INFORMED CONSENT FORM

TITLE:	**A RANDOMIZED, MULTICENTER, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE III STUDY OF THE EFFICACY AND SAFETY OF TRASTUZUMAB EMTANSINE IN COMBINATION WITH ATEZOLIZUMAB OR PLACEBO IN PATIENTS WITH HER2-POSITIVE AND PD-L1 POSITIVE LOCALLY ADVANCED OR METASTATIC BREAST CANCER WHO HAVE RECEIVED PRIOR TRASTUZUMAB- (+/- PERTUZUMAB) AND TAXANE-BASED THERAPY (KATE3)**
PROTOCOL NUMBER:	MO42319
SPONSOR:	F. Hoffmann-La Roche Ltd
STUDY DOCTOR:	Simona Borštnar, MD, PhD Phone number: 01 587 92 20
NAME OF INSTITUTION:	Institute of Oncology Ljubljana
INSTITUTION ADDRESS:	Zaloška cesta 2, 1000 Ljubljana, Slovenia
NAME OF ETHICS COMMITTEE:	Republic of Slovenia National Medical Ethics Committee
ETHICS COMMITTEE APPROVAL DATE:	{Date}

SECTION 1: STUDY OVERVIEW

1.1 INTRODUCTION

- You are being asked to take part in this research study (also known as a clinical trial) because you have locally advanced or metastatic breast cancer that has previously been treated with trastuzumab-based therapy (with or without pertuzumab) and taxane-based therapy.
- This study is testing two drugs called trastuzumab emtansine and atezolizumab.
- F. Hoffmann-La Roche Ltd (hereafter referred to as Roche) is the sponsor of this study and is paying the Institute of Oncology Ljubljana to cover the costs of this study.
- This consent form tells you what will happen if you take part. It also tells you about the possible benefits and risks of being in the study.
- Taking part in this study is your choice. Please read the information carefully and feel free to ask questions. It may be helpful for you to discuss this information with your family and friends.
- Instead of participating in this study, you may choose to
  - Get treatment for your breast cancer without being in this study
  - Join a different study
  - Get no treatment
  - Get comfort care (also called "palliative care")
- Talk to your doctor about all of your choices, and the risks and benefits of each choice. If you choose not to take part, you will not lose the regular care you receive from your doctors.
- If you decide to take part, you will be asked to sign this consent form. You will be given a copy of your signed consent form.

1.2 WHAT IS THE PURPOSE OF THIS STUDY?

The purpose of this study is to compare the effects, good or bad, of trastuzumab emtansine plus atezolizumab versus trastuzumab emtansine plus placebo on patients with locally advanced or metastatic breast cancer whose tumors express two tumor markers (HER2 and PD-L1) which are described below. In this study, you will get trastuzumab emtansine with either atezolizumab or placebo. A placebo looks like a drug but has no active ingredient.

About 350 people will take part in this study worldwide.

Trastuzumab emtansine in combination with atezolizumab is an experimental treatment, which means health authorities have not approved these drugs in combination for the treatment of locally advanced or metastatic breast cancer.

Trastuzumab emtansine is a drug that combines a chemotherapy drug (DM1) with trastuzumab. Trastuzumab is a man-made antibody (a type of protein that is normally made by your immune system to help defend the body from infection and cancer) that attaches to HER2 on the surface of cancer cells. HER2, or human epidermal growth factor 2, is a protein that is overproduced by some cancer cells and promotes the growth of this type of cancer.

Trastuzumab emtansine has been globally approved for the treatment of HER2-positive metastatic breast cancer. Trastuzumab emtansine is also approved for the treatment of HER2-positive early breast cancer.

Atezolizumab is another man-made antibody that affects the immune system by blocking the programmed death-ligand 1 (PD-L1) pathway. The PD-L1 pathway is involved in regulating the body's natural immune response, but tumors can take advantage of this regulation to partially resist or evade the immune system. By blocking the PD-L1 pathway, atezolizumab may help your immune system to stop or reverse the growth of tumors.

Atezolizumab in combination with a chemotherapy drug called nab-paclitaxel is approved for the treatment of patients with locally advanced or metastatic breast cancer who have tumors that express the PD-L1 protein, but do not express the estrogen receptor, progesterone receptor, or HER2 ('triple negative breast cancer'). Atezolizumab is also approved for the treatment of patients with non-small cell lung cancer, hepatocellular cancer, small cell lung cancer, and urothelial cancer.

You were identified as a possible participant in the study because you have locally advanced or metastatic breast cancer that is or might be positive for both HER2 and PD-L1, and you have previously been treated with trastuzumab-based therapy (with or without pertuzumab) and taxane-based therapy.

1.3 WHAT WILL HAPPEN IF I PARTICIPATE?

This study has three parts:

1. Screening (to see if you are eligible for the study)
2. Treatment
3. Follow-up (to check on you after treatment is finished)

You will be placed in one of the following treatment groups:

- Group 1 will receive trastuzumab emtansine and placebo, given as two separate intravenous infusions (into the vein; also known as a 'drip') every 3 weeks
- Group 2 will receive trastuzumab emtansine and atezolizumab, given as two separate intravenous infusions (into the vein; also known as a 'drip') every 3 weeks

Your group will be decided by chance (like tossing a coin). You will have an equal chance of being placed in either group.

Neither you nor your study doctor can choose or know the group you are in. However, your study doctor can find out which group you are in, if your safety is at risk and/or if your doctor needs to know in order to give you certain treatments.

For patients who completed the prescreening ICF: You previously provided your consent for a sample of your tumor tissue to be tested to determine whether the tumor expresses HER2 and PD-L1. These tests demonstrated that your breast cancer is positive for both HER2 and PD-L1.

For patients who did not complete the prescreening ICF: You will have certain procedures and tests performed so that we may see how much HER2 and PD-L1 tumor expression you have. Your tumor must express HER2 and PD-L1 in order for you to be able to participate in the program. The tissue sample will be sent to a laboratory to be analyzed as part of this clinical study and the results from this test will help to determine if you are eligible to participate in this clinical study. One of the laboratory tests used (VENTANA anti-PD-L1 Rabbit Monoclonal Primary Antibody) to determine eligibility has not been approved by a regulatory authority or CE marked for use in HER2-positive breast cancer screening in patient treatment. It has been approved for use in other breast cancer types. One of the HER2 tests (VENTANA HER2 Dual ISH Probe Cocktail) used to determine eligibility is under investigation for use in patients with breast cancer to inform patient treatment with trastuzumab emtansine, but has not yet been approved by a regulatory authority or CE marked for use with this treatment. This test has been approved for use in informing patient treatment with trastuzumab. The laboratory will provide your HER2 and PD-L1 status results to your physician and to Roche.

During this study, you will visit the study site approximately every 3 weeks while you are receiving treatment. Visits may last 1–5 hours. During the visits you will receive atezolizumab or placebo first, followed by trastuzumab emtansine.

The first dose of atezolizumab will last around 60 minutes. Subsequent doses may take between 30–90 minutes depending on how you react to the first infusion. The first dose of trastuzumab emtansine will last around 90 minutes. Subsequent doses may take between 30–90 minutes depending on how you react to the infusion.

You will continue to receive study treatment on a regular basis unless your breast cancer worsens, or you or your doctor decide that it is time to stop. After your final dose, your study doctor will follow up with you about every 3 months for as long as you agree to it. During this follow-up your study doctor will collect information about how you are doing and if you are taking any anti-cancer drugs.

Your total time in the study will depend on how your breast cancer responds to treatment and may be determined by your study doctor. This could range from 1 day to more than 4 years.

The study procedures are described in detail in Section 2.2. Some procedures will be the same as your regular care for breast cancer, and some procedures will be just for this study.

1.4 ARE THERE ANY BENEFITS?

Your health may or may not improve in this study, but the information that is learned may help other people who have a similar medical condition in the future.

1.5 ARE THERE ANY RISKS?

You may have side effects from the drugs or procedures used in this study, as described in Sections 2.1 and 2.2. Side effects can be mild to severe and even life threatening, and they can vary from person to person. Talk to your study doctor right away if you have any of the following during the study:

- Symptoms that are new or have worsened
- Changes in your prescribed or over-the-counter medications (including herbal therapies)
- Visits to the doctor or hospital, including urgent care or emergency room visits

There may be a risk in exposing an unborn child to study drug, and all risks are not known at this time. Women and men must take precautions to avoid exposing an unborn child to study drug, as described in Section 1.6. If you are pregnant, become pregnant, or are currently breastfeeding, you cannot take part in this study.

1.6 ARE THERE ANY SPECIAL REQUIREMENTS?

While participating in this study, there are certain requirements, as listed below:

- You should not join another research study.
- For women: If you can become pregnant, you must use a reliable birth control method during the study and for 7 months after the last dose of study treatment. Talk with your study doctor about what method may be best for you. You must not donate eggs during this same period. Tell your study doctor right away if you get pregnant during this period. If you get pregnant, the study doctor will want to follow up with you on the outcome of the pregnancy and collect information on the baby.
- For men: If your partner is able to become pregnant, you must use a condom plus an additional reliable birth control method during the study and for 7 months after the last dose of study treatment. Talk with your study doctor about what method may be best for you. You must not donate sperm during this same period. If your partner is pregnant, you must still use a condom. Tell your study doctor right away if your partner gets pregnant during this period. The study doctor may ask you and your partner for permission to collect information about the pregnancy and the baby. No matter what you and your partner decide, you can continue to take part in this study.
- You should not use certain medications during this study. Your study doctor will talk to you about these medications.
- You are not allowed to have grapefruit juice or eat grapefruit during the study and for 30 days after your final dose of study treatment. Your study doctor will explain to you why this is important.

1.7 WILL I BE PAID TO PARTICIPATE?

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

You will be reimbursed for your reasonable costs (for example, transportation, parking) to travel from your home to the study site.

Information from this study, including information from research on your samples, may lead to discoveries, inventions, or development of commercial products. You and your family will not receive any benefits or payment if this happens.

1.8 WILL IT COST ME ANYTHING?

While participating in this study, you will not have to pay for drugs or procedures that are required only for this study and are not part of your regular medical care. You or your health plan will have to pay for medicines and clinic, hospital, and doctors' services that are part of your regular medical care.

1.9 WHAT HAPPENS IF I AM INJURED?

If you get injured because you took part in this study, contact your study doctor as soon as possible at telephone number listed in Section 2.8. Your study doctor will explain your options and tell you where to get treatment.

Roche will pay for reasonable costs of immediate care for any physical injury that results from the study drug but only if all of the following are true:

- Roche and the study doctor agree that your injury resulted from the study drug and not from a preexisting medical condition
- The costs are not paid for by your medical insurance
- Your injury was not because you or the study team did not follow instructions

You will not receive any other kind of payment.

To request payment for treatment costs, contact your study doctor, who will make sure Roche takes appropriate action. Roche maintains a contract with Insurance Company Allianz Global Corporate & Specialty to ensure Roche can pay for treatment costs.

If you get injured in this study, you will not lose any of your legal rights to seek payment by signing this form.

1.10 CAN I STOP BEING IN THE STUDY?

You can leave this study at any time. Tell your study doctor if you are thinking about stopping, and your study doctor will tell you how to stop safely. If you leave this study, you will not lose access to any of your regular care.

If there are important new findings or changes in this study that may affect your health or willingness to continue, your study doctor will let you or your legally authorized representative know as soon as possible.

You may be required to stop participating in the study, even if you wish to continue. Below are some of the reasons why you may be asked to stop:

- Your safety would be at risk if you continued
- You were unable to or did not follow study instructions or procedures

- You need medical care that is not allowed by this study
- This study has been stopped by Roche or a health authority

If you decide to leave the study, no new information will be collected about you with one exception: Information may be obtained from records available to the public to help track the course of your disease. Any laboratory samples collected prior to stopping will not be tested further. However, Roche will still be able to use information that was collected prior to stopping, including information from samples that were tested prior to stopping.

SECTION 2: STUDY DETAILS

2.1 STUDY TREATMENT RISKS

You may have side effects from the drugs or procedures used in this study. Side effects can vary from mild to very serious and may vary from person to person. Everyone taking part in the study will be watched carefully for any side effects. However, Roche, the study doctor, and other doctors do not know all of the side effects that could occur. Your study doctors may give you medications to help lessen side effects, and you may need to temporarily or permanently stop taking atezolizumab/placebo or trastuzumab emtansine. Many side effects go away soon after you stop what is causing them. In some cases, side effects can be serious and may be long lasting or may never go away. There also is a rare risk of death. You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks Associated with Trastuzumab Emtansine

The side effects associated with trastuzumab emtansine are listed below. There may be side effects that are not known at this time.

SIDE EFFECTS KNOWN TO BE ASSOCIATED WITH TRASTUZUMAB EMTANSINE

Side Effects Known to Be Associated with Trastuzumab Emtansine		
Very common (occurs in more than 10% of patients)	• Shortness of breath (dyspnea) • Easily tired (fatigue) • Lack of energy (asthenia) • Nose bleed (epistaxis) • Fever • Cough • Difficulty sleeping or falling asleep (insomnia) • Feeling sick to your stomach (nausea), vomiting, constipation, loose stools (diarrhea), abdominal pain • Dry mouth, sores in mouth (stomatitis) • Temporary increased blood levels of liver enzymes (increased transaminases) • Urinary tract infection	• Low platelet count in the blood, which may make you more likely to bruise or bleed (thrombocytopenia) • Low numbers of red blood cells (may make you feel tired, as these carry oxygen in the blood) • Inflammation (swelling and redness) or degeneration of the peripheral nerves (those nerves outside of brain and spinal cord) causing numbness, tingling, burning or weakness (peripheral neuropathy) • Joint pain (arthralgia) • Muscle and bone pain (myalgia and musculoskeletal pain) • Headache or head pain • Bleeding or abnormal flow of blood (hemorrhage)
Common (occurs in 1%–10% of patients)	• Decrease in heart's ability to pump blood during the "active" phase of the heartbeat (systole) [Left ventricular dysfunction] • High blood pressure (hypertension) • Dry eye, increased tears, blurred vision, pink eye (conjunctivitis) • Swelling under skin in arms and legs (peripheral edema) • Itchy skin (pruritus) • Dizziness • Taste changes (dysgeusia) • Heartburn (dyspepsia) • Low numbers of types of white blood cell that helps fight infections (neutropenia and leucopenia) • Reaction to infusion and hypersensitivity (allergic) reaction • Skin rash	• Chills • Decreased level of potassium in blood (hypokalemia) • Trouble with memory • Increased blood level of a liver pigment (bilirubin) often a sign of liver problems • Increased blood level of a liver or bone enzyme (alkaline phosphatase) • Bleeding from the gums (gingival bleeding) • Hair loss (alopecia) • Changes in the finger or toenails • Swelling and redness of the skin on the palms of the hands and soles of the feet (Palmar-plantar erythrodysaesthesia syndrome) • Hives (urticaria)

Side Effects Known to Be Associated with Trastuzumab Emtansine		
Less common but important (occurs in less than 1% of patients)	• Inflammation of the lungs that may cause difficulty breathing and can be life-threatening (pneumonitis), and may be caused by radiation • Scarring of the lungs (interstitial lung disease)	• Severe liver dysfunction or failure, including localized high blood pressure in liver and development of benign nodules • Leaking of drug from blood vessel into tissue surrounding the injection site (extravasation)

Note: Side effects listed above were seen in clinical trials that evaluated safety in approximately 2611 patients with HER2-positive breast cancer who received 3.6 mg/kg trastuzumab emtansine every 3 weeks.

More information about some of these risks is given below.

Lung toxicity

It is possible that tissue in your lungs may become inflamed (pneumonitis, a disease of the lung tissue) or may thicken with scarring. You may experience shortness of breath, either at rest or while performing any type of activity, and you may feel overly tired or weak (fatigued). Also, you may have onset of coughing or coughing spells with a dry cough. Rare cases of severe lung inflammation, including fatal cases, have been observed with trastuzumab emtansine. These conditions are often diagnosed by chest X-ray or other imaging tests and are usually treated with medications and by stopping the study drug.

Liver toxicity

Increased liver enzyme levels (proteins produced by the liver and released into the blood) may be detected by blood tests during the study and indicate irritation or damage to cells in the liver. In most cases, increases in liver enzymes are mild and temporary. Most of the patients with increased liver enzymes did not experience any other symptoms or signs that suggested liver injury or abnormal function. Another liver abnormality that has been seen is a condition known as nodular regenerative hyperplasia of the liver (development of liver nodules with high blood pressure in the liver). Over time, this may lead to symptoms such as a bloated sensation or swelling of the abdomen caused by fluid accumulation in the abdominal cavity (portal hypertension) or bleeding from abnormal blood vessels (varices) in the esophagus, stomach, or rectum, and to severe liver damage. Rare cases of severe liver toxicity, including death resulting from drug-induced liver injury and worsening of brain function (as the liver is no longer able to remove toxic substances), have been observed in patients treated with trastuzumab emtansine. Call your doctor right away if you have symptoms that may be a sign of liver problems: unusual tiredness, abdominal (stomach area) pain, or yellowing of the skin or the whites of your eyes (jaundice). These symptoms may or may not occur with nausea, vomiting, or fever. Blood tests will be performed regularly to check the effects of trastuzumab emtansine on your liver.

Heart toxicity

Treatment with trastuzumab emtansine can cause weakness of heart muscle leading to problems pumping the blood. This can cause shortness of breath at rest, chest pain, swollen ankles or arms, and sensation of rapid or irregular heartbeats. This condition is known as left ventricular dysfunction or heart failure. You will be monitored during the study using either an ECHO or MUGA scan.

Infusion-related reaction and hypersensitivity

There is a possibility you may experience an infusion-related reaction or hypersensitivity (allergic) reaction while trastuzumab emtansine is being injected into the vein (an infusion) or on the first day of drug administration. Symptoms may include flu-like symptoms such as fever and/or chills, breathing difficulties (shortness of breath, wheezing, narrowing of the air passage leading to the lungs), low blood pressure, rapid heart rate, reduced oxygen in the blood (which may require the use of a machine to help you breathe), hives, and swelling in the throat. Such reactions may be treated by stopping the infusion of trastuzumab emtansine and administering medications to manage symptoms. Infusion-related effects generally become less severe after the first treatment. Your treatment team will monitor you during your infusions, especially during your first dose, and can adjust or stop the infusion if you are uncomfortable. Emergency equipment should be available in the clinic where you are treated. You may also experience mild reactions, including reddening, tenderness, irritation of the skin, and pain or swelling if the infusion leaks into tissue surrounding the infusion site.

Bleeding

Severe bleeding can occur in any area of the body, including your brain. In some patients, severe bleeding has resulted in a fatal outcome. Some of the patients with bleeding were receiving blood-thinner treatment (for example, warfarin, heparin) or had low platelet count. Some of the patients with bleeding did not have any known risk factors.

Thrombocytopenia (low platelet count)

Platelets help your blood to clot, so when platelets are low you might get unexpected bleeding (such as nosebleeds or bleeding from the gums). In most cases, thrombocytopenia is mild; however, there may be a need for platelet transfusions in some cases. In clinical trials, the number of patients experiencing thrombocytopenia and the severity of thrombocytopenia were higher among Asian patients than non-Asian patients. Blood tests will be done regularly to check the effects of trastuzumab emtansine on your platelets.

Neurotoxicity (nerve damage)

You may experience tingling, pain, numbness, crawling sensation, itching, or a sensation of pins and needles in your arms and legs following treatment. These symptoms may indicate nerve damage. You will be monitored during the study for signs and symptoms of neurotoxicity.

Extravasation

Extravasation refers to the leakage of fluids from a vein into the surrounding tissues during the infusion. This can occur when a medicine or fluid is being sent directly into a vein. Some patients treated with trastuzumab emtansine have experienced reactions due to extravasation. These reactions were usually mild and comprised redness, tenderness, irritation, pain, or swelling at the site where the drug is infused into the vein. Your treatment team will monitor you during your infusions for these reactions.

Risks Associated with Atezolizumab

Atezolizumab is designed to increase the number of immune system cells in your body that can fight cancer. These cells may cause inflammation within the tumor, as well as in normal tissue. Therefore, by taking atezolizumab, you may develop a condition where there is inflammation against a part of your own body (an autoimmune condition).

SIDE EFFECTS KNOWN TO BE ASSOCIATED WITH ATEZOLIZUMAB

The side effects described in this section are known to be associated with atezolizumab.

Side Effects Known to Be Associated with Atezolizumab		
Very common (occurs in more than 10% of patients)	• Easily tired (fatigue) • Joint pain (arthralgia) • Lack of energy (asthenia) • Decreased appetite (anorexia) • Loose stools (diarrhea) • Shortness of breath (dyspnea) • Urinary tract infection • Cough	• Headache • Itching of the skin (pruritis) • Feeling sick to your stomach (nausea) • Fever • Rash • Vomiting • Muscle and bone pain (myalgia, musculoskeletal pain and bone pain)

Side Effects Known to Be Associated with Atezolizumab		
Common (occurs in 1%–10% of patients)	• Chills • Difficulty swallowing (dysphagia) • Increase in liver enzymes, which may indicate inflammation of the liver (increased transaminases) • Allergic reaction or intolerance to medication (hypersensitivity) • Decreased level of potassium in blood (hypokalemia) • Decreased level of sodium in blood (hyponatremia) • Low blood pressure (hypotension) • Underactive thyroid gland (hypothyroidism) • Nasal congestion • Increased blood level of creatinine (a substance normally eliminated by the kidneys into the urine) • Dry skin • Increased blood sugar level (hyperglycemia)	• Inflammation of the intestines (colitis) • Decreased oxygen supply in body resulting in shortness of breath (hypoxia) • Flu-like symptoms • Infusion-related reaction • Inflammation of the lungs (pneumonitis) • Low platelet count in the blood, which may make you more likely to bruise or bleed (thrombocytopenia) • Inflammation of the liver (hepatitis) • Stomach area pain (abdominal pain) • Pain in the throat at the back of the mouth behind the oral cavity (oropharyngeal pain)
Less common but important (occurs in less than 1% of patients)	• Decreased production of hormones by the adrenal glands (adrenal insufficiency) • Diabetes • Overactive thyroid gland (hyperthyroidism) • Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis) • Inflammation of the pituitary gland (hypophysitis) • Inflammation of the heart muscle (myocarditis) • Inflammation of the kidneys (nephritis)	• Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome) • Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis) • Inflammation of the pancreas (pancreatitis) • Increase in pancreatic enzymes, which may indicate inflammation of the pancreas (increase in amylase and lipase) • Severe high levels of sugar and acids in the blood or urine (diabetic ketoacidosis) • Inflammation or damage of the muscles (myositis)

Among the side effects known to be associated with atezolizumab, Roche and your study doctors would like you to pay more attention to the following and report any symptoms to your study doctor:

- Inflammation of the intestines (colitis); symptoms may include diarrhea, blood in stool, and pain in stomach area

- Inflammation of the thyroid glands (hypothyroidism, hyperthyroidism); symptoms may include headaches, fatigue, weight loss, weight gain, change in mood, hair loss, and constipation
- Inflammation of the adrenal glands (adrenal insufficiency); symptoms may include dizziness, irritability, fainting, low blood pressure, skin darkening, and craving of salty foods
- Inflammation of the pituitary gland (hypophysitis); symptoms may include fatigue and headaches that will not go away, increased thirst, increased urination, and changes in vision

  Side effects that may occur at the same time include hypothyroidism and adrenal insufficiency (see above for details).
- Inflammation of the liver (hepatitis); symptoms may include yellowing of skin, pain in stomach area, nausea, vomiting, itching, fatigue, bleeding or bruising under the skin, and dark urine
- Inflammation of the brain and membrane surrounding the brain and spinal cord (meningoencephalitis); symptoms may include neck stiffness, headache, fever, chills, vomiting, seizure, irritability, and eye sensitivity to light
- Nerve damage resulting in muscle weakness (myasthenic syndrome/myasthenia gravis); symptoms may include weakness in the arm and leg muscles, double vision, and difficulties with speech and chewing
- Nerve damage that may cause muscle weakness and/or paralysis (Guillain-Barré syndrome); symptoms may include tingling in fingers and toes, fatigue, and difficulty walking
- Inflammation of the lungs (pneumonitis); symptoms may include new or worsening cough, shortness of breath, and chest pain
- Inflammation of the heart muscle (myocarditis); symptoms may include shortness of breath, decreased exercise tolerance, fatigue, chest pain, swelling of the ankles or legs, irregular heartbeat, and fainting
- Reactions associated with infusion (events occurring during or within 1 day of infusion); symptoms may include fever, chills, shortness of breath, and sudden reddening of the face, neck, or chest
- Inflammation of the pancreas (pancreatitis); symptoms may include abdominal pain, nausea, vomiting, and fever
- Condition of high levels of sugar in the blood (diabetes mellitus); symptoms may include increased thirst, increased hunger, frequent urination, irritability, and fatigue
- Inflammation of the kidneys (nephritis); symptoms may include changes in urine output and color, pain in pelvis, and swelling of the body and may lead to failure of the kidneys
- Inflammation or damage of the muscles (myositis, myopathies including rhabdomyolysis); symptoms may include muscle pain and weakness, urine with a dark brown or reddish color, nausea, and vomiting

Allergic Reactions

Allergic reactions may occur with atezolizumab and typically occur while it is being given into your vein or shortly after it has been given. Symptoms could include nausea, vomiting, skin reactions (hives or rash), difficulty breathing, or low blood pressure. These reactions could be mild or severe and might lead to death or permanent disability. If you experience any of these symptoms, your study doctor will interrupt, or even stop, the delivery of atezolizumab into your vein. Your study doctor may also give you some drugs to treat these symptoms.

SIDE EFFECTS POTENTIALLY ASSOCIATED WITH ATEZOLIZUMAB

The following are side effects that may be associated with atezolizumab:

- Development of special antibodies to atezolizumab (proteins made in the body that respond to a substance that is foreign to the body) by your immune system

  If you develop these special antibodies, it may affect your body's ability to respond to atezolizumab in the future. Blood samples will be drawn to monitor for the development of these antibodies during study treatment and at your treatment discontinuation visit.
- Potential to cause harm to a developing fetus
- Inflammation of the eye (uveitis); symptoms may include eye pain and redness, vision problems, and blurry vision
- Inflammation of the blood vessels that can lead to damage of different organs (vasculitis); symptoms may include fever, fatigue, weight loss, weakness, general aches and pains, rash, headache, lightheadedness, shortness of breath, and numbness
- Breakdown of red blood cells (autoimmune hemolytic anemia); symptoms may include fatigue, fever, lightheadedness, paleness of the skin, yellowing of the skin and/or eyes, weakness, and inability to do physical activity
- Severe skin or mucosal reactions (severe cutaneous adverse reactions); symptoms may include severe skin or mucosal blistering, shedding, scaling, and death of the skin or mucosa

Immune Reaction

In rare situations, an immune reaction can occur with administration of atezolizumab. This reaction can cause side effects related to severe inflammation and/or severe infection. Several organs in your body (for example, liver, kidney, lungs, and bone marrow) may become involved, causing a serious condition, which could lead to hospitalization, life-threatening circumstances, or even death. Symptoms may include very low blood pressure that does not respond to standard treatment, very high fever, cough, severe shortness of breath requiring oxygen therapy and/or intubation, severe dizziness, confusion, weakness, decreased urination with failure of the kidneys, abnormal liver function, very low blood cell counts, and/or bleeding within the organs.

If you experience any of these symptoms, you should notify your doctor immediately, as you may need immediate treatment and hospitalization. Your study doctor may give you drugs to treat these symptoms.

2.2 STUDY PROCEDURES AND POTENTIAL RISKS

Procedures with Associated Risks		
Procedure	Approximate Timing	Potential Risks
Tumor tissue sample (biopsy)	• Screening • In case your disease worsens (if your doctor decides it is safe) Note: A biopsy will not be needed at screening if a previously collected sample is available and meets study requirements. If you have already submitted a tumor tissue sample that meets testing requirements during the prescreening process, submission of another sample during screening is not required.	Biopsies can cause pain, redness, swelling, excessive bleeding, bruising, or draining at the needle site. Abnormal wound healing, fever, infection, and allergic reaction to the medication used to numb the skin over the biopsy site can also occur. Your doctor will explain the details and risks of the procedure, which may vary depending on how the biopsy will be obtained.
For patients who did not complete the prescreening ICF: PD-L1 and HER2 testing (tissue test)	• Screening	The potential risks of using the unapproved and non-CE marked PD-L1 assay (laboratory test) and HER2 assay (laboratory test) are related to inaccurate assessment of PD-L1 and/or HER2 status that could lead to potential exposure to side effects from experimental treatment with no benefit to your disease or denial of treatment with the drug that could potentially treat your disease.
Blood sample (about 1–4 tablespoons at each visit)	• Screening • At each treatment visit (every 3 weeks) • At a study completion visit or early termination visit • In case your disease worsens	Drawing blood can cause pain, bruising, or infection where the needle is inserted. Some people experience dizziness, fainting, or upset stomach when their blood is drawn.

Procedures with Associated Risks		
Procedure	Approximate Timing	Potential Risks
Heart function test, consisting of one of the following: • Echocardiogram that uses sound waves but does not give off radiation • Multiple-gated acquisition (MUGA) scan that gives off a small amount of radiation	• Screening • In the week before Day 1 of Cycle 2 • Every 4 cycles (12 weeks) thereafter • At a study completion visit or early termination visit (if it has not been done in the 6 weeks before the visit) • At other times if your study doctor thinks it is needed	There are no harmful effects from an echocardiogram. Although there are no proven harmful effects from the radiation from a MUGA scan, no one can say for certain that there are no long-term harmful effects of radiation exposure.
Tumor assessments: scans of your internal organs and bones that may include: • Computed tomography (CT) scan: X-ray test that gives off radiation • Positron emission tomography (PET)/CT scan: imaging test that requires a radioactive tracer to be swallowed, injected, or inhaled • Magnetic resonance imaging (MRI) scan: imaging test that uses magnets and radio signals but does not give off radiation • Bone scan: imaging test that gives off radiation To increase visibility, a contrast agent may be swallowed, injected, or inserted into the rectum (enema). You cannot have an MRI if you have any metal or electronic devices in your body or if your kidneys are not working properly. Study staff will ask questions and (if needed) run tests to make sure the scans are safe for you.	• At Screening • Every 6 weeks, unless your disease worsens or you stop taken part in the study • At other times if your study doctor thinks it is needed • You may have some of these scans as part of your regular clinical care. Your study doctor can tell you how many extra scans you may have if you participate in this research study.	• Oral contrast agents may cause nausea, constipation, diarrhea, and abdominal bloating. • Injected contrast agents may cause pain, bruising, or infection at the injection site. You may have an allergic reaction to the contrast agent. • Contrast agents given by enema may cause abdominal bloating and discomfort. • The MRI scanner may cause some anxiety and claustrophobia (fear of being in small places). You may be given a mild sedative or anti-anxiety drug to help manage your symptoms. The contrast agent may cause nausea, headache, hives, temporary low blood pressure, chest pain, back pain, fever, weakness, and seizures. • Although there are no proven harmful effects from the radiation, no one can say for certain that there are no long-term harmful effects of radiation exposure.

Non-Invasive Procedures with Minimal Risks	
Procedure	Approximate Timing
Review of medical history, including medications	• Screening
Recording of demographic information, such as age, sex, race/ethnicity	• Screening
Questionnaires about your disease, quality of life, and treatment	**Questionnaires completed at the study site:** • On Day 1 of Cycles 1, 2, and 3 • At every other treatment visit, starting from Cycle 5 (Cycle, 5, 7, 9, 11, 13, etc.) • At a study completion visit or early termination visit **Questionnaires completed at home using the internet:** • On Day 15 of Cycles 1, 2, and 3 • Approximately 3 months after the study completion visit or early termination visit
Vital signs: temperature, pulse rate, blood pressure, breathing rate	• At screening and at each treatment visit (every 3 weeks)
Complete or limited physical examination (may include height or weight)	• At screening and at each treatment visit (every 3 weeks) • At a study completion visit or early termination visit
Assessment of performance status	• At screening and at each treatment visit (every 3 weeks) • At a study completion visit or early termination visit
Review changes in your health or medications	• Every visit
Electrocardiogram (ECG): measures electrical activity of your heart	• At screening and whenever your study doctor thinks it is needed
Urine sample for urine analysis	• At screening and whenever your study doctor thinks it is needed
Urine sample for pregnancy testing (only in women who can become pregnant)	• Every third treatment visit (every 9 weeks) • At a study completion visit or early termination visit • 3 months and 6 months after the last dose of study treatment
Follow-up after you discontinue treatment: telephone call or clinic visit to check your health and find out if you are taking any anti-cancer drugs	• Every 3 months for as long as you agree to it, or until the study ends, whichever occurs first

2.3 ACCESS TO STUDY DRUG AFTER COMPLETING THE STUDY

You will be eligible to receive the Roche study drugs (trastuzumab emtansine and atezolizumab) for free after you complete the study if all of the following are true:

- You have a life-threatening or severe medical condition and require continued Roche study drug treatment for your well-being
- There are no appropriate alternative treatments available to you
- You and your study doctor meet any legal or regulatory requirements that apply

You will not be eligible to receive the Roche study drugs (trastuzumab emtansine and atezolizumab) after you complete the study if any of the following are true:

- The Roche study drug is available in your country and is reasonably accessible to you (for example, it is covered by your insurance or would not create a financial burden for you)
- Roche has discontinued development of the drug or information suggests that the drug is not effective for locally advanced or metastatic breast cancer that is positive for both HER2 and PD-L1
- Roche has safety concerns about the drug as a treatment for locally advanced or metastatic breast cancer that is positive for both HER2 and PD-L1
- Provision of the Roche study drug is not permitted under the laws and regulations of your country

You may be eligible to receive trastuzumab emtansine and atezolizumab as part of an extension study. Your study doctor can give you more information.

2.4 USE AND HANDLING OF LABORATORY SAMPLES

Sample Use

Blood, urine, and tumor tissue samples will be collected for reasons such as the following:

• Check your health through standard laboratory tests • Find out if you are pregnant • Check how quickly your blood clots • Check for an infection with hepatitis B or C • Check for a prior or current infection with human immunodeficiency virus (HIV) • Measure blood sugar level • Check your thyroid function • Find out how study drug is processed by your body • Measure antibodies produced by your immune system	• Find out if your body is making antibodies to study drug • Perform additional analyses related to processing of study drug or development of antibodies to study drug (if needed) • To find out how variations in HER2 and PD-L1 affect your disease or your response to study drug • ***For patients who did not complete the prescreening ICF:*** Test for HER2 and PD-L1 to see if you are eligible for the study • Find out how variations in other biomarkers (such as breast cancer-specific proteins or genes) affect your disease or your response to study drug and develop biomarker tests

Part of your tumor tissue samples collected at screening may be used for future research related to breast cancer or other types of cancer, common pathways (links) among diseases, the use of experimental drugs in disease therapy, and/or the development of tests or tools that help with detecting or understanding breast cancer, even if you are not eligible for or decide not to take part in this study, unless you specifically ask for your samples to be destroyed.

Genome Testing

Biomarker testing may involve analysis of your genome (DNA), an "instruction book" for the cells in your body. Your blood and tissue samples may be tested for genome variations. Some of the genome variations may be inherited. Testing may include analysis of all of your DNA (whole genome sequencing) or analysis of all of your DNA that codes for proteins (whole exome sequencing). Analyses of samples from a large number of people may help researchers learn more about trastuzumab emtansine, atezolizumab, and similar drugs, breast cancer and other diseases, possible links among diseases, genome variations and how they might affect a disease or a person's response to treatment, and new avenues for drug development and personalized therapies.

Sample Storage

Samples will be securely stored for a defined period (as described below) and will then be destroyed, with one exception: Archival tumor tissue blocks will be returned to your doctor upon request or when the final study results have been reported, whichever occurs first. If you do not participate in the Study MO42319, remaining archival tissue blocks will be returned to your doctor no later than 2 months after your enrolment status is known.

Samples will be stored until the final study results have been reported, with the following exceptions:

- Samples for whole genome sequencing or whole exome sequencing will be stored for up to 15 years after the final study results have been reported.
- Samples for other biomarker testing, pharmacokinetic analyses, and immunogenicity analyses will be stored for 5 years after the final study results have been reported.

2.5 PROTECTION, USE, AND SHARING OF INFORMATION

During this study, health and personal information ("information") about you will be collected. This section describes the protection, use, and sharing of your information, which consists of the following:

- Information in your medical record, which is held by the Institute of Oncology Ljubljana ("study site")
- Information (including imaging data) that is collected or produced during this study ("study data"), which is held by the study site, Roche, Roche affiliates, and Roche's representatives (people and companies who work for Roche)

  "Study data" includes screening information from all patients, even patients who are not eligible for or decide not to take part in the study.

Your privacy is very important, and Roche uses many safeguards to protect your privacy, in accordance with applicable data privacy laws and laws related to the conduct of clinical trials.

Your study data and samples will be labeled with a patient identification (ID) number that is unique to you and not related to or derived from information that identifies you (such as your name, your picture, or any other personally identifying information). Roche, Roche affiliates, and Roche's representatives will only have access to study data and samples labeled with a patient ID number, except when accessing your medical record under certain circumstances, as described below:

Your information (including your medical record, which contains personal information that can identify you) may need to be reviewed to make sure the study is being done properly or to check the quality of the information. This information will be kept private. The following people and groups of people may review this information:

- Authorized individuals (such as study monitors and auditors) representing Roche and Roche's collaborators and licensees (people and companies who partner with Roche)
- The Institutional Review Board or Ethics Committee (people responsible for protecting the rights and safety of people who take part in research studies)
- Regulatory authorities (government agencies involved in keeping research safe for people)

Roche, Roche affiliates, and Roche's collaborators and licensees may use study data labeled with your patient ID number. Your study data may also be shared with independent researchers or government agencies, but only after personal information that can identify you has been removed. Your study data may be combined with other people's data and/or linked to other data collected from you. Your study data may be used to help better understand why people get diseases and how to best prevent, diagnose, and treat diseases, and to develop and provide access to new medicines, medical devices, and health care solutions.

Your information will not be given to your insurance company or employer, unless required by law. If the results from this study are published in a medical journal or presented at a scientific meeting, you will not be identified.

Information from this study will be retained by the study site for 15 years after the end of the study or for the length of time required by applicable laws, whichever is longer. In addition, Roche will retain the study data for 25 years after the final study results have been reported or for the length of time required by applicable laws, whichever is longer.

HIV and hepatitis are reportable diseases where you live. If you test positive for these diseases, the law requires your study doctor to report your name to the appropriate authority. Please ask your study doctor for details if you have concerns about this report.

If you sign this consent form, you give permission to the study site to use and/or share your information, which includes study data and information in your medical record. Your study data may be used or shared for the purposes of this study and for research related to breast cancer or other types of cancer, common pathways (links) among diseases, the use of

experimental drugs in disease therapy, and/or the development of tests or tools that help with detecting or understanding breast cancer. You do not have to sign this consent form, but if you do not, you cannot take part in this study.

Your study data may be used by and/or shared with Roche, Roche affiliates, Roche's collaborators and licensees, the Institutional Review Board or Ethics Committee, and regulatory authorities. Your study data and samples may be analyzed in any country worldwide. Such countries may have less data protection safeguards and rights than the country where your study site is located.

Transfer of your study data to Roche affiliates and Roche's collaborators and licensees who are located outside of the European Economic Area is protected adequately under separate agreements such as "Standard Data Protection Clauses."

You have the right to see and get a copy of your study data. However, by signing this consent form, you agree that you generally will not be able to review or receive some of your records related to the study until after the entire study has been completed. This is to protect the scientific integrity of the study. If you believe any of the personal data (that is, information that identifies you or could reasonably be used to identify you) in these records to be inaccurate or incomplete, you have the right to request that the data be corrected. You can request the deletion of any personal data that are no longer needed. You can also request the restriction of the use of any personal data. Because Roche only maintains study data labeled with your patient ID number, Roche may not be able to fully respond to your request. Roche will try to be as responsive as possible to your requests, taking into consideration the impact on the scientific integrity of the study. To request a copy of your study data, request that your personal data be corrected or deleted, or request the restriction of the use of your personal data, contact your study doctor (see Section 2.8), who will forward your request to Roche.

You may change your mind and take back your consent at any time without penalty or loss of any benefits to which you are otherwise entitled. If you take back your consent, you will not be able to continue to take part in the study and no new information will be collected about you. However, to comply with regulatory requirements to protect the scientific integrity of the study, Roche will still be able to use and share any study data about you that have already been collected during this study. To take back your consent, you may contact your study doctor (see Section 2.8).

If you have any questions, concerns, or complaints as to how Roche is using your information, you can contact Roche's local Data Protection Officer. The study doctor can provide you with contact information for Roche's Data Protection Officer. For more information about your privacy rights or if you are not able to resolve a problem directly with Roche and wish to make a complaint, you may contact the Information Commissioner of the Republic of Slovenia (at email address gp.ip@ip-rs.si or telephone number 01 230 97 30), which is responsible for making sure that privacy law is followed in Slovenia.

2.6 HANDLING OF GENETIC INFORMATION

Testing of your samples may provide information related to your genome ("genetic information"), including information about inherited characteristics. Your samples and genetic information will not be labeled with your name, your picture, or any other personally identifying information. Roche uses many safeguards to protect your privacy.

2.7 STUDY RESULTS

Results from exploratory biomarker tests, including tests for genome variations, will not be shared with you or your doctor, unless required by law. Information from these tests will not be part of your medical record.

A clinical study report containing the results of this trial will be made available to anyone who requests a copy. Before this report is provided, additional steps will be taken to protect your information from being linked to you.

A description of this clinical trial will be available at 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.

2.8 CONTACT INFORMATION

If you have any questions, contact your study team, listed below:

	Study Doctor	Study Coordinator
Name:		
Address:		
Telephone number:		
Email address:		

If at any time during this study you feel that your study doctor has not provided you with satisfactory answers to your questions, you may also contact the following institutions, which will address your questions within their area of competence:

- Agency for Medicinal Products and Medical Devices of the Republic of Slovenia, Slovenčeva ulica 22, 1000 Ljubljana, info@jazmp.si
- Republic of Slovenia National Medical Ethics Committee, Ministry of Health, Štefanova 5, 1000 Ljubljana, kme.mz@gov.si
- Patient’s rights representative, https://www.gov.si/teme/pacientove-pravice/
- Human Rights Ombudsman of the Republic of Slovenia, Dunajska cesta 56, 1000 Ljubljana, www.varuh-rs.si
- Information Commissioner of the Republic of Slovenia, Dunajska cesta 22, 1000 Ljubljana, www.ip-rs.si

You will receive a card with the name and phone number of the study doctor. Please keep this card with you at all times, for as long as you remain in the study.

Signature

I confirm that I have read this consent form, or it has been read to me. I understand the information presented and have had my questions answered. I understand I must take precautions to avoid exposing an unborn child to study drugs and agree to use required contraception as described in Section 1.6 of this form. I understand that I will be given a copy of all 24 pages of this form after it has been signed and dated. I voluntarily agree to take part in this research study as described above and authorize the Institute of Oncology Ljubljana to use and share my information as described in this form.

Patient name (print)	
If applicable – Name of patient's legally authorized representative (print)	Relationship to patient
Patient signature or signature of patient's legally authorized representative	Date

I, the undersigned, have fully explained this informed consent to the patient named above and/or the patient's legally authorized representative.

Name of person conducting informed consent discussion (print)	
Signature of person conducting informed consent discussion	Date
Witness name [a] (print)	
Witness signature [a]	Date

Witness name [a] (print)

Witness signature [a]

Date

[a] If the investigator or Institutional Review Board or Ethics Committee deems a witness signature is necessary (as per ICH Guidelines, Good Clinical Practice [E6], 4.8.9, or local regulations).