:** (507) 266-9372 **Toll-Free:** (866) 273-4681 **E-mail:** researchsubjectadvocate@mayo.edu	▪ Rights of a research participant ▪ Any research-related concerns or complaints ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information
Patient Account Services	**Toll Free:** (844) 217-9591	▪ Billing or insurance related to this research study

Other Information:
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 are you being asked to take part in this research study?

You are being asked to take part in this research study because you are post-menopausal and have advanced breast cancer that has progressed following prior therapy.

The plan is to have 96 patients participate in this study over a total of about 13 sites.

2. Why is this research study being done?

In this study we want to find out more about the side effects of alisertib when it is added to fulvestrant. Everyone in this study will receive alisertib which is still experimental and isn't approved by the U.S. Food and Drug Administration (FDA). However, the FDA has allowed the use of this drug in this research study. We don't know all the ways that this drug may affect people. Fulvestrant is FDA approved for treatment of advanced breast cancer in post-menopausal women.

3. Information you should know

Who is Funding the Study?
Takeda-Millennium Pharmaceuticals, Inc. and Atwater Foundation are funding this study. Takeda-Millennium Pharmaceuticals, Inc. and Atwater Foundation will pay the Mayo Clinic and appropriate staff to cover costs related to running the study. Administrative support for study is being provided by Johns Hopkins University on behalf of the Translational Breast Cancer Research Foundation (TBCRC). The TBCRC is a group of academic medical centers across the United States that work together to conduct breast cancer research.

4. How long will you be in this research study?

You will be in the study and followed for a maximum of 5 years after treatment has been discontinued.

5. What will happen to you while you are in this research study?

Before beginning any research procedure you will sign this informed consent form.

If you are eligible for the study and agree to participate, we will assign you by chance (like a coin toss) to alisertib (Arm 1) or alisertib and fulvestrant (Arm 2). You and the Principal Investigator can't choose your study group. You will have an equal chance being assigned to Arm 1 or Arm 2.

If you are assigned to Arm 1 and your disease does not get better you will have the opportunity to take both alisertib and fulvestrant together as in Arm 2.

If you are in Arm 1 you will be instructed to take alisertib by mouth on days 1 through 3, days 8 through 10, and days 15 through 17 during each 28-day cycle.

If you are in Arm 2 you will be instructed to take alisertib by mouth on Days 1 through 3, Days 8 through 10, and Days 15 through 17 during each 28-day cycle. You will also receive a shot of fulvestrant on Day 1 and Day 15 of the first cycle and only on Day 1 of all subsequent 28-day cycles.

You will be given a diary to record when you take your study drug. You will need to return to Mayo Clinic every month for a re-evaluation before receiving your next cycle of treatment. You will be asked to return your diary, empty pill bottle or any remaining capsules at the end of each cycle.

Tissue and blood specimens are mandatory for this study. You will be asked to have biopsies to collect tissue, and blood draws (taken at the same times as your clinical blood tests) for this study.

Below is a table that shows the procedures and study visits.

Time	What will happen
Pre-Study	• Routine physical exam • Routine blood tests with pregnancy testing • Adverse event assessment • PET/CT/MRI scan to document tumor size • Research tumor biopsy • Research blood collection
Day 1 of each cycle (every 4 weeks or 28 days)	• Routine physical exam • Routine blood tests • Adverse event assessment • Review of your medication diary

Time	What will happen
After Cycle 1 but before Cycle 2	• Research blood collection • Research tumor biopsy
Every other cycle starting with Cycle 3 (i.e. Cycle 3, 5, 7, etc)	• PET/CT/MRI scan to document tumor size
At progression	• Routine physical exam • Routine blood tests • Adverse event assessment • PET/CT/MRI scan to document tumor size • Research blood collection • Research tumor biopsy

Crossover	• Evaluation of the estrogen receptor (ER) on the 'at progression' tumor biopsy for individuals that are ER-negative at baseline
	• On Day 1 of each crossover cycle
	  o Routine physical exam
	  o Routine blood tests
	  o Adverse event assessment
	  o Review of your medication diary
	• After crossover cycle 1 but before crossover Cycle 2
	  o Research blood collection
	• Every other cycle starting with crossover Cycle 3 (i.e. Cycle 3, 5, 7, etc)
	  o PET/CT/MRI scan to document tumor size
	• At progression after crossover
	  o Routine physical exam
	  o Routine blood tests
	  o Adverse event assessment
	  o PET/CT/MRI scan to document tumor size
	  o Research blood collection
	  o Optional research tumor biopsy

Follow-up after study discontinuation	• After you stop the study medication, you will be contacted by the study team during a clinic visit or by telephone every 6 months for a maximum of 5 years after you are randomized to treatment.

6. What are the possible risks or discomforts from being in this research study?

Your doctor will discuss the risks of procedures performed as part of the participant's standard care as these tests and procedures are part of your standard clinical care.

Alisertib:

Likely risks (events occurring greater than 20% of the time)

- Feeling tired (fatigue)
- Decrease in white blood cells, which are the infection fighting cells, which may put you at increased risk for infection.
- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Diarrhea or loose stools
- Thinning of the hair. Complete hair loss has not been reported with this drug, however it may be possible. Some women notice their thinning of the hair and it may or may not be obvious to their friends or family. Some women feel the thinning is significant enough that they prefer to wear a wig or scarf.
- Mouth sores that may be painful but would not interfere with oral intake
- Decrease in red blood cells (anemia), which are the oxygen carrying cells, which may make you feel tired
- Decrease in platelets, which are the cells involved in clotting blood, which may increase your risk of bleeding
- Loss of appetite

Less likely risks (events occurring less than or equal to 20% of the time)

- Elevated liver enzymes
- Fever with low white blood cell count which may put you at more serious risk for infection. Sometimes this may results in hospitalization for intravenous antibiotics and careful observation.
- Difficulty staying or falling asleep (insomnia)
- Fever (pyrexia)
- Abdominal pain
- Indigestion or heartburn (dyspepsia)
- Numbness, tingling, or inflammation of the nerves (peripheral neuropathy)
- Sensation of lightheadedness or vertigo (dizziness)
- Loss of coordination, including loss of balance and unsteady gait

- Rash
- Red and tender hands and feet
- Peeling and cracking of the skin on the hands and feet
- Itching sensation (pruritis)
- Low blood pressure (hypotension)
- High blood sugar (hyperglycemia)
- Abnormally low calcium in the blood stream, that can result in muscle cramps, abdominal cramps, spasms (hypocalcemia)
- Generalized weakness and loss of strength (asthenia)
- Sleepiness (sedation, somnolence)
- Constipation
- Peripheral edema (upper or lower extremity swelling)
- Headache
- Abnormally low electrolytes, such as potassium, sodium or phosphorus
- Excessive or abnormal loss of body fluid (dehydration)
- Cough
- Shortness of breath or difficulty breathing (dyspnea)
- Oral pain
- Anxiety
- Infections

Rare but serious risks (events occurring less than 2-3% *of the time)*

- Elevated levels of cholesterol in the bloodstream which may lead to heart disease or other health problems (hyperlipidemia)
- Loss of weight
- Inflammation / infection of the lungs (pneumonia/pneumonitis)
- Memory impairment
- Visual disturbance, including blurred or diminished vision
- Dry eye or inflammation of the eye
- Confusion
- Liver damage due to blood clots
- Acute kidney failure
- Potentially fatal infection
- Potentially fatal sepsis (serious, potentially life-threatening complications of infection including fever, increased heart rate, increased breathing rate, and confusion)
- Bowel obstruction
- Diminished hearing
- Serious bleeding requiring hospitalization

- Bone marrow dysfunction that may predispose to leukemia
- Blistering rash
- Blood clots in the lung
- Respiratory failure

Abnormalities in the pumping function of the heart and fast heart rates have been seen in a few patients treated with alisertib. There is not enough data however to quantify risk. <1% of patients experienced cardiac events, such as a heart attack.

Alisertib is structurally related to a class of drugs called the benzodiazepines. It may cause sleepiness, confusion, or memory loss. If you experience these side effects, contact the study team immediate and do not drive, operate dangerous machinery, or perform any other task requiring full alertness and/or coordination. These sedative effects were observed more commonly during early drug development when higher doses of alisertib were being evaluated. They have been reversible with discontinuation of the drug.

The effects of alisertib on human pregnancy are unknown. Therefore, female patients should avoid becoming pregnant and male patients should avoid impregnating a female partner. Nonsterilized female subjects of reproductive age and male subjects should use an effective method of contraception during the entire study period, ending three months after the last dose of alisertib.

Less than 1% of patients have experienced permanent bone marrow dysfunction or cancer of the blood or bone marrow (leukemia) while on trial with alisertib. These events occurred in patients with underlying blood or lymph node cancers. Some standard chemotherapy agents can increase the risk of bone marrow dysfunction or cancer of the blood or bone marrow (leukemia). The patients who experienced these events while on trial with alisertib had previously been treated with chemotherapy drugs known to increase the risk of these events. Therefore it is unknown if alisertib or the prior chemotherapy was associated with the permanent bone marrow dysfunction or cancer of the blood or bone marrow (leukemia). Additional follow up will be required and is planned.

A safety review was completed after the first 12 patients were treated on this clinical trial. Notably 3 patients died during active treatment. One patient's death was attributed as rapid progression of her metastatic breast cancer. One patient experienced hemolysis (spontaneous destruction of the red blood cells) and features of thrombotic micro-angiopathy (TMA), a condition where blood clots form in small blood vessels from injury to the wall of blood vessel. Of the more than 1300 patients that have been treated with alisertib in clinical trials, hemolysis had been reported once with alisertib prior to this event. Hemolysis may occur in association with underlying cancer; however it may also occur as a rare side effect of cancer treatment. It is unknown if this event occurred as a result of the cancer or as a rare side

effect of alisertib. One patient experienced respiratory failure as a result of acute coronary syndrome (heart attack). Of the more than 1300 patients that have been treated with alisertib in clinical trials, acute coronary syndrome and acute respiratory failure have been reported once each with alisertib prior to this event. The patient had multiple medical risk factors for coronary artery disease, and it is felt that her cardiac event was most likely related to her underlying medical conditions. It is unknown if this event occurred as a result of a rare side effect of alisertib.

Daily alcohol intake should be limited to the following: one 12-oz glass of beer, one 6-oz glass of wine, or one 1.5-oz portion of 80-proof alcohol.

Fulvestrant (Faslodex®):

Likely risks (events occurring greater than 10% but no more than 20% of the time)

- Hot flashes
- Bone or joint aches
- Elevated liver tests
- Dull ache or pain at the injection site

Less likely risks (events occurring 1-10% of the time)

- Fatigue
- Headache
- Feeling sick to your stomach (nausea)
- Loss of appetite
- Constipation
- Cough
- Shortness of breath

Rare but potentially serious risks (events occurring less than or equal to 1% of the time)

- Weight gain
- Problems with the heart (cardiovascular) such as pain or heart attacks
- Thinning of the bones (osteoporosis)
- Vaginal bleeding
- Generalized swelling
- Allergic reactions

Blood Draws

The risks of drawing blood include pain, bruising, lightheadedness, and/or fainting, or rarely, infection at the site of the needle stick.

Biopsies
Biopsies are normally performed under the guidance of an imaging technique. Each procedure requires a separate consent prior to the biopsy. The risks may include:

- Pain and discomfort. The amount of pain and discomfort will vary, depending on the location of the biopsy site. These risks can be discussed with the study doctor.
- Minor bleeding at the biopsy site.
- Tenderness at the biopsy site.
- Scarring at the biopsy site.
- Rarely, an infection at the biopsy site.

Uncommonly, complications from biopsies can be life threatening. As with any interventional procedure, other potentially serious complications from bleeding or organ damage may occur. These might require additional surgical intervention.

Lymph node biopsy
Likely: local discomfort and minor bleeding
Rare: moderate or major bleeding, need for blood transfusion, lung collapse, hospitalization due to bleeding or other complications, infection, damage to bowels, damage to nearby organs, allergic reaction to the numbing medicine

Liver biopsy
Likely: local discomfort and minor bleeding
Rare: moderate or major bleeding, need for blood transfusion, lung collapse, hospitalization due to bleeding or other complications, infection, damage to bowels, damage to nearby organs, allergic reaction to the numbing medicine

Lung biopsy
Likely: local discomfort and minor bleeding
Possible (approximately 10% risk): partial lung collapse which may be associated with shortness of breath, pain with inspiration, and need for hospitalization.
Rare: moderate or major bleeding, need for blood transfusion, complete lung collapse, hospitalization due to bleeding or other complications, infection, cough, damage to nearby organs, allergic reaction to the numbing medicine. In the event of complete lung collapse, shortness of breath, pain with inspiration, chest tube placement and hospitalization are likely.

*If you are a smoker or have COPD or other chronic pulmonary disease, your risk of complications from a lung biopsy is greater than those who do not smoke or do not have an underlying pulmonary disease.

Radiation risk from biopsies
Biopsies are performed using CT guidance. You will be exposed to radiation during these tests. The amount of radiation you would get has a low risk of harmful effects.

Unforeseeable Risks:
Many side effects go away shortly after the study drugs are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death. Some side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

7. Are there reasons you might leave this research study early?

Participation in this study is complete voluntary and you may decide to stop at any time. You should tell your physician or study staff if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the Principal Investigator or Mayo Clinic may stop you from taking part in this study at any time:

- If it is in your best interest,
- If you don't follow the study procedures,
- If the study is stopped.

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

We will tell you about any new information that may affect your willingness to stay in the research study.

8. What if you are injured from your participation in this research study?

Where to get help:
If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form. Mayo Clinic will offer care for research-related injuries, including first aid, emergency treatment and follow-up care as needed.

Who will pay for the treatment of research related injuries?
Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance.

9. What are the possible benefits from being in this research study?

This study may not make your health better. However, if the study treatment is effective you may benefit by having your tumor get smaller which may help you live longer and improve any symptoms you may be experiencing as a result of the tumor. Researchers may also gain knowledge from this study that may help other patients in the future.

10. What alternative do you have if you choose not to participate in this research study?

You don’t have to be in this study to receive treatment for your condition. Your other choices may include other chemotherapy or hormonal therapy or no treatment for your disease. Talk to the Principal Investigator or your doctor if you have any questions about any of these treatments or procedures.

11. What tests or procedures will you need to pay for if you take part in this research study?

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Study drug alisertib will be supplied by Takeda/Millennium
- Research related blood tests and tumor collection

However, you and/or your insurance will need to pay for all other tests and procedures that you would have as part of your clinical care. These tests and procedures are:

- Standard physical exams
- Standard blood testing
- Standard CT/MRI imaging
- Cost and administration of fulvestrant

You will also be responsible for any co-payments and deductibles.

If you have billing or insurance questions call Research Billing at the telephone number provided in the "Contact Information" section of this form.

12. Will you be paid for taking part in this research study?

You won't be paid for taking part in this study.

13. What will happen to your samples?

We would like to keep any of your unused samples for future research. You can still take part in this current study even if you do not want your sample used for future research. If you agree to give your sample, it will be the property of Mayo Clinic.

Other researchers at Mayo Clinic who aren't involved with this study may ask to use your sample for future research. Researchers at other institutions may also ask for a part of your sample for future studies. Your sample will be sent to researchers in a coded format, which protects your identity.

Some future studies may examine your DNA, which is the genetic information you inherited from your parents (genetic testing). The Principal Investigator may contact you if there are findings which may be useful for your health care. You would be given general information on the potential risks, benefits, and costs of choosing to learn about the findings.

Genetic Information Nondiscrimination Act (GINA)
The Genetic Information Nondiscrimination Act (GINA) may help protect you from health insurance or employment discrimination based on genetic information.

The law provides that health insurance companies and group health plans

- May not ask for genetic information from this research and
- May not use genetic information when making decision about eligibility or premiums

The law will not stop health insurance companies from using genetic information to decide whether to pay claims. The law also will not help you get other types of insurance (such as: life, disability or long-term care).

RISKS ASSOCIATED WITH GENOMIC TESTING
Despite the GINA protections and the best efforts of the research team, there may still be a risk if information about you were to become known to people outside of this study.

Genetic information is unique to you, even without your name or other identifiers. For this reason, genetic information like DNA may be used to identify you and possibly your family members. We have procedures (such as, labeling your biospecimens with a password protected code known only to select research staff) to prevent people working with your DNA from discovering if it belongs to you. However, there is the risk this can happen as new ways of tracing genetic information are being developed that may make re-identification of genetic information possible.

Please read the following statements and mark your choices:

1. I permit leftover samples to be stored and used for future research to learn about, prevent, or treat cancer.

   ☐ Yes ☐ No Please initial here: _____Date: _____

2. I permit my samples to be stored and used for future research about other health problems (for example: causes of diabetes, heart disease, and Alzheimer's, or genetic links to alcoholism).

   ☐ Yes ☐ No Please initial here: _____Date: _____

3. I agree that someone may contact me in the future to ask me to take part in more research.

   ☐ Yes ☐ No Please initial here: _____Date: _____

4. I agree to have my coded genetic information and coded medical information placed in password-protected secured databases for research analyses.

   ☐ Yes ☐ No Please initial here: _____Date: _____

There is a very small chance that some commercial value may result from the use of your donated sample. If that happens, you won't be offered a share in any profits.

You may request to have your sample destroyed by writing to the Principal Investigator. The address is found in the "Contact Information" section of this consent form.

Because we cannot predict how your sample will be used in the future, we cannot promise that samples can be retrieved and destroyed.

14. How will your privacy and the confidentiality of your records be protected?

Mayo Clinic is committed to protecting the confidentiality of information obtained about you in connection with this research study. All of your research samples transferred to the sponsor or designee will be labeled with a code number and kept in locked storage. Only your study doctor will be able to link your samples with your identity. No one working with your samples will know your identity. If the results of the research are made public, information that identifies you will not be used.

During this research, information about your health will be collected. Under Federal law called the Privacy Rule, health information is private. However, there are exceptions to this rule, and you should know who may be able to see, use and share your health information for research and why they may need to do so. Information about you and your health cannot be used in this research study without your written permission. If you sign this form, it will provide that permission.

Health information may be collected about you from:

- Past, present and future medical records.
- Research procedures, including research office visits, tests, interviews and questionnaires.

Why will this information be used and/or given to others?

- To do the research.
- To report the results.
- To see if the research was done correctly.

If the results of this study are made public, information that identifies you will not be used.

Who may use or share your health information?

- Mayo Clinic research staff involved in this study
- Takeda/Millennium Pharmaceuticals Inc.
- Johns Hopkins University on behalf of the Translational Breast Cancer Research Consortium (TBCRC)
- Translational Breast Cancer Research Consortium (TBCRC)

With whom may your health information be shared?

- The Mayo Clinic Institutional Review Board that oversees the research
- Other Mayo Clinic physicians involved in your clinical care
- Researchers involved in this study at other institutions
- Federal and State agencies (such as the Food and Drug Administration, the Department of Health and Human Services, the National Institutes of Health and other United States agencies) or government agencies in other countries that oversee or review research
- The sponsor(s) of this study and the people or groups it hires to help perform this research
- A group that oversees the data (study information) and safety of this research

Is your health information protected after it has been shared with others?

Mayo Clinic asks anyone who receives your health information from us to protect your privacy; however, once your information is shared outside Mayo Clinic, we cannot promise that it will remain private and it may no longer be protected by the Privacy Rule.

Your Privacy Rights

You do not have to sign this form, but if you do not, you cannot take part in this research study.

If you cancel your permission to use or share your health information, your participation in this study will end and no more information about you will be collected; however, information already collected about you in the study may continue to be used.

If you choose not to take part or if you withdraw from this study, it will not harm your relationship with your own doctors or with Mayo Clinic.

You can cancel your permission to use or share your health information at any time by sending a letter to the address below:

Mayo Clinic
Office for Human Research Protection
ATTN: Notice of Revocation of Authorization
200 1st Street SW
Rochester, MN 55905

Alternatively, you may cancel your permission by emailing the Mayo Clinic Research Subject Advocate at: researchsubjectadvocate@mayo.edu.

Please be sure to include in your letter or email:

- The name of the Principal Investigator,
- The study IRB number and /or study name, and
- Your contact information.

Your permission lasts forever, unless you cancel it.

ENROLLMENT AND PERMISSION SIGNATURES

Your signature documents your permission to take part in this research.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature

Person Obtaining Consent

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

Printed Name Date (mm/dd/yyyy) Time (hh:mm am/pm)

Signature