Response to CTEP Approval Letter with Recommendations from Review of Amendment #10 of Protocol #NRG-BR004 (NRG Oncology Amendment #6) dated 8/5/2022

I. Recommendations:

#	Section	Comments
1.	Cover Page Study Data Submission	*Please delete the highlighted language below:* Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions. ~~Do **not** submit study data or forms to the CTSU. Do **not** copy the CTSU on data submissions.~~ **PI Response: The change was made as requested.**
2.	8.2.1 IRB Approval	*Please revise the following, as indicated:* Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878). **PI Response: The change was made as requested.**
3.	8.2.1 IRB Approval	*It is indicated that this study is open to international sites. Therefore, please include the following language in this section:* Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes: Local IRB documentation; IRB-signed CTSU IRB Certification Form; and/or Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form. **PI Response: The change was made as requested.**
4.	8.2.4 Downloading Site Registration Documents	*Please revise the following language:* Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and its associated investigators and staff on a participating roster. To view/download stie registration forms: Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;

#	Section	Comments
		Click on *Protocols* in the upper left of the screen Enter the protocol number in the search field at the top of the protocol tree, or Click on the By Lead Organization folder to expand, then select *NRG* ~~Oncology~~, and protocol number (*NRG-BR004*); Click on *Documents*, *Protocol Related Documents*, and use the *Document Type* filter and select *Site Registration* and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.) **PI Response: The change was made as requested.**
5.	8.2.6 Delegation of Tasks Log	*Please revise the following language:* To maintain an approved site registration status, the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and to activate new task assignments requiring CI sign-off. **PI Response: The change was made as requested.**
6.	13.4 Data Quality Portal	Please delete the following highlighted text in this section: Data Quality Portal The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics. The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and forms with current status and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms. The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP. To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Forms Status, and DQP Reports modules. ~~Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.~~ **PI Response: The change was made as requested.**

II. Company Comments – Recommendations (no response required):

#	Section	Comments
7.	14.8.3.3	Minor suggestions: Type I error rate of 0.05 "(2-sided)". The last sentence: 43% at the primary analysis. What does it mean? **PI Response: The type 1 error rate of 0.05 was clarified to indicate that it is a two-sided test. Under the original design, we would have 80% power to detect a PFS HR=0.733. Under the amended design, we would have 80% power to detect a PFS HR=0.6. In this statement: "The chance to detect a PFS hazard ratio at 0.733, as originally designed, would be about 43% at the primary analysis," we basically stated that the power to detect a PFS HR=0.733 under the amended design would be about 43%.**

III. Additional Change

#	Section	Comments
8.	ICD	The date has been changed to match the most recent version of the protocol.

Research Study Informed Consent Document

Study Title for Participants: Testing the drug atezolizumab or placebo with usual therapy in first-line HER2-positive metastatic breast cancer

Official Study Title for Internet Search on http://www.ClinicalTrials.gov:

Protocol NRG-BR004, "A Randomized, Double-Blind, Phase III Trial of Taxane/Trastuzumab/Pertuzumab with Atezolizumab or Placebo in First-Line HER2-Positive Metastatic Breast Cancer," (NCT03199885)

Overview and Key Information

What am I being asked to do?

We are asking you to take part in a clinical research study. We do research studies to try to answer questions about how to prevent, diagnose, and treat diseases like cancer. We are asking you to take part in this research study because you have breast cancer that is HER2-positive and has spread (metastasized) outside your breast.

Taking part in this study is your choice.

You can choose to take part or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

This document has important information to help you make your choice. Take time to read it. Talk to your doctor, family, or friends about the risks and benefits of taking part in the study. It's important that you have as much information as you need and that all your questions are answered. See the "Where can I get more information?" section for resources for more clinical trials and general cancer information.

Why is this study being done?

This study is being done to answer the following question:

Can your breast cancer be stabilized and the time that you live with your breast cancer be lengthened by adding a new drug to the usual combination of drugs?

We are doing this study because we want to find out if this approach is better or worse than the usual approach for your breast cancer that is HER2-positive and has metastasized. The usual approach is defined as care most people get for breast cancer that is HER2-positive and has metastasized.

What is the usual approach to my HER2-positive breast cancer that has metastasized?

The usual approach for patients who are not in a study is treatment with chemotherapy combined with trastuzumab and pertuzumab which have been approved by the Food and Drug Administration (FDA). Treatments are generally continued until the disease gets worse or side effects become too severe. Your doctor can explain which treatment may be best for you. These treatments can reduce

symptoms and may stop the tumor from growing for a few months or longer. The usual approach is proven to help patients with your health condition live longer.

What are my choices if I decide not take part in this study?

- You may choose to have the usual approach described above.
- You may choose to take part in a different study, if one is available.
- You may choose to only get comfort care to help relieve your symptoms and not get treated for your cancer.

What will happen if I decide to take part in this study?

If you decide to take part in this study, you will initially get the chemotherapy drug paclitaxel or docetaxel along with trastuzumab, pertuzumab, and either placebo or atezolizumab. Treatment will continue until the disease gets worse or side effects become too severe. The paclitaxel or docetaxel will be continued for up to 6½ months in the absence of severe side effects or worsening of your disease, then stopped. The placebo or atezolizumab will be continued for up to 24 months in the absence of severe side effects or worsening of your disease, then stopped. The trastuzumab and pertuzumab will be continued until your disease gets worse, or the side effects become too severe, or you decide to stop the therapy.

After you have completed atezolizumab or placebo and you are getting trastuzumab and pertuzumab, your doctor and study team will continue to watch you for side effects. They will check you every 3 months for 3 years and then every six months for the next 5 years. This will be done at a visit to your study doctor. You will be in this study for about 10 years.

What are the risks and benefits of taking part in this study?

There are both risks and benefits to taking part in this study. It is important for you to think carefully about these as you make your decision.

Risks

We want to make sure you know about a few key risks right now. We give you more information in the "What risks can I expect from taking part in this study?" section.

If you choose to take part in this study, there is a risk that the addition of atezolizumab to the usual approach may not be as good as the usual approach for your cancer at stabilizing your cancer.

There is also a risk that you could have side effects from the atezolizumab. These side effects may be worse and may be different than you would get with the usual approach for your cancer.

Some of the most common side effects that the study doctors know about are:

- Nausea, vomiting, diarrhea
- Hair loss
- Fatigue
- Allergic reaction
- Infection, especially when white blood cell count is low
- Atezolizumab may cause your immune system to attack normal organs and cause side effects in many parts of the body.

There may be some risks that the study doctors do not yet know about.

Benefits

There is evidence that atezolizumab may be effective in stabilizing your type of cancer. It is not possible to know now if the study drug will extend how long you live with cancer and not have it get worse compared to the usual approach. This study will help the study doctors learn things that will help people in the future.

If I decide to take part in this study, can I stop later?

Yes, you can decide to stop taking part in the study at any time.

If you decide to stop, let your study doctor know as soon as possible. It's important that you stop safely. This may mean slowly stopping the study drugs so that there is not a sudden, unsafe change and risk to your health. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

Your study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

If you decide you no longer want your samples to be used, you can call the study doctor, *(*insert name of study doctor for main trial*)*, at *(*insert telephone number of study doctor for main trial*)*, who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

Are there other reasons why I might stop being in the study?

Yes. The study doctor may take you off the study if:

- Your health changes and the study is no longer in your best interest.
- New information becomes available and the study is no longer in your best interest.
- You do not follow the study rules.
- For women: You become pregnant while on the study.
- The study is stopped by the National Cancer Institute (NCI), Institutional Review Board (IRB), Food and Drug Administration (FDA), or study sponsor (NRG Oncology). The study sponsor is the organization who oversees the study.

It is important that you understand the information in the informed consent before making your decision. Please read, or have someone read to you, the rest of this document. If there is anything you don't understand, be sure to ask your study doctor or nurse.

What is the purpose of this study?

The purpose of this study is to compare the usual treatment plus placebo to the usual treatment plus atezolizumab. The addition of atezolizumab to the usual treatment could stabilize your cancer. But, it could also cause side effects, which are described in the risks section below.

This study will help the study doctors find out if this different approach is better, the same, or worse than the usual approach. To decide if it is better, the study doctors will be looking to see if the atezolizumab lengthens the time during and after the treatment of your cancer that you live with your cancer and it is stable.

Atezolizumab is already approved by the FDA for use in non-small cell lung cancer and urinary cancer. Its use in this study is considered experimental. There will be about 600 people taking part in this study.

What are the study groups?

This study has a central confirmation step. The purpose of this step is to confirm by central testing that your tumor has specific receptors. If you meet all the study requirements, you will join the study and begin therapy for your breast cancer while your tumor is being tested. The therapy you will receive is the usual therapy for your type of breast cancer. If the central testing shows that your tumor has the specific receptors, then you can continue on the study. If we find that your tumor does not have the specific receptors that are needed for this study, then your doctor will discuss other options for your care. Your tumor will also be tested to find out if it has the specific receptor PD-L1. The result of the PD-L1 test will help researchers to see if some patients benefit more than others from atezolizumab.

This study has 2 study groups. You will not be told which group you are in.

- Group 1

  If you are in this group, you will get the usual drugs used to treat this type of cancer, a chemotherapy drug, either paclitaxel or docetaxel, trastuzumab and pertuzumab, plus a placebo. A placebo is a liquid that looks like the study drug but contains no medication.

  You will get paclitaxel through a vein on Days 1, 8, 15, 22, 29, and 36 of each cycle or docetaxel through a vein on Days 1 and 22 of each cycle. You and your physician will decide which of the two chemotherapy options you will receive. You will get the trastuzumab, pertuzumab, and placebo through a vein on Days 1 and 22 of each cycle. Each cycle lasts 42 days. This part of the study has 3 cycles. Your study doctor may give you additional cycles of paclitaxel or docetaxel with trastuzumab, pertuzumab, and placebo if your cancer is responding to the drugs and your doctor thinks it is safe to keep you on them.

  After you complete the paclitaxel or docetaxel, you will continue to get trastuzumab, pertuzumab, and placebo through a vein on Days 1 and 22 of each cycle for about 13 cycles as long as your cancer responds to the drugs and as long as your doctor thinks it is safe to keep you on them. Each cycle lasts 42 days. You will then get trastuzumab and pertuzumab through a vein on Days 1 and 22 of each cycle as long as your cancer responds to the drugs and as long as your doctor thinks it is safe to keep you on them. Each cycle lasts 42 days.

  There will be about 300 people in this group.

- Group 2

  If you are in this group, you will get a study drug, atezolizumab, plus the usual drugs to treat this type of cancer, a chemotherapy drug, either paclitaxel or docetaxel, trastuzumab and pertuzumab.

  You will get paclitaxel through a vein on Days 1, 8, 15, 22, 29, and 36 of each cycle or docetaxel through a vein on Days 1 and 22 of each cycle. You and your physician will decide which of the two chemotherapy options you will receive. You will get the trastuzumab, pertuzumab, and atezolizumab through a vein on Days 1 and 22 of each cycle. Each cycle lasts 42 days. This part of the study has 3 cycles. Your study doctor may give you additional cycles

of paclitaxel or docetaxel with trastuzumab, pertuzumab, and atezolizumab if your cancer is responding to the drugs and your doctor thinks it is safe to keep you on them.

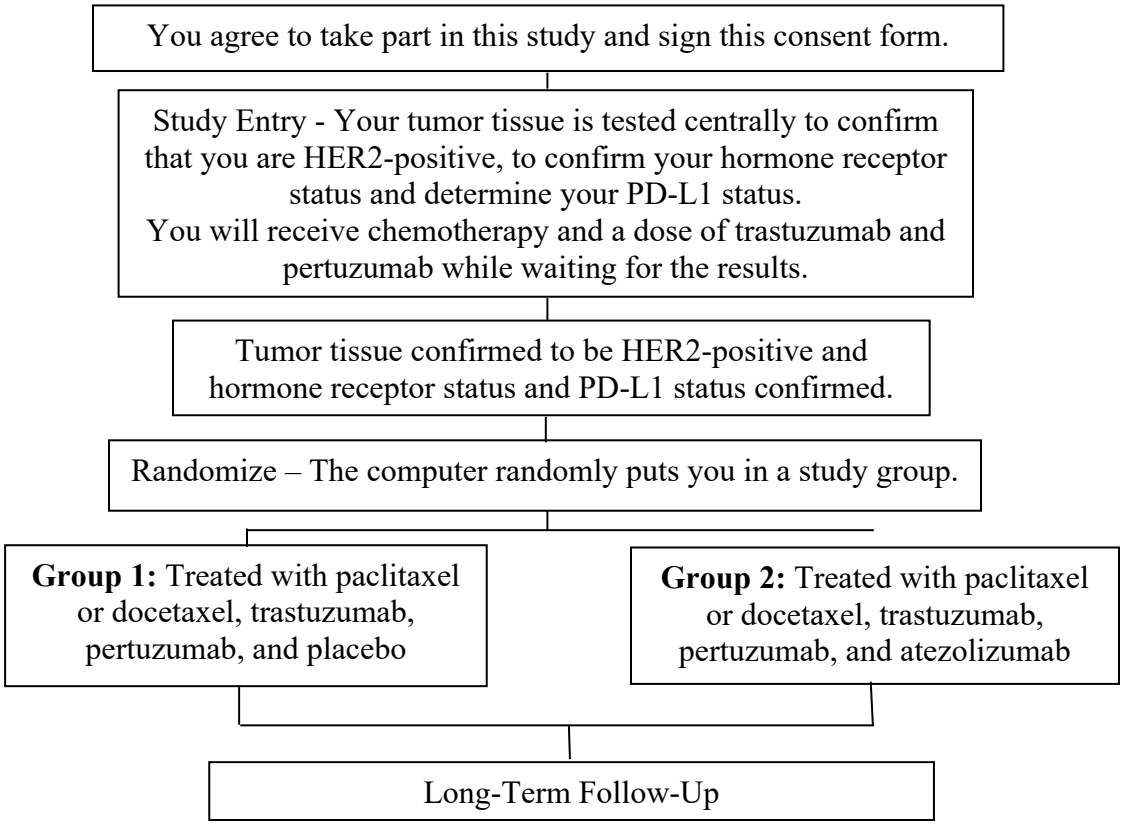
After you complete the paclitaxel or docetaxel, you will continue to get trastuzumab, pertuzumab, and atezolizumab through a vein on Days 1 and 22 of each cycle for about 13 cycles as long as your cancer responds to the drugs and as long as your doctor thinks it is safe to keep you on them. Each cycle lasts 42 days. You will then get trastuzumab and pertuzumab through a vein on Days 1 and 22 of each cycle as long as your cancer responds to the drugs and as long as your doctor thinks it is safe to keep you on them. Each cycle lasts 42 days.

You will not be able to get additional doses of atezolizumab. This drug is not approved by the FDA for treatment of your disease.

There will be about 300 people in this group.

We will use a computer to assign you to one of the study groups. This process is called "randomization." It means that your doctor will not choose and you cannot choose which study group you are in. You will be put into a group by chance. You will have an equal chance of being in Group 1 or Group 2.

Another way to find out what will happen to you during this study is to read the chart below. Start reading from the top and read to the bottom, following the lines.



What exams, tests, and procedures are involved in this study?

Before you begin the study, your doctor will review the results of your exams, tests, and procedures. This helps your doctor decide if it is safe for you to take part in the study. If you join the study, you

will have more exams, tests, and procedures to closely monitor your safety and health. Most of these are included in the usual care you would get even if you were not in a study.

Listed below are exams, tests, and procedures that need to be done as part of this study to monitor your safety and health but may not be included in the usual care. We will use them to carefully follow the effects of the study treatment, including preventing and managing side effects.

These exams, tests, and procedures to monitor your safety and health before you begin the study include:

- Blood tests to check your hormone glands (thyroid and adrenal glands).
- Blood test to check if you have hepatitis.
- Blood test to check how long it takes your blood to clot.
- Electrocardiogram to check your heart.

Some exams, tests, and procedures are a necessary part of the research study, but would not be included in usual care. Listed below are tests that will be done for research purposes only.

Your study doctor will need to use some of the tissue left over from your biopsy when you were diagnosed with cancer. This sample is a required part of the study. A tumor sample will be sent to a central lab to confirm that your tumor is positive for the protein HER2 and to confirm whether or not your tumor is sensitive to hormones. Your study doctor will get the results of this testing.

A tumor sample will also be sent to a central lab to confirm whether or not your tumor has the PD-L1 biomarker. The PD-L1 test is being done to see if some patients benefit more than others from atezolizumab. The study doctors do not know if using the test is better, the same, or worse than not using the test. If better, this test should identify those patients who will benefit from atezolizumab. This test is investigational and will not be used to determine which group you are in. Your study doctor will not get the results of this testing.

If there is not enough tissue left over from your biopsy when you were diagnosed with cancer, your study doctor may have to do another biopsy to get the tissue. The biopsy will be done after you signed the NRG-BR004 consent form so that tissue can be collected to send for central testing. The study biopsy takes small pieces of cancer tissue from your body. This is like the biopsy you had that helped diagnose your cancer. The specimen will be sent to the central labs to confirm that your tumor is positive for the protein HER2, to confirm whether or not your tumor is sensitive to hormones, and to confirm whether or not your tumor has the PD-L1 biomarker. If you agree to take part in the study, you may need to sign a separate consent form for the study biopsy at the hospital or clinic where the biopsy is done.

There will be about 600 people taking part in these tests.

Quality of Life

If you understand or read English, Spanish, or French and choose to take part in BR004, you will be asked to complete a survey with questions about your physical well-being, as well as any symptoms that you may be having. The survey will ask about things like fatigue, diarrhea, pain, loss of appetite, awareness and judgement, and difficulty sleeping. Researchers will use this information to learn more about how cancer and cancer treatment affects people.

You will have the option of completing the questionnaires and survey by paper or by an electronic device. If you choose to complete the questionnaires with an electronic device, you will enter your answers to the questionnaires via a personal electronic device such as your smart phone or tablet. In

some cases, a tablet may be provided to you at your health care institution. The use of your own electronic device on a cellular network may result in minor increases to your data plan. Whether you use a personal device or a tablet supplied by the clinic, your answers and personal information will not be stored on the device. Your answers will be sent to the research database and will be kept private in the same way listed in the section about who will see your medical records. Your e-mail address will only be used for this survey study and will not be used for mail or marketing purposes.

You will be asked to fill out this survey at 7 times and each time it will take about 15 to 30 minutes to complete:

- Before you join the study
- At 12 and 24 weeks after you joined the study
- At 12, 18, 24, and 30 months after you joined the study

If you need help using the survey application on your phone or tablet, ask for help at your treatment site. You don't have to answer any question that makes you feel uncomfortable. You may have an alternate person complete the survey on your behalf if needed, and you will need to provide that information on the survey. Since this is a research survey, the responses you provide will not be shared with your doctor. If you are having any severe symptoms, health issues or other concerns, please be sure to discuss these with your doctor or nurse right away.

Collection of Scans

Copies of scans (CT, x-rays, MRI, ultrasound) that will be done as part of routine care will be sent to Bioclinica for central review of how your tumor responds to the study treatment. Your name and other identifying information will be removed before they are sent. You or your study doctor will not get the results.

What risks can I expect from taking part in this study?

General Risks

If you choose to take part in this study, there is a risk that the atezolizumab may not be as good as the usual approach for your cancer at stabilizing your cancer.

You also may have the following discomforts:

- Spend more time in the hospital or doctor's office.
- Be asked sensitive or private questions about things you normally do not discuss.
- May not be able to take part in future studies.

The atezolizumab used in this study could be very harmful to an unborn or newborn baby. There may be some risks that doctors do not yet know about. It is very important that you check with your study doctor about what types of birth control or pregnancy prevention to use during the study and for 7 months after you have completed the study drugs.

This study will use a sample of your tissue. Generally, your hospital will keep some of your tissue. This tissue may be used to help treat your cancer in the future. Because this study will need to use some of this tissue, there is a small risk that it could be used up.

Biopsy Risks

Common side effects of a biopsy are a small amount of bleeding at the time of the procedure, bruising, and pain at the biopsy site. Pain can be treated with regular pain medications. Rarely, an

infection can occur. You may sign a separate consent form for the study biopsy that describes the risks in more detail.

Left over specimen may be stored for biobanking. This will be discussed in the section under "Optional studies that you can choose to take part in."

Side Effect Risks

The study drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will test your blood and let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from the study drugs.

Here are important things to know about side effects:

1. The study doctors do not know who will or will not have side effects.
2. Some side effects may go away soon, some may last a long time, and some may never go away.
3. Some side effects may make it hard for you to have children.
4. Some side effects may be mild. Other side effects may be very serious and even result in death.

You can ask your study doctor questions about side effects at any time. Here are important ways to make side effects less of a problem:

- If you notice or feel anything different, tell your study doctor. He or she can check to see if it is a side effect.
- Your study doctor will work with you to treat your side effects.
- Your study doctor may adjust the study drugs to try to reduce side effects.

This study is looking at a combination of the usual drugs used to treat this type of cancer plus a study drug. This different combination of drugs may increase your side effects or may cause new side effects.

Drug Risks

The tables below show the most common and most serious side effects doctors know about. Keep in mind that there might be other side effects doctors do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

Study Group 1 and Group 2 – Possible side effects of trastuzumab, pertuzumab, paclitaxel or docetaxel, and atezolizumab/placebo are listed in the tables below. Trastuzumab, pertuzumab, and paclitaxel or docetaxel are the usual approach for treating this type of cancer:

Possible Side Effects of **Trastuzumab** (Herceptin [as infusion into a vein]) or Herceptin Hylecta™ (subcutaneous trastuzumab – injected under the skin)
(Table Version Date: CAEPR Version 2.6, December 14, 2021)

COMMON, SOME MAY BE SERIOUS In 100 people receiving Trastuzumab (Herceptin [as infusion into a vein]) or Herceptin Hylecta™ (subcutaneous trastuzumab – injected under the skin), more than 20 and up to 100 may have:
• Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving Trastuzumab (Herceptin [as infusion into a vein]) or Herceptin Hylecta™ (subcutaneous trastuzumab – injected under the skin), from 4 to 20 may have:
• Anemia which may require blood transfusion • Infection, especially when white blood cell count is low • Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Fluid in the body • Abnormal heartbeat • Watering eyes • Pain • Diarrhea, nausea, vomiting • Sores in the mouth which may cause difficulty swallowing • Chills, fever • Swelling of the body • Flu-like symptoms including body aches • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Swelling and redness at the site of the medication injection with subcutaneous trastuzumab injected under the skin • Weight loss, loss of appetite • Changes in taste • Dizziness, headache • Numbness, tingling or pain of the arms and legs • Depression • Difficulty sleeping • Stuffy nose • Cough, shortness of breath • Hair loss, acne, rash, hives • Change in or loss of some or all of the finger or toenails • Hot flashes • High blood pressure which may cause headaches, dizziness, blurred vision • Low blood pressure which may cause feeling faint

RARE, AND SERIOUS In 100 people receiving Trastuzumab (Herceptin) [as infusion into a vein]) or Herceptin Hylecta™ (subcutaneous trastuzumab – injected under the skin), 3 or fewer may have:
• Change in heart function • Damage to organs (lung, others) which may cause shortness of breath • Scarring of the lungs

Possible Side Effects of **Pertuzumab**
(Table Version Date: CAEPR Version 2.4, July 6, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving pertuzumab, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness • Infection, especially when white blood cell count is low • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving pertuzumab, from 4 to 20 may have:
• Anemia which may require blood transfusion • Watering eyes • Constipation, heartburn • Sores in the mouth which may cause difficulty swallowing • Swelling of the body • Fever • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Swelling and redness of the area of radiation • Loss of appetite • Pain • Dizziness, headache • Changes in taste • Feeling of "pins and needles" in arms and legs • Muscle weakness • Numbness, tingling or pain of the arms and legs • Difficulty sleeping • Cough, shortness of breath • Nose bleed • Dry skin • Change in or loss of some or all of the finger or toenails • Redness, pain or peeling of palms and soles • Itching, rash • Hot flashes

RARE, AND SERIOUS In 100 people receiving pertuzumab, 3 or fewer may have:
• Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Change in heart function

Possible Side Effects of **Paclitaxel**
(Table Version Date: October 14, 2020)

COMMON, SOME MAY BE SERIOUS In 100 people receiving paclitaxel, more than 20 and up to 100 may have:
• Anemia which may cause tiredness, or may require blood transfusions • Infection, especially when white blood cell count is low • Diarrhea, nausea, vomiting • Sores in mouth which may cause difficulty swallowing • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat • Bruising, bleeding • Pain • Muscle weakness • Numbness, tingling or pain of the arms and legs • Hair loss

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving paclitaxel, from 4 to 20 may have:
• Abnormal heartbeat • Damage to the lungs which may cause shortness of breath • Blood clot which may cause swelling, pain, shortness of breath

RARE, AND SERIOUS In 100 people receiving paclitaxel, 3 or fewer may have:
• Heart attack or heart failure which may cause shortness of breath, swelling of ankles, and tiredness • A tear or a hole in the stomach which may cause belly pain or that may require surgery

Possible Side Effects of **Docetaxel**
(Table Version Date: October 17, 2019)

COMMON, SOME MAY BE SERIOUS In 100 people receiving docetaxel, more than 20 and up to 100 may have:
• Infection, especially when white blood cell count is low • Bruising, bleeding • Anemia which may require blood transfusions • Vomiting, diarrhea, nausea, constipation • Sores in mouth which may cause difficulty swallowing • Absence of menstrual period • Swelling and redness of the arms, leg or face • Swelling of the body • Numbness and tingling of the arms and legs • Tiredness • Fever • Pain • Watering, itchy eyes

COMMON, SOME MAY BE SERIOUS In 100 people receiving docetaxel, more than 20 and up to 100 may have:
• Hair loss • Change in nails • Rash, itching

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving docetaxel, from 4 to 20 may have:
• Abnormal heart rate • Chest pain • Shortness of breath, wheezing • Blood clot which may cause swelling, pain, shortness of breath • Kidney damage which may require dialysis • Belly pain • Severe skin rash with blisters and peeling which can involve inside of mouth and other parts of the body

RARE, AND SERIOUS In 100 people receiving docetaxel, 3 or fewer may have:
• Cancer of bone marrow (leukemia) caused by chemotherapy • Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat

Patients should be aware that docetaxel may cause them to become intoxicated from the alcohol it contains. Patients should avoid driving, operating machinery, or performing other activities that are dangerous within one to two hours after the infusion of docetaxel. In addition, some medications, such as pain relievers and sleep aids, may interact with the alcohol in the docetaxel infusion and worsen the intoxicating effects.

Possible Side Effects of **Atezolizumab/Placebo**
(CAEPR Version 2.3, March 11, 2021)

COMMON, SOME MAY BE SERIOUS In 100 people receiving atezolizumab (MPDL3280A)/placebo, more than 20 and up to 100 may have:
• Tiredness • Infection

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving atezolizumab (MPDL3280A)/placebo, from 4 to 20 may have:
• Anemia which may require blood transfusion • Diarrhea, nausea, vomiting • Difficulty swallowing • Fever • Flu-like symptoms including body aches

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving atezolizumab (MPDL3280A)/placebo, from 4 to 20 may have:

- Reaction during or following a drug infusion which may cause fever, chills, rash
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Loss of appetite
- Pain in back
- Cough, shortness of breath, stuffy nose
- Itching, acne, rash

Atezolizumab (MPDL3280A)/placebo may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

  - Hormone gland problems (especially the thyroid, pituitary and adrenal glands, and pancreas). Signs and symptoms may include: headaches that will not go away or unusual headaches, extreme tiredness or changes in mood or behavior; decreased sex drive; weight loss or weight gain; excessive thirst or urine; dizziness or fainting.
  - Pain in belly
  - Pain or swelling of the joints
- Rash that develops on skin, nails, scalp and inside of mouth or vagina that may be painful

RARE, AND SERIOUS

In 100 people receiving atezolizumab (MPDL3280A)/placebo, 3 or fewer may have:

- Bruising, bleeding

Atezolizumab (MPDL3280A)/placebo may cause your immune system to attack normal organs and cause side effects in many parts of the body. These problems may include but are not limited to:

- Heart problems including swelling and heart failure. Symptoms and signs of heart problems may include: shortness of breath, swelling of the ankles and body.
- A condition with high blood sugar which leads to tiredness, frequent urination or excessive thirst
- Swelling and redness of the eye
- Intestinal problems (colitis) that can rarely lead to tears or holes in your intestine. Signs and symptoms of colitis may include: diarrhea or increase in bowel movements, blood in your stools or dark, tarry, sticky stools, severe belly pain or tenderness.
- Liver problems (hepatitis) which can cause liver failure. Signs and symptoms of hepatitis may include: yellowing of your skin or the whites of your eyes, severe nausea or vomiting; drowsiness; pain in the right upper belly.
- Swelling of the brain (meningitis/encephalitis), which may cause: headache, confusion, sleepiness, seizures, and stiff neck
- Problem of the muscle, including swelling, which can cause muscle pain and severe muscle weakness sometimes with dark urine
- Problem of the nerves that can cause paralysis. Signs and symptoms may include: numbness, tingling of hands and feet; weakness of the arms, legs.

RARE, AND SERIOUS In 100 people receiving atezolizumab (MPDL3280A)/placebo, 3 or fewer may have:
• Kidney problems, including nephritis and kidney failure requiring dialysis. Signs of kidney problems may include: decrease in the amount of urine, blood in your urine, ankle swelling. • Lung problems (pneumonitis and pleural effusion). Symptoms may include: new or worsening cough, chest pain, shortness of breath. • Skin: blisters on the skin, including inside the mouth (can be severe), rash with blisters, skin rash developing 1-8 weeks after a drug is given, which may be accompanied by fever, lymph node swelling and organ failure.

Additional Drug Risks:

Each of the drugs used in this study have been shown to cause heart problems. It is possible that the risk of heart problems may be increased when the drugs are given together.

Rarely, there are problems getting enough supplies of the study drug. If that happens, your doctor will talk with you about your options.

What are my responsibilities in this study?

If you choose to take part in this study you will need to:

- Keep your study appointments.
- Tell your doctor about:
    - all medications and supplements you are taking
    - any side effects
    - any doctors' visits or hospital stays outside of this study
    - if you have been or are currently in another research study.

For women: Do not get pregnant or breastfeed while taking part in this study. **For men:** Do not father a baby while taking part in this study. **For all:** Tell your study doctor right away if you think that you or your partner have become pregnant during the study or within 7 months after your last dose of study treatment.

If you are a woman taking part in this study and you become pregnant:

By signing this consent form, you agree to allow NRG Oncology to collect information about the results of your pregnancy that occurred while participating in this study including 7 months after your last dose of study treatment. If you have a baby from a pregnancy that you reported while participating in this study including 7 months after your last dose of study treatment, you also agree by signing this consent form to allow NRG Oncology to collect information on your baby from birth through 12 months. This health information will become part of your study records and will be shared with NRG Oncology and Genentech/Roche so that Genentech/Roche may determine if there are any effects of the study therapy on unborn children or infants.

What are the costs of taking part in this study?

You and/or your insurance plan will need to pay for the costs of medical care you get as part of the study, just as you would if you were getting the usual care for your cancer. This includes:

- the costs of tests, exams, procedures, and drugs that you get during the study to monitor your safety, and prevent and treat side effects.

- the costs of getting the paclitaxel or docetaxel, trastuzumab, pertuzumab, and atezolizumab or placebo ready and giving it to you.
- the cost of the first dose of trastuzumab that you receive while waiting for the results of central testing.
- your insurance co-pays and deductibles.

Talk to your insurance provider and make sure that you understand what your insurance pays for and what it doesn't pay for if you take part in this clinical trial. Also, find out if you need approval from your plan before you can take part in the study.

Ask your doctor or nurse for help finding the right person to talk to if you are unsure which costs will be billed to you or your insurance provider.

You and/or your insurance provider will not have to pay for exams, tests, and procedures done for research purposes only or that are covered by the study. These include tests and exams done at the beginning of the study:

- Blood tests to check your hormone glands (thyroid and adrenal glands).
- Blood test to check if you have hepatitis.
- Blood test to check how long it takes your blood to clot.
- Electrocardiogram to check your heart.
- A biopsy to get tissue for testing, if one is needed, to confirm that your tumor is positive for the protein HER2 and to confirm whether or not your tumor is sensitive to hormones and to confirm whether or not your tumor has the PD-L1 biomarker,

You or your insurance provider will not have to pay for the atezolizumab/placebo while you take part in this study. For patients in the United States, you or your insurance provider will not have to pay for the trastuzumab after you are randomized and taking part in the study.

Taking part in this study may mean that you need to make more visits to the clinic or hospital than if you were getting the usual approach to treat your cancer. You may:

- Have more travel costs.
- Need to take more time off work.
- Have other additional personal costs.

You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What happens if I am injured because I took part in this study?

If you are injured as a result of taking part in this study and need medical treatment, please talk with your study doctor right away about your treatment options. The study sponsors will not pay for medical treatment for injury. Your insurance company may not be willing to pay for a study-related injury. Ask them if they will pay. If you do not have insurance, then you would need to pay for these medical costs.

If you feel this injury was caused by medical error on the part of the study doctors or others involved in the study, you have the legal right to seek payment, even though you are in a study. Agreeing to take part in this study does not mean you give up these rights.

Who will see my medical information?

Your privacy is very important to us. The study doctors will make every effort to protect it. The study doctors have a privacy permit to help protect your records if there is a court case. However, some of your medical information may be given out if required by law. If this should happen, the study doctors will do their best to make sure that any information that goes out to others will not identify who you are.

Some of your health information, such as your response to cancer treatment, results of study tests, and medicines you took, will be kept by the study sponsor in a central research database. However, your name and contact information will not be put in the database. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

There are organizations that may look at your study records. Your health information in the research database also may be shared with these organizations. They must keep your information private, unless required by law to give it to another group.

Some of these organizations are:

- The study sponsor and any company (Genentech, a Member of the Roche Group and F. Hoffmann-La Roche LTD) supporting the study agent now or in the future.
- Magee-Womens Hospital of UPMC, Department of Pathology, the laboratory that performs the central testing. The laboratory will receive identifiable information from your pathology report that is sent with your tumor tissue. Your identifiable information will only be used for the purposes of the study and will be kept private. It will only be shared with the members of the study team.
- HistoGeneX, the laboratory that will test tumor tissue for PD-L1.
- Ventana, the company that provides the PD-L1 testing supplies to HistoGeneX.
- Bioclinica, the company where your scans (CT, x-rays, MRI, ultrasound) will be sent for central review.
- The IRB, which is a group of people who review the research with the goal of protecting the people who take part in the study.
- The FDA and the groups it works with to review research.
- The NCI and the groups it works with to review research.
- The NCI's National Clinical Trials Network and the groups it works with to conduct research.
- Health Canada, the regulatory agency that reviews research in Canada.

Your study records also will be stored for future use. However, your name and other personal information will not be used. Some types of future research may include looking at your records and those of other patients to see who had side effects across many studies or comparing new study data with older study data. However, we don't know what research may be done in the future using your information. This means that:

- You will not be asked if you agree to take part in the specific future research studies using your health information.
- You and your study doctor will not be told when or what type of research will be done.
- You will not get reports or other information about any research that is done using your information.

There are laws that protect your genetic information. However, there is a risk that someone could get access to your genetic information and identify you by name. In some cases, employers could use your genetic information to decide whether to hire or fire you. The study doctors believe the risk of this happening is very small. However, the risk may increase in the future as people find new ways of tracing information. For more information about the laws that protect you, ask your study doctor.

As part of this study, we will collect information from an application downloaded from the Internet and/or from a personal electronic device such as your smart phone or tablet or from an electronic device such as a tablet that you may use at your health care institution.

The electronic device at your health care institution is only for use while you are at the health care institution. It will not be given to you to take home for use in this study.

The maker of the application and/or device may collect and store personal information, such as health information, location data, and internet usage. A complete description of what data will be collected and what the company will do with it can be found in the Terms of Service. You will need to agree to the Terms of Service to participate in this study.

The researchers in this study may not have any control over what the company does with your information. The application and/or device may collect and transmit more information to the company than is needed for this study.

Where can I get more information?

You may visit the NCI web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on 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. You can search this Web site at any time.

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor *(*insert name of study doctor[s]*)* at *(*insert telephone number, and email address if appropriate*)*.

For questions about your rights while in this study, call the (*insert name of organization or center*) Institutional Review Board at *(*insert telephone number*)*.

*^Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.^*

Optional studies that you can choose to take part in

This part of the consent form is about optional studies that you can choose to take part in. They are separate from the main study described above. These optional studies will not benefit your health. The researchers leading these optional studies hope the results will help other people with cancer in the future. The results will not be added to your medical records and you or your study doctor will not know the results.

Taking part in these optional studies is your choice. You can still take part in the main study even if you say “no” to any or all of these studies. There is no penalty for saying “no.” You and your

insurance company will not be billed for these optional studies. If you sign up for, but cannot complete any of these studies for any reason, you can still take part in the main study.

Circle your choice of "yes" or "no" for each of the following studies.

Optional sample collections for known laboratory studies and/or storage for possible future studies

Researchers are trying to learn more about cancer and other health problems using blood and tissue samples from people who take part in clinical trials. By studying these samples, researchers hope to find new ways to prevent, detect, treat, or cure diseases.

Some of these studies may be about how genes affect health and disease. Other studies may look at how genes affect a person's response to treatment. Genes carry information about traits that are found in you and your family. Examples of traits are the color of your eyes, having curly or straight hair, and certain health conditions that are passed down in families. Some of the studies may lead to new products, such as drugs or tests for diseases.

Known future studies

If you choose to take part in this optional study, researchers will collect blood to look for cancer cells that may be circulating in the blood stream. A test will be done on a sample of blood to look for cancer cells that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood. The characteristics of any tumor cells or DNA in your blood will be compared to the characteristics of a tumor sample from a sample of tissue left over from your biopsy when you were diagnosed with cancer. The information may be used to find out how well treatment is working. Being able to take multiple samples of blood over time may also help doctors understand what kind of molecular changes are taking place in a tumor. The research study will include sequencing of all or part of your DNA called genomic sequencing. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece.

Unknown future studies

If you choose to take part in this optional study, a sample of tissue left over from your biopsy when you were diagnosed with cancer or from the study biopsy if you had one will be collected and stored. If you stop the study therapy because you are no longer benefitting from the study therapy and a biopsy is done for routine care, a sample of the tissue from the biopsy will be collected and stored. Any tumor sample that was sent to the central lab that was not used to confirm that your tumor is positive for the protein HER2 and to confirm whether or not your tumor is sensitive to hormones will be sent from the central lab to the biobank to be stored. Also, any blood left over from the research study done to look for cancer cells that are circulating in the blood or for pieces of DNA from tumor cells that are in the blood will be stored. Storing samples for future studies is called "biobanking." The biobank is being run by NRG Oncology and is supported by the NCI. Also, any health-related information, such as your response to cancer treatment, results of study tests, and medicines you took, will be stored for future use.

This is a publicly funded study. Samples from publicly funded studies are required to be shared as broadly as possible. However, we will protect your privacy. The goal of this is to make more research possible that may improve people's health.

The biobank is a public research resource. It has controlled access. This means that researchers who want to get samples and data from it must submit a specific research request. The request

identifies who they are and what their planned research project is. Before getting the samples and data, the researchers must agree to keep the data private, only use it for their planned research project, and never use it to try to identify you.

We don't know what research may be done in the future using your tissue samples. This means that:

- You will not be asked if you agree to take part in the future research studies.
- You and your study doctor will not be told when or what type of research will be done.
- Future research studies may include sequencing of all or part of your DNA called genomic sequencing. All your genetic information makes up your genome. Genomic sequencing is a test that records all or part of the pieces of DNA that are in your genes, piece by piece. This is usually done to look for changes in your genome that may cause health problems.
- You will not get reports or other information about any research that is done using your samples.

What is involved in this optional sample collection?

If you agree to take part, here is what will happen next:

1. About 4 teaspoons of blood will be collected from a vein at 15 times during the study.
   - Before you begin study therapy
   - At weeks 10, 19, and 28 after you joined the study
   - At 9, 12, 18, and 24 months after you joined the study
   - Every 6 months during Year 3 through Year 5, if your cancer is still responding to the study therapy
   - If your cancer no longer responds to study therapy

   A sample of tissue left over from your biopsy when you were diagnosed with cancer or from the study biopsy if you had one will be sent to the biobank. Also, if you are no longer benefitting from the study therapy and a biopsy is done for routine care, a sample of tissue from the biopsy will be sent to the biobank. Also, any tumor sample that was sent to the central lab that was not used to confirm that your tumor is positive for the protein HER2 and to confirm whether or not your tumor is sensitive to hormones will be sent from the central lab to the biobank.
2. Your samples will be stored in the biobank. There is no limit on the length of time we will keep your samples and research information. The samples will be kept until they are used for research or destroyed.
3. Researchers can only get samples from the biobank after their research has been approved by experts. Researchers will not be given your name or contact information.
4. Some of your genetic and health information may be placed in central databases for researchers to use. The databases will not include your name or contact information.

What are the risks in this optional sample collection?

- The most common risks related to drawing blood from your arm are brief pain and maybe a bruise.
- Generally, hospitals will keep some of your tissue. This tissue may be used to help treat your cancer in the future. There is a small risk that when this tissue sample is submitted to the biobank for this optional sample collection, your tissue could be used up.

- Your medical and genetic information is unique to you. There is a risk that someone outside of the research study could get access to your study records or trace information in a database back to you. They could use that information in a way that could harm you. Researchers believe the chance that someone could access and misuse your information is very small. However, the risk may increase in the future as people find new ways of tracing information.
- In some cases, this information could be used to make it harder for you to get or keep a job and get or keep health insurance. There are laws against the misuse of genetic information, but they may not give full protection. For more information about the laws that protect you, ask your study doctor or visit: https://www.genome.gov/10002328/

How will information about me be kept private?

Your privacy is very important to the study researchers and biobank. They will make every effort to protect it. Here are just a few of the steps they will take:

1. They will remove identifiers, such as your initials, from your sample and information. They will replace them with a code number. There will be a master list linking the code numbers to names, but they will keep it separate from the samples and information.
2. Researchers who study your sample and information will not know who you are. They also must agree that they will not try to find out who you are.
3. Your personal information will not be given to anyone unless it is required by law.
4. If research results are published, your name and other personal information will not be used.

What are the benefits to taking part in this optional sample collection?

You will not benefit from taking part.

The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments to this optional sample collection?

There are no costs to you or your insurance. You will not be paid for taking part in this study. The research may lead to new tests, drugs, or other products for sale. If it does, you will not get any payment.

What if I change my mind about this optional sample collection?

If you decide you no longer want your samples to be used, you can call the study doctor, *(*insert name of study doctor for main trial*)*, at *(*insert telephone number of study doctor for main trial*)*, who will let the biobank know. Then, any sample that remains in the biobank will be destroyed or returned to your study doctor. This will not apply to any samples or related health information that have already been given to or used by researchers.

What if I have questions about this optional sample collection?

If you have questions about the use of your samples for research, contact the study doctor, *(*insert name of study doctor for main trial*)*, at *(*insert telephone number of study doctor for main trial*)*.

Please circle your answer below to show if you would or would not like to take part in each optional study:

Samples for known future studies:

I agree that my tissue and blood samples and related health information may be used for the laboratory study described above.

YES NO

Samples for unknown future studies:

I agree that my tissue and blood samples and related health information may be kept in a biobank for use in future health research.

YES NO

Contact for Future Research

I agree that my study doctor, or someone on the study team, may contact me or my doctor to see if I wish to participate in other research in the future.

YES NO

This is the end of the section about optional studies.

My signature agreeing to take part in the study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed and dated copy of this form. I agree to take part in the main study. I also agree to take part in any additional studies where I circled "yes".

Print patient's name_____

Patient's signature_____

Date of signature_____

Print name of person(s) conducting the informed consent discussion_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

[Additional signature lines may be added as required by local policies or regulations.